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Letter

Enhanced Plasma Stability and Potency of Aryl/Acyloxy Prodrugs of a BTN3A1 Ligand

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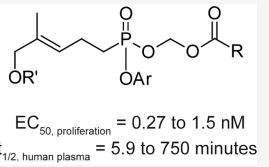
ABSTRACT: While ester-based phosphonate prodrugs excel at delivering payloads into cells, their instability in plasma is a hurdle for their advancement. Here, we synthesized new aryl/acyloxy prodrugs of a phosphonate BTN3A1 ligand. We evaluated their phosphoantigen potency by flow cytometry and ELISA and their plasma and cellular metabolism by LC-MS. These compounds displayed low nanomolar to high picomolar potency. Addition of a *p*-isopropyl group to the phenyl substituent and use of cyclohexyl or *p*-methoxybenzyl groups as the acyloxy substituent significantly increased human, but not mouse or rat, plasma stability without negatively impacting potency. Combinations of these prodrug moieties further improved stability, with the best combination achieving a half-life of over 12 h in human plasma, a marked improvement on prior compounds. In contrast, oxane analogs improved water solubility and cellular payload delivery but remained unstable in human plasma. The studies suggest that certain ester-based phosphonate prodrugs quickly deliver active payloads inside cells and show substantial stability in human plasma.



KEYWORDS: *phosphonate, prodrug, butyrophilin, isoprenoid, ligand*

The human immune system includes multiple lines of defense against bacterial infection and malignant cell types, including both innate and adaptive responses. While the innate response is rapid and general, the adaptive response is stronger and allows a memory component for more rapid defense against repeated challenges by the same agent. The most abundant facet of the adaptive immune system comprises the $\alpha\beta$ T cells, which recognize peptide antigens with the assistance of the major histocompatibility complex (MHC) and immune coreceptors, which are often good therapeutic targets. In contrast, the smaller subset of Vγ9Vδ2 T cells does not rely upon the MHC or recognize peptides.[1] Instead, it responds to small organophosphorus compounds, or phosphoantigens, especially the diphosphates produced in the nonmevalonate biosynthesis of isoprenoids found in bacterial but not human metabolism.[2] To detect these compounds, Vγ9Vδ2 T cells recognize the co-receptors of the butyrophilin (BTN) family.[3] Because Vγ9Vδ2T cells have not been studied exhaustively, their therapeutic manipulation may have untapped potential for treatment of various cancers.[4]

The most potent natural stimulant of Vγ9Vδ2 T cell proliferation is (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate (HMBPP, **1**) (Figure 1),[5] which is the final intermediate unique to bacterial biosynthesis of higher isoprenoids.[6] To stimulate proliferation, this compound must penetrate the cell membrane to reach its binding site on the butyrophilin receptor BTN3A1,[7,8] part of the BTN3/BTN2A1 complex.[9−15] That this binding site is within the cell rather than on the cell surface may be the result of an evolutionary response to intracellular bacterial infections. Unfortunately, although therapeutic manipulation of Vγ9Vδ2 T cells may have significant potential, HMBPP itself is unlikely to be an attractive drug candidate. The highly charged diphosphate

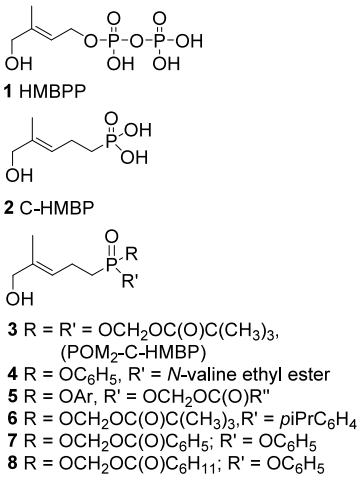


Figure 1. Structures of HMBPP, C-HMBP, and selected prodrug forms.

