ACS Medicinal Chemistry Letters

Patent Highlight

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Irreversible Inhibitors of Cysteine Proteases

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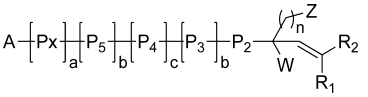
Title:	Irreversible Inhibitors of Cysteine Proteases		
Patent/Patent Application Number:	WO 2012/140500 A1	**Publication Date:**	October 18, 2012
Priority Application:		**Priority Date:**	April 15, 2011
Inventors:	Ahlfors, J. E.; Mekoular, K.		
Assignee Company:	New World Laboratories Inc., Canada		
Disease Area:	Neurodegenerative disease, stroke, spinal cord injury, cancer, myocardial infarction	**Biological Target:**	Cystein proteases, caspases

Summary:

The patent application claims modified peptides/peptide mimetics as selective and irreversible inhibitors of cyteine proteases and caspases for the treatment of a variety of diseases. Compounds of the invention are composed of 1−5 natural or non-natural amino acids and electrophilic "war head" moieties.

Important Compound Classes:



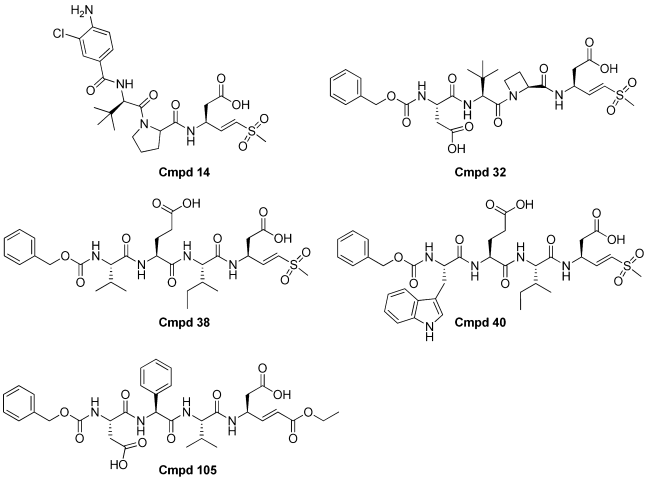
Definitions:

Px, P5, P4, P3, and P2 are natural or non-natural amino acids.

n is 0−3.

W is H, alkyl, OH, OR9, CN, NH2, NHR9, NHSOR9, halogen, COR4, COR9, CN, OCOR9, OCO2R9, NO, NO2, NR7R8, NHSO2R9, NHCOR9, SO2R9, or SR9.

Key Structures:



Biological Assays:

Caspase 1−10 inhibitor screening assay. Enzymatic assay using commercially available caspase inhibitor drug screening kits. IC_{50} values for 31 compounds tested against caspases 1−10 are described.

Received: January 15, 2013
Published: January 28, 2013

Pharmacological Data: Enzymatic screening assay:

Enzyme (IC_{50} μM)	Cmpd 14	Cmpd 32	Cmpd 38	Cmpd 40	Cmpd 105
Caspase 1	0.02	13.2	2.7	0.026	1.05
Caspase 2	>100	13.1	>100	>100	>100
Caspase 3	>100	0.28	6.9	6.5	0.03
Caspase 4	0.09	5.6	0.37	0.18	0.51
Caspase 5	0.56	35.2	19.5	0.75	>100
Caspase 6	>100	>100	0.6	~100	>100
Caspase 7	24.5	0.5	>100	23.7	0.15
Caspase 8	12.9	4.1	0.6	5.93	2.62
Caspase 9	2.3	1.1	0.8	1.74	1.0
Caspase 10	2.67	0.42	0.13	3.3	0.59

Synthesis: The synthesis of 162 compounds is exemplified.

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Notes

The authors declare no competing financial interest.