

Article

Synthesis and Characterization of a Methoxypolyethylene Glycol-Modified Bortezomib Prodrug

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Abstract

To overcome the challenges of low water solubility, nonspecific biodistribution, limited tumor penetration, and easy inactivation of bortezomib (BTZ) under physiological conditions, we designed and synthesized a novel methoxypolyethylene glycol-modified bortezomib prodrug (mPEG₂₀₀₀-DEA-BTZ). This prodrug employs diethanolamine as a linker and mPEG₂₀₀₀ as the polymer chain, synthesized through a three-step reaction, with its chemical structure confirmed by ¹H NMR. Solubility studies demonstrated that in PBS buffer at pH 7.4, the solubility of mPEG₂₀₀₀-DEA-BTZ was ≥ 436.0 mg/mL, corresponding to a bortezomib solubility of ≥ 66.7 mg/mL, over 167-fold higher than that of free BTZ (399 μ g/mL). In vitro release experiments showed that only approximately 2% of BTZ was released from the prodrug within 24 h at pH 7.4, indicating excellent physiological stability. In contrast, drug release was significantly accelerated under acidic conditions (pH 6.5 and pH 5.0), with the cumulative release exceeding 90% at pH 5.0 within 4 h and approaching complete release at 24 h. Compared to the previously reported mPEG₅₀₀₀-CA-BTZ prodrug, the lower molecular weight mPEG₂₀₀₀ and diethanolamine linker employed in this study significantly improved the drug release rate and completeness. This pH-sensitive prodrug is expected to enhance the pharmacokinetic profile of bortezomib and achieve acidic tumor microenvironment-triggered targeted release, demonstrating significant potential for clinical translation.

Keywords: bortezomib; PEGylation; prodrug; pH sensitivity; drug release

1. Introduction

Multiple myeloma (MM) is a malignant tumor of terminally differentiated plasma cells and the second most common hematologic malignancy, following non-Hodgkin lymphoma [1]. Globally, an estimated 188,000 new cases of MM and 121,000 deaths were reported in 2022. By 2045, the incidence and mortality rates of MM are projected to increase by 71% and 79%, respectively, compared to 2022 levels [2].

Bortezomib (BTZ, **1**, Figure 1), a dipeptide boronic acid-based proteasome inhibitor with potent protease inhibitory activity, is clinically approved for the treatment of multiple myeloma and mantle cell lymphoma [3]. However, bortezomib exhibits poor water solubility, nonspecific biodistribution, and limited tumor penetration, which severely restrict its broader clinical application. Additionally, the use of bortezomib is often associated with severe adverse effects, including drug-induced liver injury, acute and chronic cardiac dysfunction, arrhythmia, and peripheral neuropathy [4–6]. Critically, bortezomib faces dual



Academic Editor: Giuseppe Cavallaro

Received: 7 June 2026

Revised: 20 July 2026

Accepted: 23 July 2026

Published: 27 July 2026

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inactivation due to the simultaneous presence of a peptide bond and a boronic acid moiety: the peptide bond is susceptible to hydrolysis by plasma proteases, while the boronic acid group undergoes nonspecific complexation with plasma proteins and endogenous hydroxyl compounds [7–10]. These two mechanisms collectively result in high nonspecific protein binding, rapid systemic clearance, and low plasma concentrations of bortezomib, ultimately significantly compromising its antitumor efficacy.

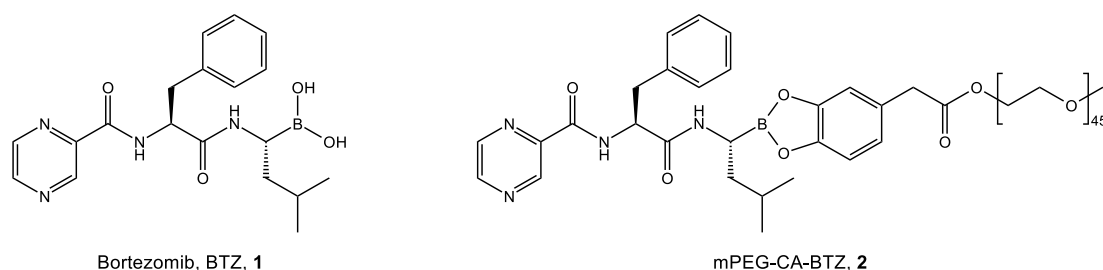


Figure 1. Chemical structures of BTZ (1) and mPEG-CA-BTZ (2).

To overcome the limitations of bortezomib, Fu et al. reported a PEGylated bortezomib prodrug (mPEG₅₀₀₀-CA-BTZ, **2**, Figure 1), in which mPEG is conjugated to BTZ via a catechol linker [11]. Prodrug **2** self-assembles into uniformly sized, colloiddally stable nanostructures under physiological pH conditions (pH 7.4). Moreover, prodrug **2** responds to the acidic tumor microenvironment, enabling pH-controlled release of bortezomib through acid-triggered cleavage of the boronate ester bond, prodrug **2** decomposition, and nanoparticle disassembly [11].

