

Inhibition of HIV-1 Protease by a Boronic Acid with High Oxidative Stability

Brian J. Graham, Ian W. Windsor, and Ronald T. Raines*



Cite This: *ACS Med. Chem. Lett.* 2023, 14, 171–175



Read Online

ACCESS |

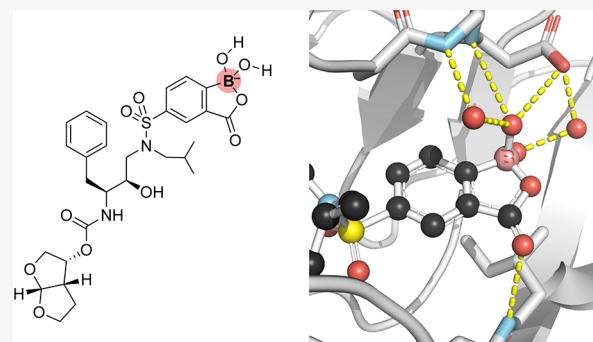
Metrics & More

Article Recommendations

Supporting Information

ABSTRACT: HIV-1 protease is an important target for pharmaceutical intervention in HIV infection. Extensive structure-based drug design led to darunavir becoming a key chemotherapeutic agent. We replaced the aniline group of darunavir with a benzoaborolone to form BOL-darunavir. This analogue has the same potency as darunavir as an inhibitor of catalysis by wild-type HIV-1 protease and, unlike darunavir, does not lose potency as an inhibitor of the common D30N variant. Moreover, BOL-darunavir is much more stable to oxidation than is a simple phenylboronic acid analogue of darunavir. X-ray crystallography revealed an extensive network of hydrogen bonds between the enzyme and benzoaborolone moiety, including a novel direct hydrogen bond from a main-chain nitrogen to the carbonyl oxygen of the benzoaborolone moiety that displaces a water molecule. These data highlight the utility of benzoaborolone as a pharmacophore.

KEYWORDS: Benzoaborolone, boronic acid, darunavir, HIV-1 protease, oxidative stability, pharmacophore



The human immunodeficiency virus (HIV) remains a global health scourge.¹ Inhibitors of HIV protease are an important tool in the management of HIV infection. Years of drug-design have led to highly potent inhibitors such as darunavir (**1**),² which is among the most resilient of protease inhibitors.^{3,4} Recently, we reported on a boronic acid derivative of darunavir (B-darunavir; **2**) with subpicomolar affinity toward the protease, 20-fold greater than darunavir itself.⁵ Despite its high affinity, phenylboronic acid **2** proved to be less efficient than expected at inhibiting the reproduction of HIV in human cells.⁶ The low activity is likely due to oxidative deboronation, as has been seen with other boronic acid-based pharmaceuticals.⁷ The phenol metabolite of B-darunavir has substantially reduced affinity for the protease and will be excreted readily by phenol conjugation through phase II metabolism. Thus, the high affinity of B-darunavir is outweighed by its oxidative instability.

Recently, we reported that benzoaborolone exhibits dramatically improved stability toward oxidation compared to phenylboronic acid while retaining its desirable attributes as a ligand.⁸ Moreover, the oxygen-rich benzoaborolone scaffold can provide additional opportunities for hydrogen bonding. Thus, we reasoned that BOL-darunavir (**3**), which is the benzoaborolone analogue of B-darunavir (Figure 1), could display improved oxidative stability while maintaining high affinity for HIV-1 protease. Here, we describe the synthesis and analysis of BOL-darunavir.

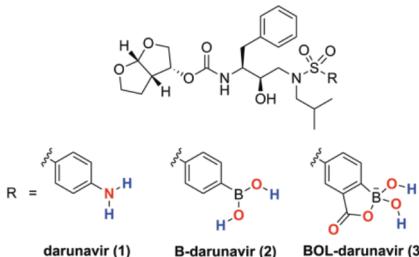


Figure 1. Structures of darunavir (**1**), B-darunavir (**2**), and BOL-darunavir (**3**) at pH 7. Potential hydrogen-bond acceptors are in red, and potential hydrogen-bond donors are in blue.

