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Design, synthesis, and biological evaluation of bone-targeted proteasome inhibitors for multiple myeloma

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ABSTRACT

Multiple myeloma (MM) is an incurable neoplasm characterized by devastating and progressive bone destruction. Standard chemotherapeutic agents have not been effective at significantly prolonging the survival of MM patients and these agents are typically associated with often severe, dose-limiting side effects. There is great need for methods to target the delivery of novel, effective cytotoxic agents specifically to bone, where myeloma cells reside. We have synthesized and evaluated the effects of the bone-targeted proteasome inhibitors PS-341-BP-1, PS-341-BP-2 and MG-262-BP on cell proliferation using the mouse 5TGM1 and human RPMI 8226 cell lines in vitro. The compounds exhibit strong cytotoxicity on MM cell lines and reduce the number of viable cells in a dose dependent manner.

Several proteasome inhibitors have been identified, including peptide boronates (Bortezomib, its bidendate analog BU-32,[1] and MG-262), epoxiketones (Carfilzomib, also called Kyprolis, which has recently been approved for treatment of multiple myeloma (MM) patients by the FDA), PR047, and Epoxomicin, peptide aldehydes (MG-132 and PSI), and β-lactones (NPI-0052, also called salinosporamide A and lactacystin).[2–5] Several proteasome inhibitors that are currently in clinical trials including MLN9708, CEP-18770, Carfilzomib, PR-047, and NPI-0052, a β-lactone.[6] In addition, allosteric chemical inhibitors that target the proteasome outside of the active site have been developed, including chloroquine and its analog 5-amino-8-hydroxyquinoline (5AHQ).[7] The inhibitory potency and target selectivity towards the 20S proteasome of boronic acid-based inhibitors are quite remarkable (in the nM range). This is presumably due to the fact that an empty *p*-orbital on a boron atom is positioned to accept the oxygen lone pair of the amino terminal threonine residue of the 20S proteasome to form a stable tetrahedral intermediate.[8] To date, Bortezomib and carfilzomib are the only proteasome inhibitors approved for treatment of MM. Despite its remarkable effect in myeloma therapy, significant toxicities, such as peripheral neuropathy and thrombocytopenia, have restricted the intensity of bortezomib dosing and its clinical efficacy has been hampered by the emergence of resistance. There is an urgent need for new approaches to selectively target the delivery of effective anticancer drugs such as bortezomib specifically to bone tissue, where myeloma cells reside, to ameliorate and/or prevent the toxic side effects arising from systemic distribution of these drugs and to make dose escalation possible in order to improve therapeutic outcome.

Almost all patients with MM have an early excessive bone resorption leading to lytic lesions and sometimes to hypercalcemia.[9,10] Interactions between myeloma cells and bone cells and the extracellular matrix proteins within the bone microenvironment underlie the progression of multiple myeloma and are mediated through cell surface receptors.[11] These interactions trigger a self-amplifying cascade of events that result in the secretion of cytokines and growth factors that promote the growth and proliferation of myeloma cells, increase bone resorption and enhance drug resistance by inducing antiapoptotic pathways.[11–13] Bisphosphonates, which are degradation-resistant analogs of inorganic pyrophosphate, exhibit exceptional affinity for bone and have traditionally been the mainstay therapy for the treatment of skeletal related events associated with myeloma.[13] However, there may be a greater role for the use of bisphosphonates than has previously been considered. Recent reports suggest that they may act as antitumor agents,[14] able to delay disease progression and prolong survival in multiple myeloma,[15] and in solid tumors such as breast[16] and prostate cancers.[17,18] These observations, together with the efficacy of proteasome inhibitors in myeloma treatment and recent reports that suggest that proteasome inhibitors may stimulate new