The covalent conjugation of polyethylene glycol to therapeutic agents, known as PEGylation, is a well-established and clinically validated drug delivery strategy that enhances the pharmacokinetics and pharmacodynamics of drugs. Specifically, PEGylation improves the solubility of the parent drug, prolongs systemic circulation, and reduces its immunogenicity. PEGylation technology has been applied to various therapeutic modalities, including small molecules [12], aptamers [13–15], peptides [13,14,16], and proteins [13,14,16]. Currently, over 30 PEGylated drugs are approved for clinical use, and numerous others are undergoing clinical trials [17]. In addition, PEGylated drugs reduce dosing frequency, enhance patient adherence, and further lower the risk of toxicity associated with peak plasma concentration (C_{max}) [18,19]. To date, various PEGylated drugs have been successfully applied in the clinic, including PEGylated naloxone (Movantik™), where PEGylation reduces the bioavailability of naloxone in the central nervous system [20]. Pegcetacoplan (Syfovre™) is a PEGylated synthetic cyclic peptide, and PEGylation significantly extends its circulating half-life [21,22]. These studies highlight that PEGylation plays an irreplaceable role in improving the stability, bioavailability, and clinical safety of both biologic and small-molecule drugs [17].

Although prodrug **2** improved BTZ solubility and enabled acidic microenvironment-triggered release, it exhibited slow and incomplete drug release—only approximately 65% at 4 h and 80% at 7.5 h under pH 5.0 [11]. An ideal prodrug should remain stable under normal physiological pH while rapidly and completely releasing the active ingredient in the acidic environment of tumor tissue, thereby enhancing the targeting and efficacy of the antitumor drug. The rate of active ingredient release from a PEGylated prodrug is closely associated with PEG molecular weight. High-molecular-weight PEG chains can form a thicker “protective shell,” shielding the ester bonds or other degradable chemical bonds in the prodrug, which hinders the approach of nucleophiles or enzymes and consequently delays the hydrolysis rate [23–25]. The selection of mPEG₅₀₀₀, with a polymerization degree of 5000 for prodrug **2** accounts for its slow release of the active ingredient. The

extent of active ingredient release from a PEGylated prodrug is also likely related to the structure of the linker. For prodrug **2**, the hydrolysis of the boronate ester under acidic conditions and the esterification reaction constitute a dynamic equilibrium. The use of catechol as the linker in prodrug **2** may have contributed to the incomplete release of the active ingredient bortezomib. Studies have demonstrated that diethanolamine is widely used as a reagent for deprotecting other boronate esters (such as catechol esters and pinacol esters) [26]. The strategy involves first undergoing transesterification of the boronate ester with diethanolamine to generate a more stable, isolable N→B coordination complex, followed by stirring in dilute hydrochloric acid (e.g., 0.1 M HCl) for several minutes to half an hour to hydrolyze and obtain the free boronic acid in high yield.

To elucidate the effects of PEG molecular weight and linker structure on BTZ release kinetics and completeness, and to develop a prodrug with rapid, complete tumor-specific release, we designed a novel PEGylated BTZ prodrug **3** (mPEG₂₀₀₀-DEA-BTZ). The chemical structure of prodrug **3** is shown in Figure 2.

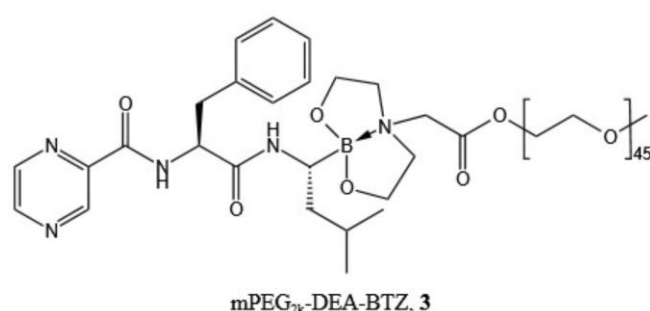


Figure 2. Chemical structure of mPEG-DEA-BTZ (**3**).

This prodrug **3** employs diethanolamine as the linker and mPEG with a polymerization degree of 2000. Although mPEG₅₀₀₀ offers better encapsulation and stability than mPEG₂₀₀₀, mPEG₂₀₀₀ is more favorable for the hydrolysis of the boronate ester and the release of the active ingredient. Furthermore, replacing the ortho-diphenol linker with diethanolamine allows more complete release of bortezomib under acidic conditions.