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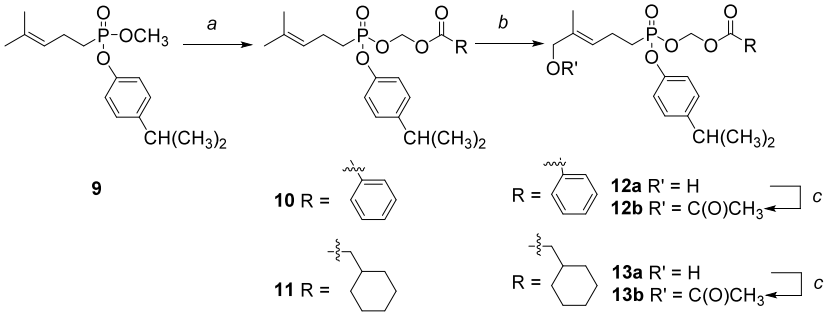
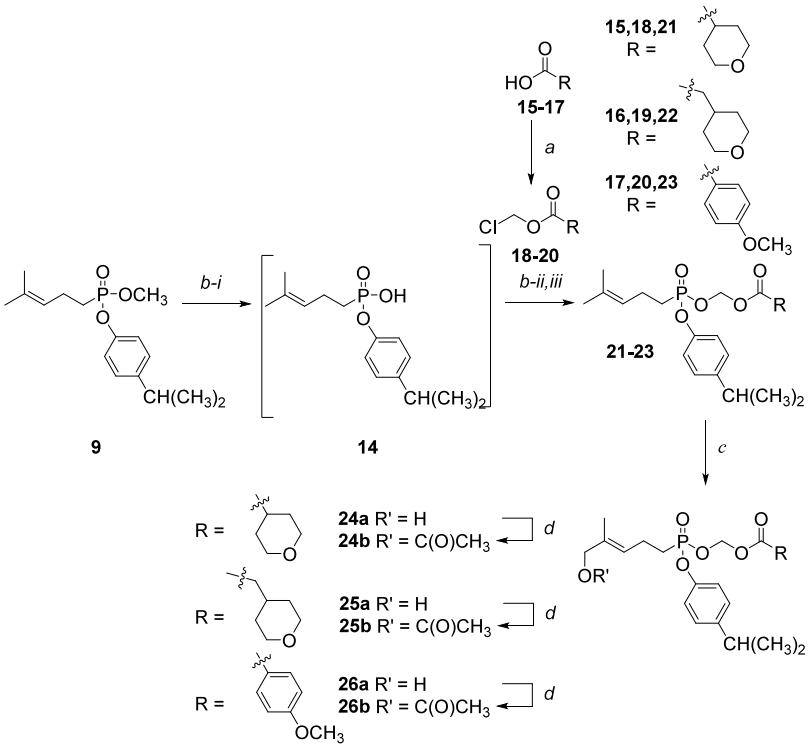
Scheme 1. Combination of *p*-Isopropylphenyl Ester with Acyloxymethyl Esters[a]



[a]Reagents and conditions: (a) $RCOCH_2OCl$,[34,35] NaI, CH_3CN (anhyd), reflux, 24 to 48 h, 18−23%; (b) SeO_2, *t*-BuOOH, 4-hydroxybenzoic acid, CH_2Cl_2, 0 °C, 3−4 days, 14%; (c) Ac_2O, Et_3N, rt, overnight, 85−92%.

Scheme 2. Synthesis of New Mixed Aryl/Acyloxymethyl Phosphonate Esters[a]



[a]Reagents and conditions: (a) $NaHCO_3$, Bu_4NHSO_4, chloromethyl chlorosulfate, CH_2Cl_2:H_2O 1:1, 88−90%; (b) (i) TMSCl, dichloromethane, 0 °C to rt, overnight, 90−95%; (ii) H_2O: THF (10:1), 1 h; (iii) Ag_2CO_3, DMF, 30 min, TBAI, $RCOCH_2OCl$,[34,35] acetonitrile, 80 °C, 48 h 18−35%; (c) SeO_2, *t*-BuOOH, 4-hydroxybenzoic acid, CH_2Cl_2, 0 °C, 3−4 days, 14−17%; (d) Ac_2O, Et_3N, rt, overnight, 84−92%.

