

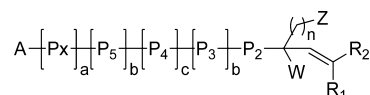
## Irreversible Inhibitors of Cysteine Proteases

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



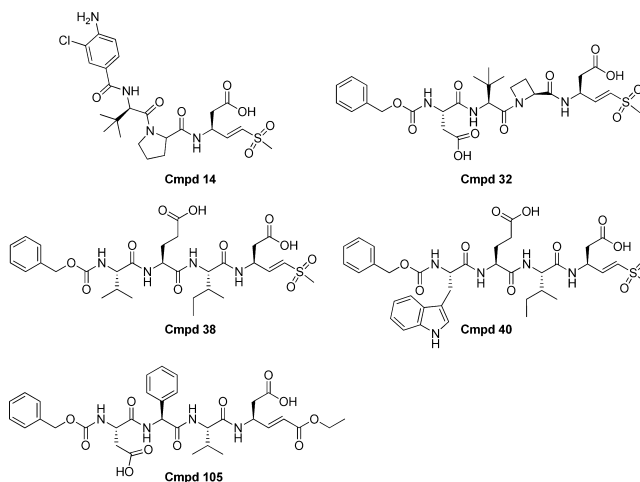
## Definitions:

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<sub>50</sub> values for 31 compounds tested against caspases 1–10 are described.

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Pharmacological Data:

Enzymatic screening assay:

Enzyme (IC <sub>50</sub> 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.

## ■ AUTHOR INFORMATION

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### Notes

The authors declare no competing financial interest.