The preparation of the bortezomib prodrug **3** (mPEG₂₀₀₀-DEA-BTZ) starting from bromoacetyl bromide and mPEG₂₀₀₀ as raw materials is illustrated in Figure 3. In dichloromethane (DCM) solvent, with diisopropylethylamine as a base, mPEG₂₀₀₀-BAB (**4**) was synthesized by condensation at room temperature. Subsequently, condensation with diethanolamine under K₂CO₃/CH₃CN/60 °C conditions afforded the key intermediate mPEG₂₀₀₀-DEA (**5**). Under CH₃CN/N₂/room temperature conditions, compound **5** reacted with bortezomib (**1**) to yield the methoxypolyethylene glycol-modified bortezomib prodrug (mPEG₂₀₀₀-DEA-BTZ, **3**). Its structure was characterized by ¹H NMR spectroscopy.

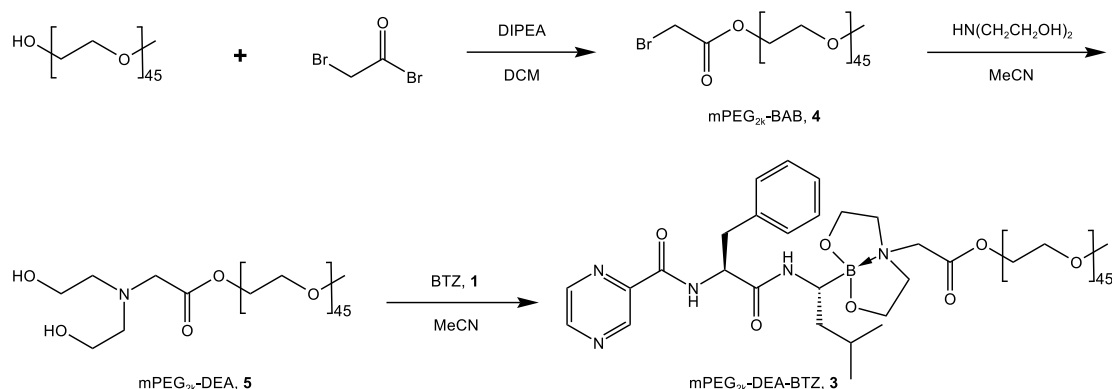


Figure 3. Synthetic route of bortezomib prodrug mPEG₂₀₀₀-DEA-BTZ.

2. Materials and Methods

2.1. Materials and Supplements

Bortezomib (BTZ, 99%) was purchased from Sichuan d-Innovation Pharmaceutical Co., Ltd. (Chengdu, China). Methoxy polyethylene glycol (mPEG, $M_n = 2000$ Da) and other chemicals and reagents were purchased from MACKLIN (Shanghai, China) and used without further purification. NMR spectra were recorded on an AVANCE NEO 600 MHz NMR spectrometer (Bruker, Rheinstetten, Germany) ($CDCl_3$ as solvent). Ultraviolet absorption was measured by Shimadzu UV-2700 UV-vis spectrophotometer (Shimadzu, Kyoto, Japan).

2.2. Synthesis of mPEG₂₀₀₀-BAB (Compound 4)

To a 250 mL three-necked flask, diisopropylethylamine (3.90 g, 30.2 mmol) was added, followed by dichloromethane (50 mL). After stirring to achieve a uniform mixture, mPEG₂₀₀₀ (30.0 g, 14.9 mmol) was added to the flask. The mixture was stirred until fully dissolved, then cooled in an ice–water bath under a nitrogen atmosphere. Bromoacetyl bromide (6.0 g, 29.7 mmol) was dissolved in 10 mL of dichloromethane, mixed thoroughly, and transferred to a constant-pressure dropping funnel. The solution was added dropwise to the reaction flask at 5 °C, maintaining the reaction temperature below 10 °C during the addition. After the addition was complete, the mixture was slowly warmed to room temperature and stirred for 24 h (monitored by TLC until the disappearance of the starting material mPEG₂₀₀₀). Approximately 320 mL of dichloromethane was added to the reaction mixture, which was then washed three times with 80 mL of 1 N hydrochloric acid and once with 80 mL of saturated aqueous sodium chloride. After drying over anhydrous Na_2SO_4 and filtration, the filtrate was concentrated under reduced pressure to yield a pale-yellow oily substance (approximately 30.6 g, 96.2% yield). 1H NMR (600 MHz, $CDCl_3$) δ : 4.33–4.32 (m, 2H), 3.89–3.87 (m, 2H), 3.86–3.43 (m, 178H), 3.37 (s, 3H).

