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Letter

Sulfonamide Prodrugs with a Two-Stage Release Mechanism for the Efficient Delivery of the TLR4 Antagonist TAK-242

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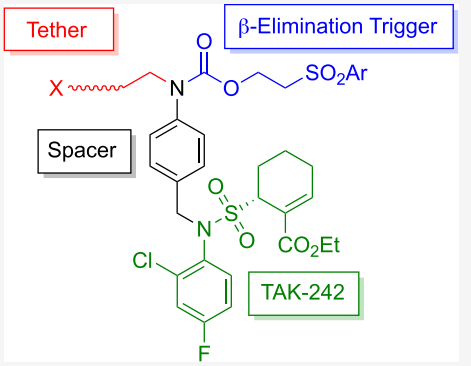
ABSTRACT: We previously demonstrated that the potent TLR4 inhibitor TAK-242 could be covalently conjugated to pancreatic islets using a linker that afforded an effective sustained delivery of the active drug after transplant. This drug-eluting tissue achieved local inhibition of TLR4-linked inflammation and proved beneficial to the islet graft survival. Here, we describe a new family of prodrugs with a modular design featuring a self-immolative para-aminobenzyl spacer bonded directly to the TAK-242 sulfonamide nitrogen, a tether for bioconjugation, and a *β*-eliminative arylsulfone "trigger". The inclusion of the para-aminobenzyl spacer affords a more stable prodrug which exhibits complex drug-release kinetics due to a two-stage release mechanism. This manuscript reports the preparation and characterization of several TAK-242 prodrugs fitted with different triggers and linkers and demonstrates that these second-generation prodrugs effectively release TAK-242 while avoiding non-productive sulfonamide hydrolysis.



KEYWORDS: *Prodrug, TLR4, sulfonamide, TAK-242, resatorvid*

Our group is exploring strategies to protect transplant tissue by the localized and sustained delivery of small-molecule immunomodulators. The delivery of the potent toll-like receptor 4 (TLR4) signaling inhibitor TAK-242 (**1**, Figure 1)[1] is of particular interest, as adverse effects from the early post-transplantation activation of TLR4 have been demonstrated in a wide range of transplants including kidney,[2] heart,[3] lung,[4] bone,[5] islets,[6] liver,[7] and stem cell.[8] Using a murine model of pancreatic islet transplantation, we demonstrated that free TAK-242 reduced sterile inflammation-mediated stress in islets during isolation and promoted successful transplant outcomes.[9] In order to evaluate advantages of localized delivery, we developed a TAK-242 prodrug (**2**)[10] that featured an arylsulfone *β*-elimination release mechanism that has been extensively exploited by Santi et al. for the delivery of amine-linked prodrugs (and the dissolution of hydrogels) with tunable half-lives.[11] A bioorthogonal strain-promoted alkyne/azide "click" reaction[12] was used *ex vivo* to conjugate this prodrug (**2**) to the surface of murine pancreatic islets that had been acylated with a dibenzocyclooctyne *N*-hydroxysuccinimide ester. The prodrug-modified islets thus prepared remained viable and functional and slowly released active TAK-242 to the local environment after transplantation (Scheme 1), suppressing innate inflammation and significantly improving transplantation outcomes.[10]

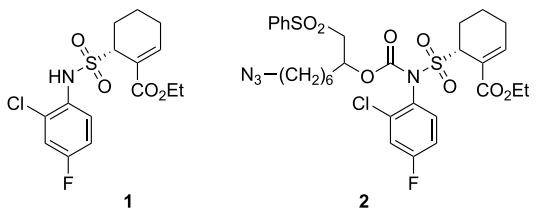
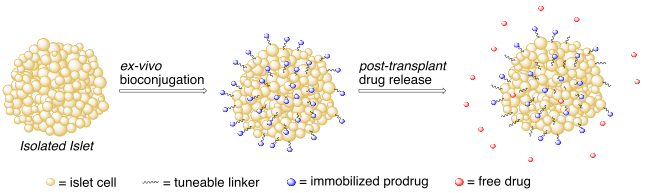


Figure 1. Sulfonamide toll-like receptor 4 inhibitor TAK-242 (**1**) and our previously reported prodrug (**2**).