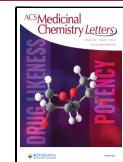
SYNTHESIS OF BOL-DARUNAVIR

Initially, we attempted to synthesize benzoaborolone **3** by modification of our synthetic route to phenylboronic acid **2**⁵ using a carboxy-modified phenyl bromide. Unfortunately, the catalytic borylation and subsequent deprotection of the boronate and carboxy esters produced no isolable product.

Received: October 25, 2022

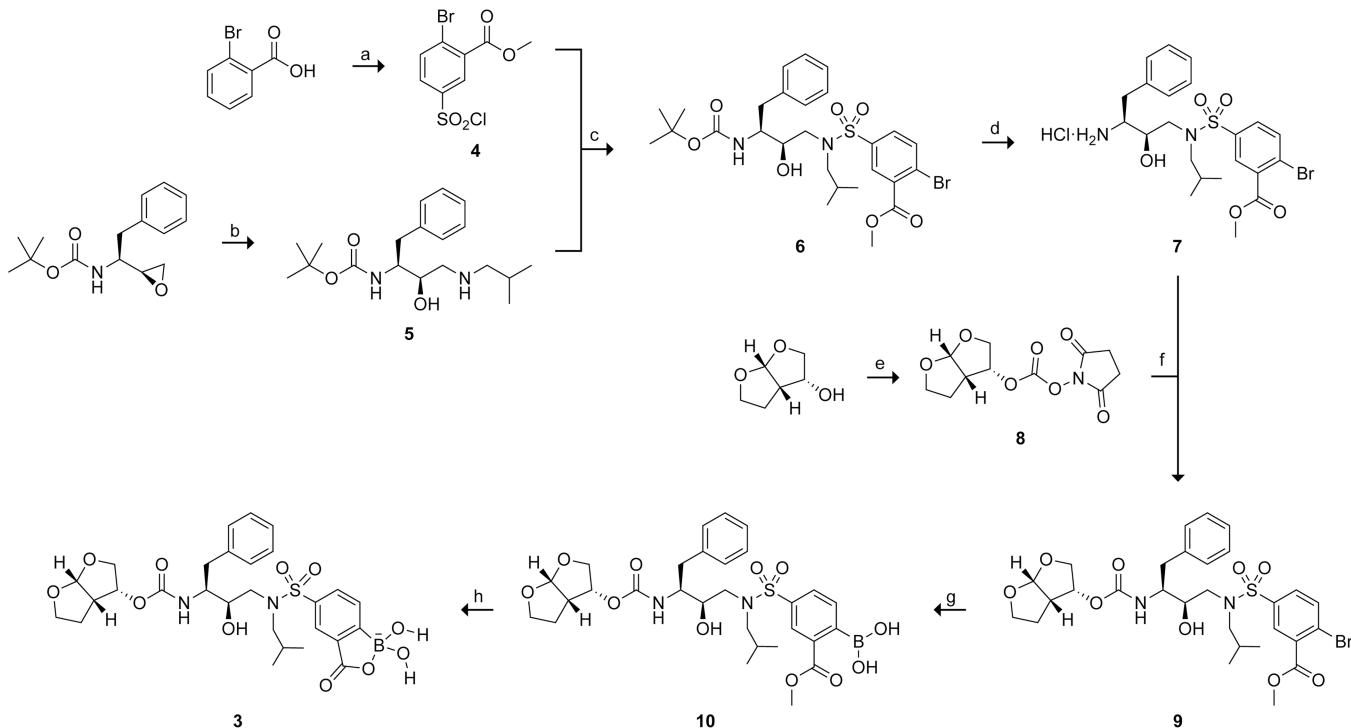
Accepted: January 17, 2023

Published: January 25, 2023



ACS Publications

© 2023 American Chemical Society

Scheme 1. Synthetic Route to BOL-Darunavir (3)^a

^aConditions: (a) (i) chlorosulfonic acid, 110 °C, (ii) thionyl chloride, MeOH; (b) isobutylamine, *i*PrOH; (c) Et₃N, DCM; (d) 4 M HCl in 1,4-dioxane; (e) disuccinimidyl dicarbonate, pyridine, DCM; (f) pyridine, DCM; (g) (i) B₂PiN₂, KOAc, Pd(dppf)Cl₂ (1 equiv), 1,4-dioxane, 80 °C, 1 h, (ii) KHF₂(aq), MeOH, (iii) TMS-Cl, H₂O; (h) sat. NaHCO₃(aq).

