Search for Leads of Therapeutic Agents which Regulate Ubiquitin Ligases from Natural Resources

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The ubiquitin-proteasome proteolytic pathway plays a major role in selective protein degradation and regulates various cellular events including cell cycle progression, transcription, DNA repair, signal transduction, and immune response. In this pathway, ubiquitin, a highly conserved small protein in eukaryotes, attaches to a target protein prior to degradation. The polyubiquitin chains are recognized by the 26S proteasome, and the protein portion is degraded by the proteolytic active sites in a cavity in the 26S proteasome. The potential of specific proteasome inhibitors, which act as anti-cancer agents, is now under intensive investigation, and bortezomib (PS-341, Velcade^{TM}), a proteasome inhibitor, was approved by FDA for multiple myeloma treatment in 2003. Since ubiquitination of proteins requires the sequential action of three enzymes, ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin-protein ligase (E3), and polyubiquitination is a prerequisite for proteasome-mediated protein degradation, inhibitors of E1, E2, and E3 are reasonably thought to be drug candidates for treatment of diseases related to ubiquitination. In the course of our search for new classes of inhibitors against the ubiquitin-proteasome proteolytic pathway from natural resources for drug development, we succeeded in isolating agosterols, secomycalolides A, and 1,3-diphenylpropane derivatives as inhibitors of chymotrypsin-like activity of the proteasome, himeic acid A as an E1 inhibitor, and (*R*)-hexylitaconic acid as an inhibitor of p53-HDM2 interaction.