2.3. Synthesis of mPEG₂₀₀₀-DEA (Compound 5)

To a 250 mL reaction flask, compound 4 (30.0 g, 14.0 mmol) and anhydrous acetonitrile (75 mL) were sequentially added, and the mixture was stirred until completely dissolved. Diethanolamine (2.2 g, 20.9 mmol) was dissolved in 10 mL of anhydrous acetonitrile and added in one portion to the reaction flask, followed by anhydrous potassium carbonate powder (2.5 g, 18.1 mmol). The mixture was stirred and heated in an oil bath under gentle reflux for 24 h (monitored by TLC until the disappearance of starting material 4). Dichloromethane (450 mL) was added, and the mixture was washed twice with 200 mL of 1 N hydrochloric acid and twice with 200 mL of saturated sodium chloride solution. After drying over anhydrous sodium sulfate and filtration, the filtrate was concentrated under reduced pressure to obtain a pale yellow oily substance. The product was dissolved in 20 mL of dichloromethane at room temperature, and 180 mL of methyl *tert*-butyl ether was slowly added under ice–water cooling. Crystals precipitated, and after stirring for 1 h, the mixture was filtered to afford a white powdery solid (7.34 g, 24.3% yield). 1H NMR (600 MHz, $CDCl_3$) δ : 4.35–4.33 (m, 2H), 4.19 (s, 2H), 3.83–3.48 (m, 186H), 3.37 (s, 3H).

2.4. Synthesis of Bortezomib Prodrug mPEG₂₀₀₀-DEA-BTZ (Compound 3)

To a 50 mL reaction flask, anhydrous acetonitrile (20 mL) and compound 5 (1.70 g, 0.787 mmol) were added, and the mixture was stirred until completely dissolved. Bortezomib (0.30 g, 0.781 mmol) was then added, and the mixture was stirred under a nitrogen protection for 24 h (monitored by TLC until the disappearance of starting material 5). The solvent was removed under reduced pressure to yield a yellow oily substance, which was dissolved in 15 mL of dichloromethane. Methyl *tert*-butyl ether (120 mL) was slowly added at room temperature, causing a precipitate to form. After stirring for 30 min, the

mixture was filtered. The filter cake was redissolved in 10 mL of dichloromethane, and 80 mL of methyl *tert*-butyl ether was slowly added at room temperature. After stirring for an additional 30 min, the mixture was filtered again. The product was dried under reduced pressure at room temperature to afford a white powdery solid (0.31 g, 15.8% yield). ^1H NMR (600 MHz, CDCl_3) δ : 9.29 (m, 1H), 8.75–8.70 (m, 1H), 8.54–8.45 (m, 1H), 8.36–8.32 (m, 1H), 7.30–7.24 (m, 6H), 6.93 (s, 1H), 5.10–4.60 (m, 2H), 4.55–3.10 (m, 196H), 2.93 (s, 2H), 2.75–2.00 (m, 6H), 1.65–1.10 (m, 3H), 1.00–0.70 (m, 6H).

2.5. Determination of the Solubility of mPEG2000-DEA-BTZ (3)

An accurately weighed amount of mPEG₂₀₀₀-DEA-BTZ (65.4 mg) was placed in a 2 mL sample vial, and 100 μL of PBS buffer (pH 7.4) was precisely pipetted into it. The suspension was sonicated for 2 min in an ultrasonic bath, then shaken in a constant-temperature oscillator at $25 \pm 0.5^\circ\text{C}$ for 24 h to observe dissolution. If the solution appeared turbid upon visual inspection, a fresh sample of mPEG₂₀₀₀-DEA-BTZ was weighed, and the volume of PBS buffer (pH 7.4) was increased by 50 μL , repeating the procedure described above. This process was continued until no visible solute particles or droplets were observed by visual inspection, at which point the sample was considered completely dissolved.

2.6. In Vitro Release Experiments of mPEG2000-DEA-BTZ (3)

An accurately weighed amount of mPEG₂₀₀₀-DEA-BTZ (65.4 mg) was placed in a 40 mL sample vial, and 20 mL of PBS buffer (pH 7.4) was accurately pipetted. The suspension was sonicated for 2 min in an ultrasonic bath and then shaken in a constant-temperature oscillator for 24 h at $25 \pm 0.5^\circ\text{C}$. The solution became completely clear, yielding a mPEG₂₀₀₀-DEA-BTZ solution. A 2.0 mL aliquot of this solution was transferred to a dialysis bag with a molecular weight cutoff of 1000 Da and immersed in 20 mL of PBS buffer at pH 7.4, 6.5, and 5.0, respectively, maintained at $37 \pm 0.5^\circ\text{C}$ in a shaker set to 100 rpm. At predetermined time intervals, 3.0 mL of the release medium was withdrawn and replaced with an equal volume of fresh buffer. The concentration of released bortezomib was determined by UV-Vis spectrophotometry at 270 nm. The cumulative drug release percentage (E_r) was calculated using the following formula:

$$E_r(\%) = \frac{V_e \times \sum_{i=1}^{n-1} C_i + V_0 \times C_n}{m\text{BTZ}} \times 100\% \quad (1)$$

where V_e is the volume of the replenished buffer (3.0 mL), V_0 is the total volume of the release medium (20 mL), C_i and C_n are the concentrations of bortezomib, i and n represent the sampling time points, respectively, and $m\text{BTZ}$ is the total amount of BTZ in the mPEG₂₀₀₀-DEA-BTZ solution. The release profile of bortezomib was determined by UV spectrophotometry. Details of the analytical method and its validation are provided in the Supplementary Information.