Attempts with other halides and more sterically bulky carboxy esters did not increase the yield. A synthetic route relying on magnesium–halogen exchange⁹ proved successful on a model compound but incompatible with the full molecule. Similarly, attempts to use other metal-catalyzed reactions and more reactive electrophiles were unsuccessful. The synthesis of a boronated sulfonyl chloride succumbed to protodeboronation of the boronic acid moiety.

We reasoned that the failure of the catalytic borylation reaction could be due to a competitive protodeboronation or protodehalogenation reaction. If so, then stoichiometric palladium could decrease the reaction time, allowing borylation to outcompete degradation. By using stoichiometric palladium, we were indeed able to elicit C–B bond formation. Borylation was followed by mild deprotection of the pinacol ester through its potassium trifluoroborate salt (which allowed for purification of the borylated product), and subsequent hydrolysis to boronic acid 10 using chlorotrimethylsilane and water.¹⁰ Hydrolysis of the methyl ester in a mild sodium bicarbonate solution resulted in benzoxaborolone 3 (Scheme 1).

■ OXIDATIVE STABILITY OF B-DARUNAVIR AND BOL-DARUNAVIR

As a proxy for in vivo oxidation of the boronic acid derivatives, we used ¹H NMR spectroscopy to obtain rate constants for the oxidation of compounds 2 and 3 by hydrogen peroxide, which is the major reactive oxygen species in humans.^{11,12} As expected,⁸ the use of the benzoxaborolone moiety resisted oxidation, with benzoxaborolone 3 oxidizing ~50-fold more slowly than phenylboronic acid 2 (Figure S1; Table 1).

Table 1. Parameters for the Oxidation of and HIV-1 Protease Inhibition by Darunavir (1), B-Darunavir (2), and BOL-Darunavir (3)

compound	oxidation		inhibition <i>K_i</i> (pM) ^b
	<i>k_{obs}</i> (M ⁻¹ s ⁻¹) ^a	<i>k_{rel}</i>	
1			10 ± 1 ^c
2	0.12 ± 0.01	1	0.5 ± 0.3 ^c
3	0.0026 ± 0.0004	0.021	10 ± 2

^aFor oxidation by hydrogen peroxide in 1:1 50 mM sodium phosphate buffer in D₂O, pH 7.4/CD₃CN. ^bFor inhibition of the cleavage of RE(EDANS)SGIFLETSK(DABCYL)R in sodium acetate buffer, pH 5.0, containing NaCl (0.10 M), DMF (2% v/v). ^cValues are from ref 13.

The strongly electron-withdrawing sulfonamide group differentially affects the oxidative stability of compounds 2 and 3. Compound 2 is more oxidatively stable than phenylboronic acid itself (which has *k_{obs}* = 2.4 M⁻¹ s⁻¹; ref 8), presumably because of the stabilization of its anionic form. By contrast, compound 3 is less stable than benzoxaborolone itself (which has *k_{obs}* = 0.00015 M⁻¹ s⁻¹; ref 8). This decrease could reflect an increase in the stability of the dianion that is formed upon hydrolysis of the boralactone ring of compound 3 due to the electron-withdrawing nature of its sulfonamide group. Indeed, DFT calculations of a model compound indicate that the dianion has a much faster oxidation rate than does the intact boralactone (Table S1). Regardless, substitution of the phenylboronic acid with a benzoxaborolone enhances the oxidative stability of benzoxaborolone 3 to be well beyond that of typical boronic acids.

