# Proteasome inhibitors/2. generation

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## Current situation

The following substances are currently in clinical trials[1]: **MLN9708** (Millenimu Pharmaceuticals), **CEP-18770** (Cephalon & Cell Therapeutics Europe), **Carfilzomib** (Proteolix) and **NPI-0052** (Nereus Pharmaceuticals).

### MLN9708

It is chemically similar to bortezomib and, like bortezomib, inhibits the 20S proteasome reversibly (after some time it is released from its binding site on the 20S proteasome). Compared to bortezomib, it is also effective when administered orally. Four ongoing clinical trials (phase 1-2) of this agent (multiple myeloma, solid tumors, lymphoma) can be found at NCI (https://www.cancer.gov).

### CEP-18770

Also a reversible 20S proteasome inhibitor (again chemically similar to bortezomib), but given intravenously. Currently, there is only one clinical trial of this substance (phase 2, multiple myeloma).

Both other agents are irreversible 20S proteasome inhibitors and belong to completely different chemical classes: unlike bortezomib, which is derived from a combination of monoalkylboronic acid and a dipeptide, carfilzomib is a combination of an epoxy ketone and a tetrapeptide, and NPI-0052 is a bicyclic γ-lactam-β-lactone.

### NPI-0052

It is also known as salinosporamide A and was originally isolated from a single marine bacterium. Four ongoing clinical trials (intravenous, phase 1, multiple myeloma, solid tumors, lymphomas) can be found on the NCI website for this substance.

### Carfilzomib

It is being tested in eight clinical trials (intravenous, phase 1-2, lymphomas, leukemia, solid tumors), in combination with other drugs even in phase 3 in patients with multiple myeloma. However, VELCADE (bortezomib) still remains the only clinically used proteasome inhibitor.

## Future

However, Hershk's original idea in his conversation with Adams was not to stop protein degradation per se. **20S Proteasome Inhibitors** interfere with too many cellular processes at once. Rather, Hershko was thinking about how to influence the degradation of specific selected proteins known to play a significant role in the development and progression of cancer. For such an approach, it is necessary to inhibit specific **E3 ligases** that decide on ubiquitination and degradation of these proteins.

### MLN4924

It is the first such inhibitor, entered clinical trials very recently and comes from Millenium Pharmaceuticals[2]. In fact, it is not an inhibitor of an E3 ligase directly, but rather a **NAE enzyme inhibitor** (NEDD8-activating enzyme), which regulates one group of E3 ligases. In this sense, MLN4924 represents a completely unique approach to the treatment of cancer that has not been tried before. Four clinical trials of this substance can be found on the NCI website (intravenous, phase 1, melanoma, leukemia, lymphomas, multiple myeloma, and also solid tumors).

## Links

### Related Articles

- Degradative system of the cell
- Ubiquitination
- Deubiquitination
- Proteasome and its inhibitors
- Studies on Proteasome Inhibitors
- History of Proteasome Inhibitors
- Antabuse

### Source

- ws:Inhibitory proteazomu/2. generace
- CVEK, Boris. From ubiquitin to antabuse. *Britské listy: a daily about everything that is not talked about much in the Czech Republic* [online]. 2011, vol. 1, p. 1, Available from <https://blisty.cz//legacy.blisty.cz/art/56680.html>. ISSN 1213-1792.

## References


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2. SOUCY, Teresa A – SMITH, Peter G – MILHOLLEN, Michael A. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. *Nature* [online]. 2009, vol. 458, no. 7239, p. 458, Available from <https://www.ncbi.nlm.nih.gov/pubmed/19360080>. ISSN 0028-0836 (print), 1476-4687.