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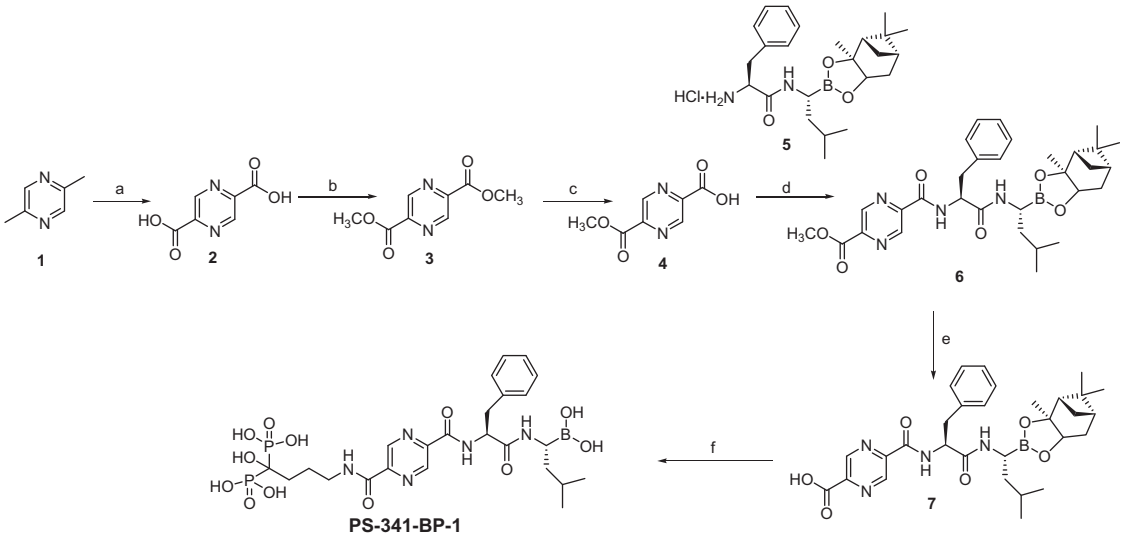
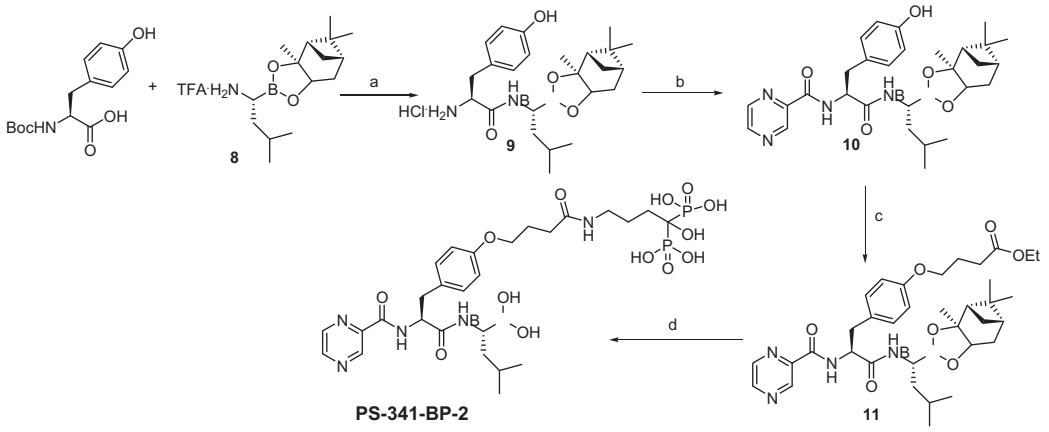
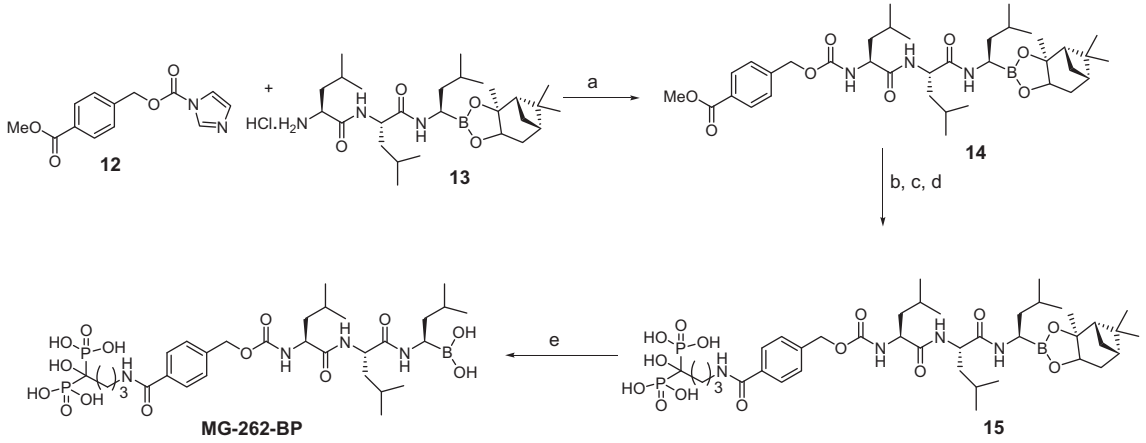
bone formation,[19,20] strongly argue for the use of proteasome inhibitor-bisphosphonate conjugates to target these potent drugs selectively to bone tissue in order to reduce off-target adverse effects and improve treatment outcomes. The important message is that by targeting proteasome inhibitors to bone, it may be possible to accentuate the beneficial bone anabolic effects of these



Scheme 1. Synthesis of PS-341-BP-1. Reagents and conditions: Key: (a) SeO_2, H_2O, pyridine, 68%; (b) MeOH, HCl gas, 94%; (c) MeOH, NaOH, 73%; (d) **5**, TBTU, DIEA, DMF, 60%; (e) LiOH, THF/MeOH/H_2O, 47%; (f) (i) NHS, DCC, DME; (ii) alendronate, DIEA, 2-propanol/H_2O; (iii) (2-methylpropyl)boronic acid, MeOH/Hexane/2 M HCl.



Scheme 2. Synthesis of PS-341-BP-2. Reagents and conditions: Key: (a) TBTU, DIEA, DMF, followed by deprotection with HCl in dioxane; (b) 2-pyrazine carboxylic acid, TBTU, DIEA, DMF, 40%; (c) ethyl 4-bromobutyrate, K_2CO_3, DMF; (d) (i) LiOH, MeOH/H_2O/THF; (ii) NHS, DCC, DME; (iii) alendronate, DIEA, H_2O/2-propanol; (iv) (2-methylpropyl)boronic acid, MeOH/hexane/2 M HCl



Scheme 3. Synthesis of MG-262-BP. Reagents and conditions: Key: (a) DMAP, CH_2Cl_2; (b) LiOH, THF/MeOH/H_2O; (c) NHS, DCC, DMF; (d) alendronate, DIEA, H_2O/2-propanol; (e) (2-methylpropyl)boronic acid, MeOH/hexane/2 M HCl.