functionality does not diffuse readily through the cell membrane[16] and has only limited plasma stability.[17] To obtain more drug-like compounds, several modifications of the HMBPP ligand have been explored. Incorporation of a C−P bond (**2**, C-HMBP) in place of the phosphate ester in compound **1** renders C-HMBP phosphatase resistant[18] while preserving significant phosphoantigen activity.[8,19] Many strategies have been developed to enhance the membrane permeability of charged molecules,[20] including phosphates and phosphonates, through the use of prodrugs,[21−24] but until our initial report on compound **3** (POM_2-C-HMBP) no one had explored a prodrug strategy with phosphoantigens.[8] Because it readily crosses the cell membrane and then undergoes hydrolysis to deliver the charged ligand, the prodrug **3** displays significantly higher potency than phosphonate **2**.[8]

Since our first report on the potency of compound **3**, several other prodrug forms have been explored with phosphoantigens, including aryl phosphonamidates (e.g., **4**),[25,26] bisamidates,[27,28] mixed aryl/acyloxy diesters (e.g., **5**),[29,30] and double prodrug forms that included acetate protection of the requisite allylic alcohol.[31,32] While several of these compounds have cellular potency in the low nanomolar or even high picomolar range, for improved *in vivo* capabilities, the ideal prodrug form would have rapid cellular uptake, display high plasma stability, and yield benign fragments upon drug release.

Of the possible prodrug forms that we have studied, the dimethyl ester of the parent phosphonate **2** was found to be highly stable but had little or no potency, perhaps because it is too stable to cellular metabolism.[8] The bis-pivaloyloxymethyl (POM) compound **3** (POM_2-C-HMBP) has good potency in

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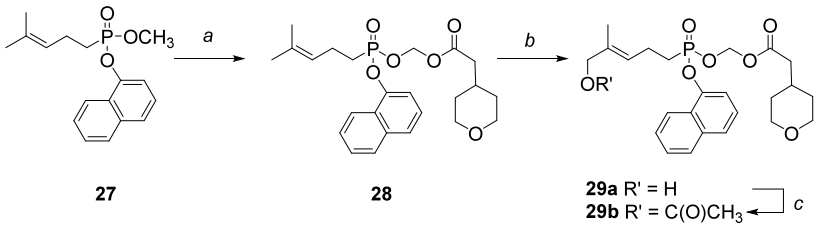
Scheme 3. Synthesis of the Potential Prodrugs 29a and 29b[a]



[a]Reagents and conditions: (a) (i) TMSCl, dichloromethane, 0 °C to rt, overnight, 90%; (ii) H_2O:THF (10:1), 1 h; (iii) Ag_2CO_3, DMF, 30 min, TBAI, **19**, acetonitrile, 80 °C, 48 h, 19%; (b) SeO_2, *t*-BuOOH, 4-hydroxybenzoic acid, CH_2Cl_2, 0 °C, 3−4 days, 17%; (c) Ac_2O, Et_3N, rt, overnight, 86%.

bioassays for cell proliferation but rapidly undergoes hydrolysis in plasma, which makes it less attractive for use in animals. As a group, the aryl amidates **4** have activity in the low nanomolar range upon 72-h exposure, but their potency drops significantly when exposure time is restricted.[33] Furthermore, if there is a stereogenic center within the amino acid unit, then the stereogenic center at phosphorus renders the initially prepared compounds mixtures of diastereomers.[26] This may complicate determination of the kinetics of drug release even though the released drug **2** has no stereochemistry.

The general prodrug structure that we have found most intriguing is a mixed ester that includes one aryl group and one acyloxymethyl group (**5**).[30] The mixed esters **5** have attractive potency and rapid target engagement in cell assays. Furthermore, the ester and acyloxy substituents can be selected so that the only stereocenter in the prodrug is at phosphorus, and thus, drug release could convert a racemic prodrug to a compound without stereochemistry. The fast plasma metabolism of mixed esters **5** remains an area that could be improved and potentially could rival that of the aryl phosphonamidate forms.

To explore the activity of aryl/acyloxymethyl ester prodrugs of phosphonate **2**, we recently reported the preparation and bioassay of a small set of compounds representative of this family.[34] Of the 11 aryl groups examined with a constant POM group as the acyloxy substituent, the best potency was delivered by a *p*-isopropylphenyl ester group (i.e., compound **6**). Conversely, with a constant phenyl group as the aryl ester, the most potent examples of the acyloxy group examined were those derived from benzoic acid (**7**) or cyclohexylacetic acid (**8**). The cyclohexylacetic acid acyloxy ester, but not the benzoic acid acyloxy ester, showed some improvements to plasma stability. To build upon these studies, the substituents that individually delivered the most attractive potency and stability were combined to create new prodrugs of the same phosphonate ligand, and then, once the next generation bioassay results were in hand, additional prodrug forms were designed and prepared, including novel oxanecarboxylic acid derivatives and a methoxyphenyl derivative. These efforts are the subject of this report.