■ INTERACTION OF BOL-DARUNAVIR WITH HIV-1 PROTEASE

Benzoxaborolone 3 proved to be an effective inhibitor of catalysis by HIV protease. Using the hypersensitive assay developed in our laboratory,¹³ we obtained an inhibitory constant (K_i) of 10 ± 2 pM with the wild-type enzyme. This value indicates a loss of affinity relative to phenylboronic acid 2 but is indistinguishable from the inhibitory constant observed for darunavir itself (Figure S1; Table 1).¹³

D30N is a common substitution in clinical isolates of HIV-1 protease.¹⁴ The ensuing loss of a hydrogen bond between Asp30 and the aniline moiety of darunavir leads to a drop in potency of 30-fold.¹⁵ In contrast, we did not observe a decrease in affinity of BOL-darunavir to the D30N variant ($K_i = 7 \pm 5$ pM; Figure S2).

To characterize the interaction of benzoxaborolone 3 with HIV-1 protease further, we obtained an X-ray crystal structure of the enzyme-inhibitor complex. In previous work, we found that a benzoxaborolone moiety in a transthyretin ligand forms a covalent B–O bond with a serine side chain.⁸ In that protein-ligand complex, the boron adopts a trigonal geometry. In contrast, BOL-darunavir binds to HIV-1 protease in a noncovalent manner, and its boron adopts a tetrahedral geometry (Figure 2). Both covalent^{16–18} and noncovalent¹⁹ binding modes have been observed in FDA-approved and investigational pharmaceutical agents that contain boronic acid moieties.^{20–22} These differences showcase the high versatility of the benzoxaborolone pharmacophore and indicate its adaptability to local environments.

The benzoxaborolone moiety of BOL-darunavir forms an extensive network of intermolecular hydrogen bonds with HIV-1 protease (Figure 2). Of particular note is the replacement of a canonical bridging water molecule with a hydrogen bond directly with the main-chain nitrogen of Gly48 (Figure 2A,B). Gly48 is in one of the two flexible flaps that closes to bind an enzymic substrate (Figure 2C). Highly mutated proteases exhibit a resistance mechanism wherein the closed state of the flaps is destabilized, allowing transient closure for substrate hydrolysis but weakening the binding of known inhibitors.²³ To our knowledge, no other hydroxyethylamine sulfonamide accepts a hydrogen bond from the main-chain nitrogen of Gly48; importantly, such an interaction cannot be averted simply by a mutation that installs a new side chain.^{24–26} Overall, two hydrogen bonds are formed by the benzoxaborolone moiety with the protease main chain (Asp29 and Gly48), one with a side chain (Asp30) and two with bridging water molecules. The extent of this hydrogen-bonding network is unique and could offer affinity to protease variants that resist darunavir or other drugs.^{3,4,27–29}

■ CONCLUSION

BOL-darunavir is a 10 pM inhibitor of HIV-1 protease. This darunavir analogue is equipotent with darunavir itself and avoids the potential for genotoxic metabolites that can arise from aniline moieties.^{30,31} This darunavir analogue is equipotent with darunavir itself and displays significantly enhanced oxidative stability while affording a unique pattern of hydrogen-bond donors and acceptors. The dense hydrogen-bond network could be less sensitive to point mutations than with other pharmacophores. We suspect that the benefits of a benzoxaborolone moiety could be generalizable to other targets of pharmacological importance.