3. Results and Discussion

3.1. Solubility Determination Results of mPEG₂₀₀₀-DEA-BTZ (3)

The shake-flask method is the most reliable and widely used technique for determining the solubility of poorly soluble compounds. This method involves adding an excess amount of the drug to the solubility medium, ensuring that the drug quantity is sufficient to form a saturated solution in equilibrium with the solid phase [27,28]. At 25°C , 65.4 mg of mPEG₂₀₀₀-DEA-BTZ did not completely dissolve in 100 μL of PBS buffer (pH 7.4), and the solution remained slightly turbid. However, when the volume of PBS buffer (pH 7.4) was increased to 150 μL , the solution fully dissolved, with no visible solute particles or droplets observed after 24 h. Therefore, the solubility of mPEG₂₀₀₀-DEA-BTZ was determined to be

≥ 436.0 mg/mL. The average molecular weight of mPEG₂₀₀₀-DEA-BTZ is 2507, and the mass fraction of bortezomib in mPEG₂₀₀₀-DEA-BTZ is approximately $384/2507 \approx 15.3\%$. Based on the solubility of mPEG₂₀₀₀-DEA-BTZ (≥ 436.0 mg/mL), the solubility of bortezomib is calculated to be ≥ 66.7 mg/mL. This means that 15 mL of purified water is required to dissolve mPEG₂₀₀₀-DEA-BTZ containing 1 g of bortezomib, classifying it as “soluble”.

The reported solubility of bortezomib in PBS buffer (pH 7.4) at 25 °C is 399 μ g/mL [29]; therefore, mPEG₂₀₀₀-DEA-BTZ increased the solubility of bortezomib by more than 167-fold.

3.2. In Vitro Release Experimental Results of mPEG₂₀₀₀-DEA-BTZ (3)

To verify the pH-controlled release behavior of BTZ from the mPEG₂₀₀₀-DEA-BTZ pro-drug, a dialysis method was employed to compare the in vitro release profiles of mPEG₂₀₀₀-DEA-BTZ at pH 7.4 (extracellular pH of normal tissue), pH 6.5 (extracellular pH of tumor tissue), and pH 5.0 (lysosomal/endosomal pH of tumor cells) at 37 °C. The results are shown in Figure 4. At pH 7.4, the release rate of BTZ from mPEG₂₀₀₀-DEA-BTZ nanoparticles was very low, with only approximately 2% of the drug released within 24 h, indicating that the boronate ester bond between BTZ and the mPEG₂₀₀₀-DEA chain is highly stable under physiological conditions (pH 7.4). As the pH decreased, the release of BTZ was significantly accelerated at pH 6.5 and pH 5.0, demonstrating a distinct pH-dependent release profile. As shown in Figure 3, the cumulative release at pH 6.5 reached approximately 60% at 24 h. At pH 5.0, rapid release of BTZ was observed within 2 h, with cumulative release exceeded 90% at 4 h and approaching 100% at 24 h. These experimental results demonstrate that, compared with the mPEG₅₀₀₀-CA-BTZ prodrug [11], mPEG₂₀₀₀ facilitates faster hydrolysis of the boronate ester and thus faster release of BTZ; meanwhile, replacing the ortho-diphenol with diethanolamine as the linker enables fuller release of BTZ under acidic conditions. In summary, the mPEG₂₀₀₀-DEA-BTZ prodrug exhibits superior pH sensitivity and more complete release behavior, which is advantageous for targeted tumor therapy.