Synthesis of the first four compounds in this new set followed a straightforward manner from our previous work. Treatment of the mixed aryl methyl ester **9**[34] with the acyl chloromethyl ester derived from benzoic acid or cyclohexylacetic acid gave the expected mixed esters **10** and **11** (Scheme 1). Treatment of these two mixed esters with selenium dioxide gave the desired allylic alcohols **12a** and **13a** in modest yields, and treatment of each alcohol with acetic anhydride gave the corresponding acetate esters **12b** and **13b**.

Preliminary bioassays on the four new prodrugs, **12a,b** and **13a,b**, were encouraging in terms of their potency, but the formation of slightly cloudy solutions raised concerns about solubility. Therefore, a second group of compounds was prepared to improve solubility while retaining potency. When efforts to employ a reaction sequence parallel to that in Scheme 1 with the chloromethyl esters derived from cyclic ethers gave low conversions, a modified strategy was employed (Scheme 2). Upon treatment with TMSCl followed by an aqueous workup, the aryl methyl ester **9** readily undergoes partial hydrolysis to afford the monoacid **14**. After minimal purification, treatment of this acid with silver carbonate gives the desired silver salt. This salt reacts smoothly with the chloromethyl esters **18**−**20**, which in turn are readily prepared through reaction of the carboxylic acids **15**−**17** with chloromethyl chlorosulfate.[36−38] After preparation of the mixed esters **21**−**23**, oxidation mediated by selenium dioxide provides the allylic alcohols **24a**−**26a**,[39] and a final reaction with acetic anhydride affords the corresponding acetates **24b**−**26b**.

To provide a second perspective on the impact of the oxane group, the known mixed ester **27**[30] was subjected to the same reaction sequence. Upon treatment with TMSCl followed by an aqueous workup, the aryl methyl ester **27** was converted to the monoacid. Again, treatment of this acid with silver carbonate gives a salt, which then reacts smoothly with the chloromethyl ester **19** to obtain the aryl acyloxy ester **28**. Oxidation mediated by selenium dioxide provides allylic alcohol **29a**, and subsequent reaction with acetic anhydride affords the corresponding acetate **29b** (Scheme 3).

The novel aryl ester prodrugs were first evaluated for their ability to stimulate the proliferation of primary human Vγ9Vδ2 T cells (Table 1). All of the test compounds stimulated proliferation, with EC_{50} values between 0.27 nM (compound **12b**) and 1.5 nM (compound **26a**). This addition of the *p*-iPr group to compounds **12a** and **13a** slightly decreased their potency relative to the reported values for **7** and **8**, but this decrease was within the margin of error. The oxane group, which improved the solubility by about 2 log units as measured by cLogP (Table S1), also resulted in highly potent compounds, with the methylene linker of compounds **25a/b** further boosting potency relative to the smaller **24a/b**. The potency of the methylene oxanes was similar whether the aryl group was *p*-iPr phenyl (**25a/b**) or 1-naphthyl (**29a/b**). Addition of the *p*-MeO group to compounds **26a/b** moderately decreased activity relative to **12a/b** while only somewhat improving solubility. At the same time, compounds showed weak toxicity toward K562 cells (Table S1), with modest growth inhibition observed only at concentrations of

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Table 1. Stimulation of Human Vγ9Vδ2 T Cell Proliferation (n = 3)