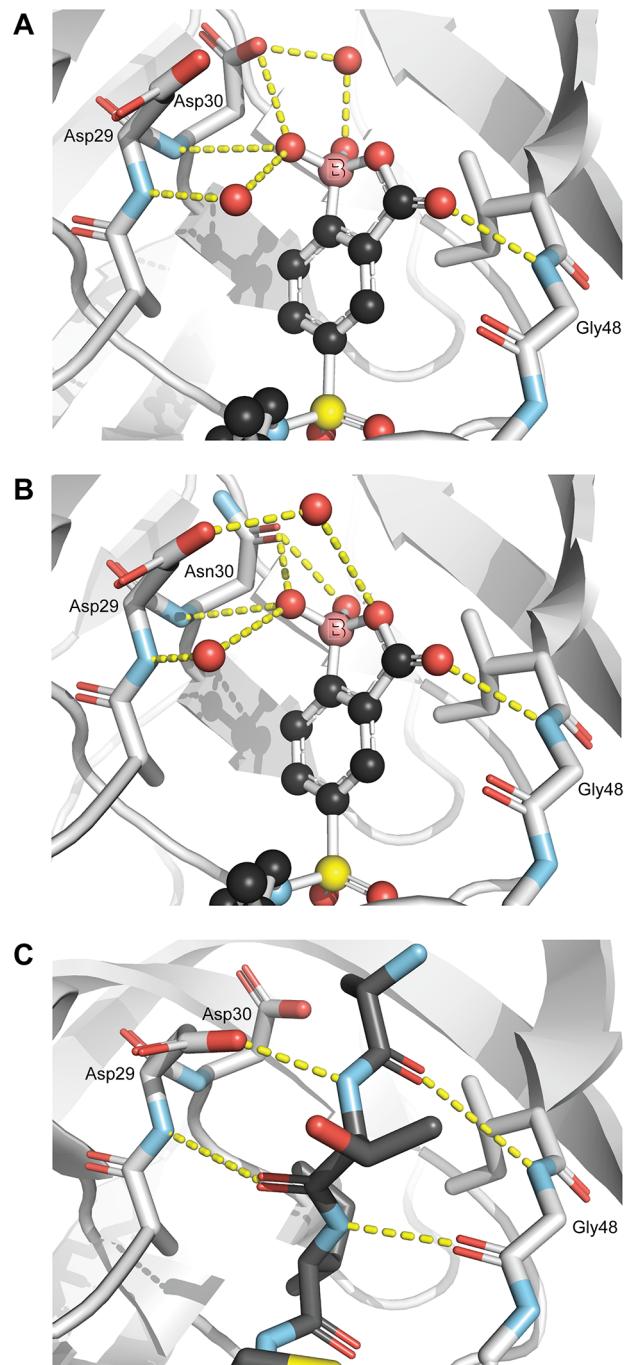


Figure 2. Structural analysis of the inhibition of HIV-1 protease by BOL-darunavir (3) with X-ray crystallography. (A) Structure of BOL-darunavir bound to wild-type HIV-1 protease (PDB entry 8esx; resolution of 1.35 \AA , R -value of 0.19). (B) Structure of BOL-darunavir bound to D30N HIV-1 protease (PDB entry 8esy; resolution of 1.35 \AA , R -value of 0.20). (C) Structure of a peptide substrate (PATIMMQRGN) bound to D25N HIV-1 protease, which is inactive (PDB entry 1kj7). Images were created with the program PyMOL (Schrödinger). Yellow dashed lines indicate putative hydrogen bonds.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsmedchemlett.2c00464>.

Experimental procedures, computational data, and NMR spectra ([PDF](#))

■ AUTHOR INFORMATION

Corresponding Author

Ronald T. Raines – Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; [orcid.org/0000-0001-7164-1719](#); Email: rtraines@mit.edu

Authors

Brian J. Graham – Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; [orcid.org/0000-0001-9985-3553](#)

Ian W. Windsor – Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; Present Address: Discovery Sciences, Medicine Design, Pfizer Worldwide Research and Development, Groton, Connecticut, 06340, United States; [orcid.org/0000-0002-6289-6928](#)

Complete contact information is available at:
<https://pubs.acs.org/10.1021/acsmedchemlett.2c00464>

Funding

This work was supported by Grant R01 GM044783 (NIH). GM/CA@APS was supported by Grants ACB-12002, AGM-12006, and P30 GM138396 (NIH). This research used resources of the Advanced Photon Source, a U.S. Department of Energy (DOE) Office of Science User Facility operated for the DOE Office of Science by Argonne National Laboratory under Contract DE-AC02-06CH11357. The Eiger 16M detector was supported by Grant S10 OD012289 (NIH).

Notes

The authors declare the following competing financial interest(s): The Massachusetts Institute of Technology has applied for a patent on the use of benzoxaborolone as a pharmacophore.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Craig A. Bingman (Department of Biochemistry, University of Wisconsin—Madison) for data collection and Dr. Craig M. Ogata (GM/CA@APS) for beamline support.

