

# Non-covalent and Reversible Proteasome Inhibitors with an Oxadiazole-isopropylamide Core



*Novel drug-like, non-covalent and reversible proteasome inhibitors with an oxadiazole-isopropylamide core have been identified. These are inhibitors for proteasome chymotrypsin-like (CT-L) activity. The most promising molecule inhibits CT-L activity with an  $IC_{50}$  of 32 nM in vitro and an  $IC_{50}$  of 1  $\mu$ M in MDA-MB-468 human breast cancer cells. Two further promising analogues inhibit CT-L activity in vitro with  $IC_{50}$ 's of 39 nM and 32 nM.*

## COMMERCIAL OPPORTUNITY

- Proteasome inhibition is a validated approach to cancer therapy, as shown by the FDA approval of Velcade for the treatment of multiple myeloma and relapsed mantle cell lymphoma. Velcade is a dipeptidyl boronic acid that is also a reversible inhibitor of CT-L activity by a different mechanism of action.
- Velcade had approximately \$700 million in sales in the US alone in 2011, and is approved in more than 90 countries, and is sold by Millennium: The Takeda Oncology Company.
- An attractive market as evidenced by the other proteasome inhibitors in clinical development include MLN9708 (a second generation proteasome inhibitor also from Millennium), CEP-1877 (Cephalon—acquired by Teva), Carfilzomib (Onyx Pharmaceuticals), and NPI-0052 (Nereus Pharmaceuticals).

## TECHNOLOGY

Novel drug-like, non-covalent and reversible proteasome inhibitors with an oxadiazole-isopropylamide core have been identified. The molecule PI-1833 was identified in an initial screen, and then optimization by focused library synthesis and medicinal chemistry resulted in further superior derivatives, including the analog 11ad that inhibits CT-L activity with an  $IC_{50}$  of 32 nM in vitro and an  $IC_{50}$  of 1  $\mu$ M in MDA-MB-468 human breast cancer cells. Two further promising analogues 11ae and 11al inhibit CT-L activity in vitro with  $IC_{50}$ 's of 39 nM and 32 nM, respectively. The ATP-dependent ubiquitin-proteasome pathway is responsible for the controlled degradation of proteins in eukaryotic cells. The three main peptidase catalytic activities of the proteasome (peptidylglutamyl peptide hydrolyzing, trypsin-like, and CT-L) are mediated by three distinct catalytic subunits. The development of proteasome inhibitors for CT-L activity for the treatment of cancer is due to the critical role of the CT-L activity in the degradation of apoptotic and tumor suppressor proteins.

## PUBLICATION/PATENT

- PCT Patent application was filed March 30, 2012 for Drs. Harshani Lawrence, Said Sebti, and Sevil Ozcan
- Presented at the AACR Annual Meeting in April 2011 and March 2012
- Manuscript in preparation.

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## LICENSING OPPORTUNITY