Compd	R^1 aryl	R^2 ester	OH/AC	72-h EC_{50} (nM)
6	*p*-iPr-Ph	POM	OH	1.9[34]
7	Ph	Bn	OH	0.34[34]
8	Ph	CH_2-Cy	OH	0.6[34]
12a	*p*-iPr-Ph	Bn	OH	0.43 (0.0017 to 1.1)
12b	*p*-iPr-Ph	Bn	Ac	0.27 (0.023 to 3.2)
13a	*p*-iPr-Ph	CH_2-Cy	OH	1.1 (0.73 to 1.5)
13b	*p*-iPr-Ph	CH_2-Cy	Ac	0.54 (0.24 to 1.2)
24a	*p*-iPr-Ph	Oxane	OH	0.97 (0.49 to 1.9)
24b	*p*-iPr-Ph	Oxane	Ac	1.2 (0.16 to 9.4)
25a	*p*-iPr-Ph	CH_2-oxane	OH	0.53 (0.056 to 5.0)
25b	*p*-iPr-Ph	CH_2-oxane	Ac	0.44 (0.0083 to 23)
26a	*p*-iPr-Ph	*p*-MeO-Bn	OH	1.5 (1.0 to 2.1)
26b	*p*-iPr-Ph	*p*-MeO-Bn	Ac	0.84 (0.027 to 26)
29a	1-Nap	CH_2-oxane	OH	0.37 (0.0019 to 74)
29b	1-Nap	CH_2-oxane	Ac	0.66 (0.46 to 0.94)

100 μM, a concentration well above their nanomolar activity as butyrophilin agonists.

Next, we evaluated interferon γ production by Vγ9Vδ2 T cells following their exposure to K562 cells loaded with the test compounds. In this assay,[40] the cells were exposed to test compounds for just 1 h. This restricted exposure time allows for larger differences to be observed among test compounds, if applicable, relative to the 3-day exposure in the proliferation assay. In this assay, the range of EC_{50} values was also tightly clustered, from 0.89 nM (compound **24a**) to 7 nM (compound **12a**) (Table 2). These values were in a similar

Table 2. Stimulation of Human Vγ9Vδ2 T Cell Interferon γ Release (n = 4)

Compd	R1 aryl	R2 ester	OH/AC	1-h EC_{50} [nM]
6	*p*-iPr-Ph	POM	OH	3.8[34]
7	Ph	Bn	OH	4.1[34]
8	Ph	CH_2-Cy	OH	7.2[34]
12a	*p*-iPr-Ph	Bn	OH	7.0 (5.3 to 9.3)
12b	*p*-iPr-Ph	Bn	Ac	2.6 (1.8 to 3.9)
13a	*p*-iPr-Ph	CH_2−Cy	OH	2.8 (1.6 to 4.7)
13b	*p*-iPr-Ph	CH_2−Cy	Ac	3.0 (1.5 to 6.0)
24a	*p*-iPr-Ph	Oxane	OH	0.89 (0.60 to 1.3)
24b	*p*-iPr-Ph	Oxane	Ac	2.2 (1.4 to 3.6)
25a	*p*-iPr-Ph	CH_2-oxane	OH	2.2 (1.1 to 4.5)
25b	*p*-iPr-Ph	CH_2-oxane	Ac	3.5 (2.4 to 5.3)
26a	*p*-iPr-Ph	*p*-MeO-Bn	OH	6.4 (4.8 to 8.4)
26b	*p*-iPr-Ph	*p*-MeO-Bn	Ac	4.1 (2.1 to 8.1)
29a	1-Nap	CH_2-oxane	OH	4.8 (4.3 to 5.4)
29b	1-Nap	CH_2-oxane	Ac	5.4 (3.1 to 9.4)

single digit nanomolar range as previously determined values for control compounds **6**−**8**. While these modifications did not improve potency significantly, they also did not negatively affect it. When both functional assays were considered, compound **25a** was the most potent alcohol form ($EC_{50,prolif}$ = 0.53 nM, $EC_{50,IFN}$ = 2.2 nM), while compound **12b** was the most potent acetate form ($EC_{50,prolif}$ = 0.27 nM, $EC_{50,IFN}$ = 2.6 nM). Compound **26a** was the least potent compound, although with an $EC_{50,IFN}$ of 6.4 nM it still displays significant activity.