■ REFERENCES

- (1) Makam, P.; Matsa, R. “Big Three” Infectious Diseases: Tuberculosis, Malaria and HIV/AIDS. *Curr. Top. Med. Chem.* **2021**, *21*, 2779–2799.
- (2) Ghosh, A. K.; Kincaid, J. F.; Cho, W.; Walters, D. E.; Krishnan, K.; Hussain, K. A.; Koo, Y.; Cho, H.; Rudall, C.; Holland, L.; Buthod, J. Potent HIV Protease Inhibitors Incorporating High-Affinity P₂-Ligands and (R)-(Hydroxyethylamino)sulfonamide Isostere. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 687–690.
- (3) Ghosh, A. K.; Chapsal, B. D.; Weber, I. T.; Mitsuya, H. Design of HIV Protease Inhibitors Targeting Protein Backbone: An Effective Strategy for Combating Drug Resistance. *Acc. Chem. Res.* **2008**, *41*, 78–86.
- (4) Matthew, A. N.; Leidner, F.; Lockbaum, G. J.; Henes, M.; Zephyr, J.; Hou, S.; Rao, D. N.; Timm, J.; Rusere, L. N.; Ragland, D. A.; Paulsen, J. L.; Prachanronarong, K.; Soumana, D. I.; Nalivaika, E. A.; Kurt Yilmaz, N.; Ali, A.; Schiffer, C. A. Design Strategies to Avoid Resistance in Direct-Acting Antivirals and Beyond. *Chem. Rev.* **2021**, *121*, 3238–3270.
- (5) Windsor, I. W.; Palte, M. J.; Lukesh, J. C.; Gold, B.; Forest, K. T.; Raines, R. T. Sub-picomolar Inhibition of HIV-1 Protease with a Boronic Acid. *J. Am. Chem. Soc.* **2018**, *140*, 14015–14018.
- (6) Ghosh, A. K.; Xia, Z. L.; Kovela, S.; Robinson, W. L.; Johnson, M. E.; Kneller, D. W.; Wang, Y. F.; Aoki, M.; Takamatsu, Y.; Weber, I. T.; Mitsuya, H. Potent HIV-1 Protease Inhibitors Containing Carboxylic and Boronic Acids: Effect on Enzyme Inhibition and Antiviral Activity and Protein–Ligand X-Ray Structural Studies. *ChemMedChem* **2019**, *14*, 1863–1872.
- (7) 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.
- (8) Graham, B. J.; Windsor, I. W.; Gold, B.; Raines, R. T. Boronic Acid with High Oxidative Stability and Utility in Biological Contexts. *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118*, e2013691118.
- (9) Demory, E.; Blandin, V.; Einhorn, J.; Chavant, P. Y. Noncryogenic Preparation of Functionalized Arylboronic Esters through a Magnesium–Iodine Exchange with in Situ Quench. *Org. Process Res. Dev.* **2011**, *15*, 710–716.
- (10) Yuen, A. K. L.; Hutton, C. A. Deprotection of Pinacolyl Boronate Esters via Hydrolysis of Intermediate Potassium Trifluoroborates. *Tetrahedron Lett.* **2005**, *46*, 7899–7903.
- (11) Decker, H.; van Holde, K. E. *Oxygen and the Evolution of Life*; Springer: New York, NY, 2011.
- (12) Sies, H.; Berndt, C.; Jones, D. P. Oxidative Stress. *Annu. Rev. Biochem.* **2017**, *86*, 715–748.