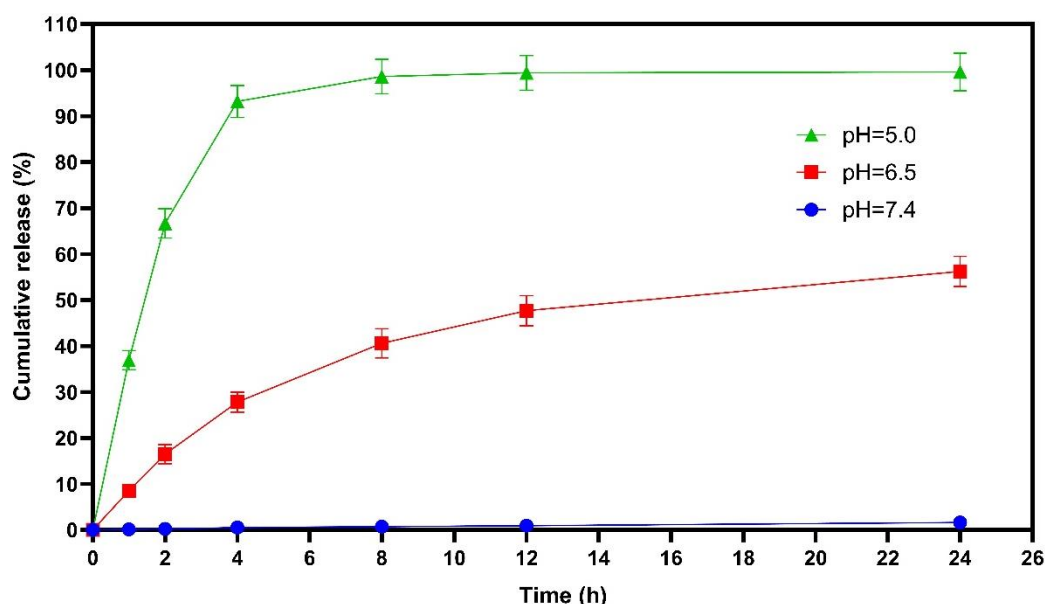


Figure 4. Drug cumulative release profiles of mPEG₂₀₀₀-DEA-BTZ in PBS at pH 7.4, 6.5, and 5.0.

4. Conclusions

To address the slow and incomplete release of catechol-based PEGylated bortezomib prodrugs in the acidic tumor microenvironment, this study designed and synthesized a novel bortezomib prodrug, mPEG₂₀₀₀-DEA-BTZ, using diethanolamine as the linker and

mPEG₂₀₀₀ as the hydrophilic modification chain. The solubility and in vitro acid-responsive drug-release behavior of the prodrug were subsequently evaluated. The structures of all intermediates and the final product were confirmed by ¹H NMR.

Using the shake-flask method, the solubility of mPEG₂₀₀₀-DEA-BTZ was determined to be ≥ 436.0 mg/mL, corresponding to a bortezomib-equivalent solubility of ≥ 66.7 mg/mL. This represents at least a 167-fold increase over the intrinsic solubility of bortezomib (399 μ g/mL), clearly demonstrating the significant capacity of PEGylation to enhance the aqueous solubility of hydrophobic drugs. Additionally, in vitro release studies were conducted using a dialysis method to systematically evaluate the release profiles of mPEG₂₀₀₀-DEA-BTZ in three buffers with different pH values. Under pH 7.4 conditions, which mimic the normal physiological environment, less than 2% of the drug was released within 24 h, indicating excellent chemical stability of the prodrug in systemic circulation. At pH 6.5, simulating the extracellular matrix of tumor tissue, the cumulative release reached approximately 60% at 24 h, demonstrating moderate sustained-release behavior. Notably, at pH 5.0, which mimics the endosomal/lysosomal environment of tumor cells, the cumulative release reached 90% within 4 h and approached 100% at 24 h. Both the release rate and completeness were markedly superior to those reported for the catechol-based prodrug mPEG₅₀₀₀-CA-BTZ in the literature.

In summary, this study strategically integrated linker chemistry and PEG molecular weight optimization to develop a novel bortezomib prodrug that remains highly stable in systemic circulation while enabling rapid and nearly complete drug release in the acidic tumor microenvironment. The results provide clear evidence that the chemical strategy of diethanolamine linker-mediated irreversible acidolysis can overcome the incomplete release typically associated with catechol-type boronate ester prodrugs. Additionally, low-molecular-weight PEG offers moderate steric shielding, balancing circulatory stability with acid-responsive release kinetics. Therefore, the structure-property relationship established in this study may offer valuable guidance for designing PEGylated prodrugs of boronic acid-containing drugs. The synthesized mPEG₂₀₀₀-DEA-BTZ prodrug demonstrates promising potential for tumor-targeted precision therapy. Future studies should further evaluate its in vivo pharmacokinetics, antitumor efficacy, and safety, as well as investigate the generalizability of this design strategy to other boronic acid-containing drugs, such as ixazomib.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/macromol6030050/s1>, Figure S1: UV-vis absorption spectrum of bortezomib. Figure S2: The calibration curve in pH 7.4 PBS buffer. Figure S3: The calibration curve in pH 6.5 PBS buffer. Figure S4: The calibration curve in pH 5.0 PBS buffer. Figure S5: ¹H NMR of mPEG₂₀₀₀-BAB (Compound 4). Figure S6: ¹H NMR of mPEG₂₀₀₀-DEA (Compound 5). Figure S7: ¹H NMR of mPEG₂₀₀₀-DEA-BTZ (Compound 3).

Author Contributions: The manuscript was conceived by F.G.; X.C. collected the primary data and compiled draft manuscripts. Z.C. and F.G. supervised the development of the manuscript, and Z.C., J.H. assisted in data interpretation, manuscript evaluation, and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Acknowledgments: The authors thank ZhiMing Zhu and Juan Wang for assistance and the collaboration in organic synthesis experiments.