We next evaluated the compounds for their human plasma stability (Table 3). In contrast to the activity assays, where

Table 3. Stability in 50% Human Plasma in TBS (n = 2−3)

Compd	R1 aryl	R2 ester	OH/AC	2 h, % remaining	Half-life (min)
6	*p*-iPr-Ph	POM	OH	22	78[34]
7	Ph	Bn	OH	0	4[34]
8	Ph	CH_2-Cy	OH	0	6.6[34]
12a	*p*-iPr-Ph	Bn	OH	13	44
12b	*p*-iPr-Ph	Bn	Ac	34	66
13a	*p*-iPr-Ph	CH_2-Cy	OH	80	94
13b	*p*-iPr-Ph	CH_2-Cy	Ac	90	750
24a	*p*-iPr-Ph	Oxane	OH	0	11
24b	*p*-iPr-Ph	Oxane	Ac	0	16
25a	*p*-iPr-Ph	CH_2-oxane	OH	0	ND
25b	*p*-iPr-Ph	CH_2-oxane	Ac	28	42
26a	*p*-iPr-Ph	*p*-MeO-Bn	OH	71	500
26b	*p*-iPr-Ph	*p*-MeO-Bn	Ac	62	180
29a	1-Nap	CH_2-oxane	OH	0	5.9
29b	1-Nap	CH_2-oxane	Ac	7	15

potencies were quite similar (5.6-fold range of proliferation, 7.9-fold range of interferon), major differences were observed in human plasma stability (>127-fold range in half-lives). Addition of the *p*-iPr to the benzyl analog improved stability by about 10-fold (**7**, $t_{1/2}$ = 4 min, **12a** $t_{1/2}$ = 44 min). Likewise, a 14-fold improvement in plasma stability was noted for the cyclohexyl analogs (**8** $t_{1/2}$ = 6.6 min, **13a** $t_{1/2}$ = 94 min). Taken together, this improved plasma stability was the basis for pursuing additional compounds based on the *p*-iPr phenyl ester scaffold. Notably, the 750-min half-life of compound **13b** was the highest we have observed in an aryl/acyloxyester prodrug, which is impressive considering this is also a compound with high potency in the functional assays. Unfortunately, the oxanes demonstrated low plasma stability, though oxane **25b** did achieve a reasonable plasma half-life of 42 min. Although the oxanes were highly potent and quite soluble, their human plasma stability was viewed as disappointing. At the same time, incorporation of the *p*-MeO group into compound **26a** improved stability about 11-fold relative to **12a** (**12a** $t_{1/2}$ = 44 min, **26a** $t_{1/2}$ = 500 min). Compounds **26a**/**b** were the only ones out of six pairs tested in which the acetate form did not have better stability. The plasma enzymes could readily remove the acyloxy group and the allylic acetate but could not form the dianion payload (Table 4). Taken together, compounds **13b** and **26a** are highly potent phosphoantigens with substantial plasma stabilities.

The compounds were also assessed for their stability in rat and mouse plasma (Table S2), which would facilitate preclinical in vivo models. In contrast to human plasma, the compounds had generally lower stability in rat and mouse plasma, consistent with their higher esterase activity. Compound **29a** was the most stable compound in both rat and mouse plasma, with 65% remaining after 2 h in rat plasma and a half-life of 5.6 min in mouse plasma. Compound **29a** was among the least stable in human plasma, with a half-life of 5.9 min. It appears based on this data that different rules govern the stability structure−activity relationship (SAR) of phosphonate prodrugs in human and rodent plasma. The current set of compounds was chosen based on a prior SAR study focused on human plasma.[34]

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Table 4. Formation of Plasma Metabolites (t = 1 h, n = 3)

Compd	R1 aryl	R2 ester	OH/AC	Ac-monoanion[a]	Monoanion[a]	Dianion[a]
12a	*p*-iPr-Ph	Bn	OH		7900 ± 3600	0
12b	*p*-iPr-Ph	Bn	Ac	12000 ± 1600	300 ± 100	0
13a	*p*-iPr-Ph	CH_2-Cy	OH		4500 ± 1100	0
13b	*p*-iPr-Ph	CH_2-Cy	Ac	2400 ± 430	330 ± 170	0
24a	*p*-iPr-Ph	Oxane	OH		13000 ± 1800	0
24b	*p*-iPr-Ph	Oxane	Ac	9900 ± 3200	3200 ± 1000	0
25a	*p*-iPr-Ph	CH_2-oxane	OH		16000 ± 4100	0
25b	*p*-iPr-Ph	CH_2-oxane	Ac	6100 ± 1700	3000 ± 2300	0
26a	*p*-iPr-Ph	*p*-MeO-Bn	OH		5900 ± 1600	0
26b	*p*-iPr-Ph	*p*-MeO-Bn	Ac	3500 ± 1200	830 ± 370	0
29a	1-Nap	CH_2-oxane	OH		11000 ± 3700	0
29b	1-Nap	CH_2-oxane	Ac	2900 ± 980	2800 ± 2400	0

[a]Values shown are integrated peak intensities ± st dev.

