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*Extended Abstract*

# Synthesis and Bioactivity Studies of Some Naphthoquinone Derivatives as Potential Proteasome Inhibitors †

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The ubiquitine–proteasome pathway (UPP) plays a major role in protein degradation in eukaryotic cells. It has been shown that this pathway is involved in many physiologically critical cellular processes. As the main component of the UPP, the 26S proteasome unit is responsible for the degradation of polyubiquitinated proteins and has multicatalytic proteinase activities. Increased levels of this enzyme have been implicated in many disorders, including inflammation, neurodegenerative, immune diseases, and cancer. Thus, the development of proteasome inhibitors has emerged as an attractive target for the treatment of these diseases, especially cancer [1]. Bortezomib, Ixazomib, and Carfilzomib have been approved by the US Food and Drug Administration (FDA) for the treatment of multiple myeloma. Despite the remarkable success of these inhibitors in the clinic, they have several shortcomings. Therefore, there is still a need to develop new and selective proteasome inhibitors [2]. The compound named PI-083, bearing naphthoquinone group, has recently been reported as a proteasome inhibitor. It has been shown that PI-083 has a broader antitumor activity and is more selective against cancer cells compared to Bortezomib [3]. On the basis of these findings, using a PI-083 lead compound, we designed and synthesized some sulfonamide and carboxamide derivatives bearing naphthoquinone pharmacophoric group as potential proteasome inhibitors and then evaluated their cytotoxic and proteasome inhibitory activities on a human breast cancer cell line (MCF-7). According to the biological activity results, the compounds showed cytotoxic activity at various ratios, and the sulfonamide derivative bearing 2-chloro-3-pyridyl group on amide nitrogen exhibited significant proteasome chymotripsin-like activity inhibition compared to the lead compound PI-083.

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