Conflicts of Interest: Author Jian Hou and Zaixin Chen was employed by the company Bioscene Pharma. Author Feng Gao was employed by Southwest Jiaotong University. Author Xuhuan Chen worked at Southwest Jiaotong University. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Kumar, S.; Rajkumar, V.; Kyle, R.; Duin, M.; Sonneveld, P.; Mateos, M.; Gay, F.; Anderson, K. Multiple myeloma. *Nat. Rev. Dis. Primers* **2017**, *3*, 17046. [[CrossRef](#)] [[PubMed](#)]
2. Mafra, A.; Laversanne, M.; Marcos-Gragera, R.; Chaves, H.V.S.; Mcshane, C.; Bray, F.; Znaor, A. The global multiple myeloma incidence and mortality burden in 2022 and predictions for 2045. *J. Natl. Cancer Inst.* **2025**, *117*, 907–914. [[PubMed](#)]
3. Richardson, P.G.; Barlogie, B.; Berenson, J.; Singhal, S.; Jagannath, S.; Irwin, D.; Rajkumar, S.V.; Srkalovic, G.; Alsina, M.; Alexanian, R.; et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N. Engl. J. Med.* **2003**, *348*, 2609–2617. [[CrossRef](#)] [[PubMed](#)]
4. Karam, K.; Chebbo, H.; Saleh, S.; Dib, E.Y.; Fiani, E.; Sadek, M. Bortezomib-induced hepatotoxicity in a patient with multiple myeloma: A case report. *Med. Rep.* **2024**, *6*, 100099. [[CrossRef](#)]
5. Arastu-Kapur, S.; Anderl, J.L.; Kraus, M.; Parlati, F.; Shenk, K.D.; Lee, S.J.; Muchamuel, T.; Bennett, M.K.; Driessen, C.; Ball, A.J.; et al. Nonproteasomal targets of the proteasome inhibitors bortezomib and carfilzomib: A link to clinical adverse events. *Clin. Cancer Res.* **2011**, *17*, 2734–2743. [[CrossRef](#)] [[PubMed](#)]
6. Chen, D.; Frezza, M.; Schmitt, S.; Kanwar, J.; Dou, Q.P. Bortezomib as the first proteasome inhibitor anticancer drug: Current status and future perspectives. *Curr. Cancer Drug Targets* **2011**, *11*, 239–253. [[CrossRef](#)] [[PubMed](#)]
7. Silva, M.P.; Saraiva, L.; Pinto, M.; Sousa, M.E. Boronic acids and their derivatives in medicinal chemistry: Synthesis and biological applications. *Molecules* **2020**, *25*, 4323. [[CrossRef](#)] [[PubMed](#)]
8. Hu, X.; Chai, Z.; Lu, L.; Ruan, H.; Wang, R.; Zhan, C.; Xie, C.; Pan, J.; Liu, M.; Wang, H.; et al. Bortezomib dendrimer prodrug-based nanoparticle system. *Adv. Funct. Mater.* **2019**, *29*, 1807941. [[CrossRef](#)]
9. Pekol, T.; Daniels, J.S.; Labutti, J.; Parsons, I.; Nix, D.; Baronas, E.; Hsieh, F.; Gan, L.-S.; Miwa, G. Human metabolism of the proteasome inhibitor bortezomib: Identification of circulating metabolites. *Drug Metab. Dispos.* **2005**, *33*, 771–777. [[CrossRef](#)] [[PubMed](#)]
10. Su, J.; Chen, F.; Cryns, V.L.; Messersmith, P.B. Catechol polymers for pH-responsive, targeted drug delivery to cancer cells. *J. Am. Chem. Soc.* **2011**, *133*, 11850–11853. [[CrossRef](#)] [[PubMed](#)]
11. Fu, N.; Zeng, Y.; Zhang, J.; Zhang, P.; Zhang, H.; Yang, S.; Zhang, J. A facile strategy for PEGylated nanoprodrug of bortezomib with improved stability, enhanced biocompatibility, pH-controlled disassembly, and release. *Macromol. Biosci.* **2025**, *25*, e2400383. [[PubMed](#)]
12. Li, W.; Zhan, P.; De Clercq, E.; Lou, H.; Liu, X. Current drug research on PEGylation with small molecular agents. *Prog. Polym. Sci.* **2013**, *38*, 421–444. [[CrossRef](#)]
13. Turecek, P.L.; Bossard, M.J.; Schoetens, F.; Ivens, I.A. PEGylation of biopharmaceuticals: A review of chemistry and nonclinical safety information of approved drugs. *J. Pharm. Sci.* **2016**, *105*, 460–475. [[CrossRef](#)] [[PubMed](#)]
14. Ivens, I.A.; Achanzar, W.; Baumann, A.; Brändli-Baiocco, A.; Cavagnaro, J.; Dempster, M.; Depelchin, B.O.; Irizarry Rovira, A.R.; Dill-Morton, L.; Lane, J.H.; et al. PEGylated biopharmaceuticals: Current experience and considerations for nonclinical development. *Toxicol. Pathol.* **2015**, *43*, 959–983. [[CrossRef](#)] [[PubMed](#)]
15. Haruta, K.; Otaki, N.; Nagamine, M.; Kayo, T.; Sasaki, A.; Hiramoto, S.; Takahashi, M.; Hota, K.; Sato, H.; Yamazaki, H. A novel PEGylation method for improving the pharmacokinetic properties of anti-interleukin-17A RNA aptamers. *Nucleic Acid. Ther.* **2017**, *27*, 36–44. [[PubMed](#)]
16. Li, C.; Li, T.; Tian, X.; An, W.; Wang, Z.; Han, B.; Tao, H.; Wang, J.; Wang, X. Research progress on the PEGylation of therapeutic proteins and peptides (TPPs). *Front. Pharmacol.* **2024**, *15*, 1353626. [[CrossRef](#)] [[PubMed](#)]
17. Gao, Y.; Joshi, M.; Zhao, Z.; Mitragotri, S. PEGylated therapeutics in the clinic. *Bioeng. Transl. Med.* **2024**, *9*, e10600. [[PubMed](#)]
18. Rowinsky, E.K.; Rizzo, J.; Ochoa, L.; Takimoto, C.H.; Forouzes, B.; Schwartz, G.; Hammond, L.A.; Patnaik, A.; Kwiatek, J.; Goetz, A.; et al. A phase I and pharmacokinetic study of pegylated camptothecin as a 1-hour infusion every 3 weeks in patients with advanced solid malignancies. *J. Clin. Oncol.* **2003**, *21*, 148–157. [[CrossRef](#)] [[PubMed](#)]
19. Heo, Y.-A.; Syed, Y.Y.; Keam, S.J. Pegaspargase: A review in acute lymphoblastic leukaemia. *Drugs* **2019**, *79*, 767–777. [[CrossRef](#)] [[PubMed](#)]
20. Leppert, W.; Woron, J. The role of naloxegol in the management of opioid-induced bowel dysfunction. *Ther. Adv. Gastroenterol.* **2016**, *9*, 736–746. [[CrossRef](#)] [[PubMed](#)]