Table 5. Internalization of the Payload into K562 Cells (t = 1 h, n = 3)

Compd	R1 aryl	R2 ester	OH/AC	Ac-monoanion[a]	Monoanion[a]	Dianion[a]
12a	*p*-iPr-Ph	Bn	OH		10000 ± 2200	830 ± 290
12b	*p*-iPr-Ph	Bn	Ac	180 ± 63	8800 ± 2000	870 ± 99
13a	*p*-iPr-Ph	CH_2-Cy	OH		4800 ± 2100	500 ± 200
13b	*p*-iPr-Ph	CH_2-Cy	Ac	54 ± 31	3900 ± 2300	410 ± 67
24a	*p*-iPr-Ph	Oxane	OH		18000 ± 3800	1500 ± 410
24b	*p*-iPr-Ph	Oxane	Ac	67 ± 6.7	8200 ± 3800	1700 ± 430
25a	*p*-iPr-Ph	CH_2-oxane	OH		6600 ± 650	640 ± 24
25b	*p*-iPr-Ph	CH_2-oxane	Ac	49 ± 6.7	6300 ± 2100	1000 ± 770
26a	*p*-iPr-Ph	*p*-MeO-Bn	OH		6000 ± 3200	590 ± 370
26b	*p*-iPr-Ph	*p*-MeO-Bn	Ac	18 ± 6.0	3900 ± 1900	360 ± 24
29a	1-Nap	CH_2-oxane	OH		3200 ± 790	690 ± 110
29b	1-Nap	CH_2-oxane	Ac	4.0 ± 6.9	3000 ± 1400	880 ± 370

[a]Values shown are integrated peak intensities ± st dev.

The compounds were further evaluated for their ability to deliver the dianionic phosphonate payload into K562 cells (Table 5). In contrast to the plasma stability studies, K562 cells were able to generate significant levels of free payload for all compounds (4.7-fold range) and more completely removed the allylic acetate. While one cannot directly compare the monoanion peak intensities due to potential differences in compound ionization during sample acquisition, the dianion peak intensities represent the same metabolite and are directly comparable with each other. Here, we found that the oxanes **24a/b** were able to drive the highest accumulation of payload in the cells, consistent with their strong potency in the K562 ELISA. Compound **13b** delivered about 4-fold less payload into K562 cells relative to **24b** in this time frame. However, the plasma stability of **13b** is 46-fold higher than that of **24b**. Likewise, compound **26a** delivered about 2.5-fold lower payload into K562 cells relative to **24a** in this time frame, but its stability in human plasma was 45-fold higher.

Overall, this data set demonstrates the similarities and differences among aryl/acyloxy phosphoantigen prodrugs, with each compound having strengths in specific areas. Considering potency alone, compound **12b** was the strongest ($EC_{50,prolif}$ = 0.27 nM, $EC_{50,IFN}$ = 2.6 nM), comparing favorably with prior compound **7**. However, the oxane compound **24a** was 2 log units more soluble, delivered high payload levels, and was the most potent in ELISA. At the same time, it had low plasma stability. Human plasma stability is where the largest range of differences was observed among the compounds, suggesting that compounds **13b** and **26a**, each with outstanding plasma stability, are the most attractive compounds of the group, despite ranking lower in the other assays. Taken together, this study shows that specific ester-based phosphonate prodrugs such as compounds **13b** and **26a** can provide rapid payload internalization, potency, and high human plasma stability. Although lower stability was found in rodent plasma, we believe the profile of **29a** suggests it is likely that rodent plasma stability could be similarly improved with different prodrug forms.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.4c00371.

Experimental procedures for synthetic chemistry, HRMS for assayed compounds, bioassay protocols, LC traces, and ^{1}H, ^{13}C, and ^{31}P NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

BTN, butyrophilin; HMBPP, (*E*)-4-hydroxy-3-methyl-but-2-enyl diphosphate; POM, pivaloyloxymethyl

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