- (13) Windsor, I. W.; Raines, R. T. Fluorogenic Assay for Inhibitors of HIV-1 Protease with Sub-picomolar Affinity. *Sci. Rep.* **2015**, *5*, 11286.
- (14) Rhee, S.-Y.; Taylor, J.; Fessel, W. J.; Kaufman, D.; Towner, W.; Troia, P.; Ruane, P.; Hellinger, J.; Shirvani, V.; Zolopa, Z.; Shafer, R. W. HIV-1 Protease Mutations and Protease Inhibitor Cross-Resistance. *Antimicrob. Agents Chemother.* **2010**, *54*, 4253–4261.
- (15) Kovalevsky, A.; Tie, Y.; Liu, F.; Boross, P. I.; Wang, Y.-F.; Leshchenko, S.; Ghosh, A. K.; Harrison, R. W.; Weber, I. T. Effectiveness of Nonpeptide Clinical Inhibitor TMC-114 on HIV-1 Protease with Highly Drug Resistant Mutations D30N, I50V, and L90M. *J. Med. Chem.* **2006**, *49*, 1379–1387.
- (16) Groll, M.; Berkers, C. R.; Ploegh, H. L.; Ovaa, H. Crystal Structure of the Boronic Acid-Based Proteasome Inhibitor Bortezomib in Complex with the Yeast 20S Proteasome. *Structure* **2006**, *14*, 451–456.
- (17) Rock, F. L.; Mao, W.; Yaremchuk, A.; Tukalo, M.; Crépin, T.; Zhou, H.; Zhang, Y.-K.; Hernandez, V.; Akama, T.; Baker, S. J.; Plattner, J. J.; Shapiro, L.; Martinis, S. A.; Benkovic, S. J.; Cusack, S.; Alley, M. R. K. An Antifungal Agent Inhibits an Aminoacyl-tRNA Synthetase by Trapping tRNA in the Editing Site. *Science* **2007**, *316*, 1759–1761.
- (18) Hecker, S. J.; Reddy, K. R.; Totrov, M.; Hirst, G. C.; Lomovskaya, O.; Griffith, D. C.; King, P.; Tsivkovski, R.; Sun, D.; Sabet, M.; Tarazi, Z.; Clifton, M. C.; Atkins, K.; Raymond, A.; Potts, K. T.; Abendroth, J.; Boyer, S. H.; Loutit, J. S.; Morgan, E. E.; Dursou, S.; Dudley, M. N. Discovery of a Cyclic Boronic Acid β-Lactamase Inhibitor (RPX7009) with Utility vs Class A Serine Carbapenemases. *J. Med. Chem.* **2015**, *58*, 3682–3692.
- (19) Freund, Y. R.; Akama, T.; Alley, M. R. K.; Antunes, J.; Dong, C.; Jarnagin, K.; Kimura, R.; Nieman, J. A.; Maples, K. R.; Plattner, J. J.; Rock, F.; Sharma, R.; Singh, R.; Sanders, V.; Zhou, Y. Boron-Based Phosphodiesterase Inhibitors Show Novel Binding of Boron to PDE4 Bimetal Center. *FEBS Lett.* **2012**, *586*, 3410–3414.
- (20) Das, B. C.; Thapa, P.; Karki, R.; Schinke, C.; Das, S.; Kambhampati, S.; Banerjee, S. K.; Van Veldhuizen, P.; Verma, A.; Weiss, L. M.; Evans, T. Boron Chemicals in Diagnosis and Therapeutics. *Future Med. Chem.* **2013**, *5*, 653–676.
- (21) Plescia, J.; Moitessier, N. Design and discovery of boronic acid drugs. *Eur. J. Med. Chem.* **2020**, *195*, 112270.
- (22) Song, S.; Gao, P.; Sun, L.; Kang, D.; Kongsted, J.; Poongavanam, V.; Zhan, P.; Liu, X. Recent developments in the