21. Crass, R.L.; Prem, K.; Gaudreault, F.; Lusk, E.; Ribeiro, R.; Chapel, S.; Baupal, C.R. Pharmacokinetic/pharmacodynamic analysis of geographic atrophy lesion area in patients receiving pegcetacoplan treatment or sham. *CPT Pharmacomet. Syst. Pharmacol.* **2025**, *14*, 257–267.
22. Crass, R.L.; Smith, B.; Adriaens, S.; Chapel, S.; Langdon, G. Population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria. *Drugs RD* **2024**, *24*, 563–573. [[CrossRef](#)]
23. Godin, B.; Gu, J.; Serda, R.E.; Bhavane, R.; Tasciotti, E.; Chiappini, C.; Liu, X.; Tanaka, T.; Decuzzi, P.; Ferrari, M. Tailoring the degradation kinetics of mesoporous silicon structures through PEGylation. *J. Biomed. Mater. Res. A* **2010**, *94*, 1236–1243. [[CrossRef](#)] [[PubMed](#)]
24. Nguyen, A.; Rouhollahi, E.; Böttger, R.; Ong, C.Y.; Chao, P.-H.; Wu, J.; Chen, Y.; Li, S.-D. Interplay between the linker and polymer molecular weight of a self-assembling prodrug on the pharmacokinetics and therapeutic efficacy. *Biomater. Sci.* **2022**, *10*, 3122–3136. [[CrossRef](#)] [[PubMed](#)]
25. Rabanel, J.-M.; Faivre, J.; Paka, G.D.; Ramassamy, C.; Hildgen, P.; Banquy, X. Effect of polymer architecture on curcumin encapsulation and release from PEGylated polymer nanoparticles: Toward a drug delivery nanoplatform to the CNS. *Eur. J. Pharm. Biopharm.* **2015**, *96*, 409–420. [[CrossRef](#)] [[PubMed](#)]
26. Sun, J.; Perfetti, M.T.; Santos, W.L. A method for the deprotection of alkylpinacolyl boronate esters. *J. Org. Chem.* **2011**, *76*, 3571–3575. [[CrossRef](#)] [[PubMed](#)]
27. Veseli, A.; Žakelj, S.; Kristl, A. A review of methods for solubility determination in biopharmaceutical drug characterization. *Drug Dev. Ind. Pharm.* **2019**, *45*, 1717–1724. [[CrossRef](#)] [[PubMed](#)]
28. Higuchi, T.; Shih, F.M.; Kimura, T.; Rytting, J.H. Solubility determination of barely aqueous-soluble organic solids. *J. Pharm. Sci.* **1979**, *68*, 1267–1272. [[CrossRef](#)] [[PubMed](#)]
29. Benedik, N.S.; Šterman, A.; Smrdel, L.; Pajk, S.; Gobec, S.; Časar, Z.; Gobec, M.; Sosič, I. α -Aminoboronic acid moieties in boro dipeptides modulate proteasome subunit selectivity and provide access to compounds with potent anticancer and anti-inflammatory activity. *J. Med. Chem.* **2025**, *68*, 26405–26417. [[CrossRef](#)]

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