medicinal chemistry of single boron atom-containing compounds.

Acta Pharm. Sin. B **2021**, *11*, 3035.

(23) Agnieszamy, J.; Shen, C.-H.; Aniana, A.; Sayer, J. M.; Louis, J. M.; Weber, I. T. HIV-1 Protease with 20 Mutations Exhibits Extreme Resistance to Clinical Inhibitors through Coordinated Structural Rearrangements. *Biochemistry* **2012**, *51*, 2819–2828.

(24) Ghosh, A. K.; Anderson, D. D.; Weber, I. t.; Mitsuya, H. Enhancing Protein Backbone Binding—A Fruitful Concept for Combating Drug-Resistant HIV. *Angew. Chem., Int. Ed.* **2012**, *51*, 1778–1802.

(25) Ghosh, A. K.; Chapsal, B. D.; Steffey, M.; Agnieszamy, J.; Wang, Y.-F.; Amano, M.; Weber, I. T.; Mitsuya, H. Substituent Effects on P2-Cyclopentyltetrahydrofuran Urethanes: Design, Synthesis, and X-Ray Studies of Potent HIV-1 Protease Inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2308–2311.

(26) Aoki, M.; Hayashi, H.; Yedidi, R. S.; Martyr, C. D.; Takamatsu, Y.; Aoki-Ogata, H.; Nakamura, T.; Nakata, H.; Das, D.; Yamagata, Y.; Ghosh, A. K.; Mitsuya, H. C-5-Modified Tetrahydropyrano-Tetrahydrofuran-Derived Protease Inhibitors (PIs) Exert Potent Inhibition of the Replication of HIV-1 Variants Highly Resistant to Various PIs, including Darunavir. *J. Virol.* **2016**, *90*, 2180–2194.

(27) Koh, Y.; Aoki, M.; Danish, M. L.; Aoki-Ogata, H.; Amano, M.; Das, D.; Shafer, R. W.; Ghosh, A. K.; Mitsuya, H. Loss of Protease Dimerization Inhibition Activity of Darunavir Is Associated with the Acquisition of Resistance to Darunavir by HIV-1. *J. Virol.* **2011**, *85*, 10079–10089.

(28) Aoki, M.; Das, D.; Hayashi, H.; Aoki-Ogata, H.; Takamatsu, Y.; Ghosh, A. K.; Mitsuya, H. Mechanism of Darunavir (DRV)'s High Genetic Barrier to HIV-1 Resistance: A Key V32I Substitution in Protease Rarely Occurs, but Once It Occurs, It Predisposes HIV-1 To Develop DRV Resistance. *mBio* **2018**, *9*, 17.

(29) Ghosh, A. K.; Rao, K.; Nyalapatla, P. R.; Kovela, S.; Brindisi, M.; Osswald, H. L.; Reddy, B. S.; Agnieszamy, J.; Wang, Y.-F.; Aoki, M.; Hattori, S.-I.; Weber, I. T.; Mitsuya, H. Design of Highly Potent, Dual-Acting and Central-Nervous-System-Penetrating HIV-1 Protease Inhibitors with Excellent Potency against Multidrug-Resistant HIV-1 Variants. *ChemMedChem* **2018**, *13*, 803–815.

(30) Bomhard, E. M.; Herbold, B. A. Genotoxic Activities of Aniline and its Metabolites and Their Relationship to the Carcinogenicity of Aniline in the Spleen of Rats. *Crit. Rev. Toxicol.* **2005**, *35*, 783–835.

(31) Makhdoumi, P.; Hossini, H.; Ashraf, G.; Limoe, M. Molecular Mechanism of Aniline Induced Spleen Toxicity and Neuron Toxicity in Experimental Rat Exposure: A Review. *Curr. Neuropharmacol.* **2019**, *17*, 201–213.

□ Recommended by ACS

The Development and Design Strategy of Leucine-Rich Repeat Kinase 2 Inhibitors: Promising Therapeutic Agents for Parkinson's Disease

Xu Tang, Haopeng Sun, et al.

FEBRUARY 09, 2023

JOURNAL OF MEDICINAL CHEMISTRY

READ ▶

Discovery of Novel Human Constitutive Androstane Receptor Agonists with the Imidazo[1,2-a]pyridine Structure

Ivana Mejdrová, Radim Nencka, et al.

FEBRUARY 09, 2023

JOURNAL OF MEDICINAL CHEMISTRY

READ ▶

MSC-1186, a Highly Selective Pan-SRK Inhibitor Based on an Exceptionally Decorated Benzimidazole-Pyrimidine Core

Martin Schröder, Timo Heinrich, et al.

DECEMBER 14, 2022

JOURNAL OF MEDICINAL CHEMISTRY

READ ▶

Discovery of Highly Potent and BMPR2-Selective Kinase Inhibitors Using DNA-Encoded Chemical Library Screening

Ram K. Modukuri, Martin M. Matzuk, et al.

JANUARY 31, 2023

JOURNAL OF MEDICINAL CHEMISTRY

READ ▶

Get More Suggestions >