While those studies provided proof of principle for the potential of functionalized drug-eluting transplants, the efficiency of the first generation prodrug design was compromised by an undesirable decomposition of prodrug **2**

Scheme 1. Pancreatic Islets Covalently Modified with Prodrug 2 Slowly Release Active TAK-242 after Transplantation



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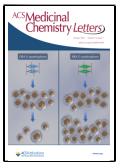

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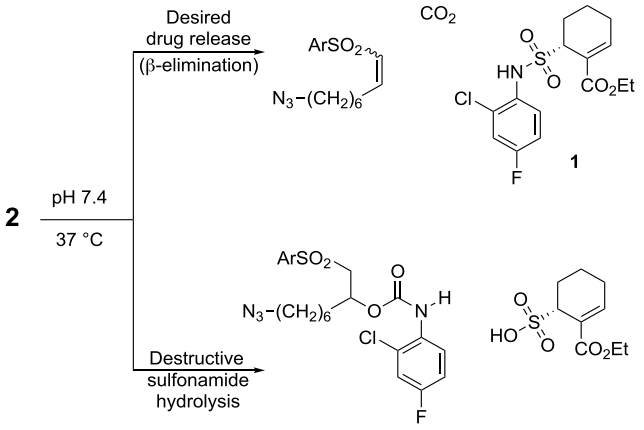
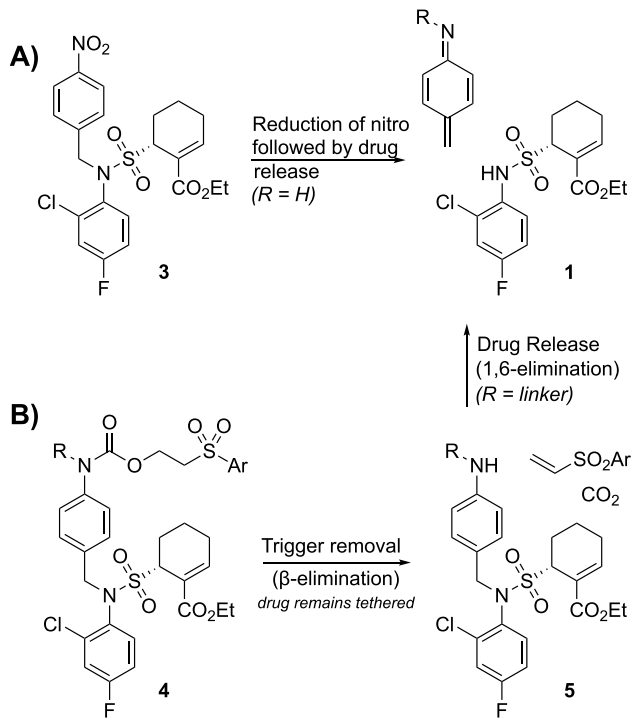
(Scheme 2). Our work with TAK-242 has revealed that while the TAK-242 sulfonamide bond is relatively stable, introducing

Scheme 2. In Buffer, Prodrug 2 Undergoes Unproductive Sulfonamide Hydrolysis That Competes with the Desired β-Elimination and Drug Release



a carbamate linker results in a significant destabilization of the sulfonamide bond. Fortunately, our recent studies of TAK-242 prodrugs activated by enzymatic or Pd(II) catalysis[13] revealed that this sulfonamide drug is a reasonable leaving group and can be directly released from sp^3 carbons (Scheme 3A). While the 1,6-elimination of TAK-242 from the *p*-aminobenzyl group was sluggish, the benzyl substituent did not activate the

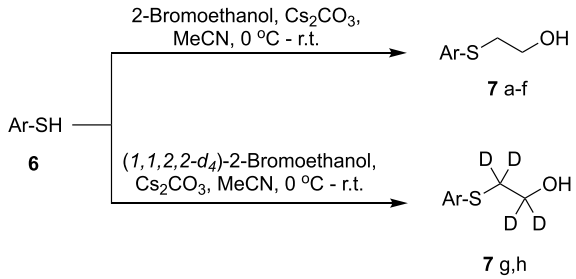
Scheme 3. (A) Recently Reported Nitrobenzyl Prodrug (3) Releases Free TAK-242 by 1,6-Elimination after Reduction of Nitro Group and (B) Prodrug Design Reported Herein (4) Involves β-Elimination To Form Intermediate 5 Which Subsequently Undergoes 1,6-Elimination To Release TAK-242



sulfonamide to hydrolysis, and so we chose to utilize this strategy for the development of a "generation 2" TAK-242 prodrug **4** for bioconjugation to transplant tissue (Scheme 3B).

Compound **4** is a modular prodrug design comprised of a tether R (typically terminated with an azide group for click conjugation), an arylsulfone substituted carbamate trigger that deactivates the aniline toward 1,6-elimination, a self-immolative aniline spacer, and the sulfonamide drug. Two sequential reactions are required for the release of free TAK-242 from **4**: a sulfone β-elimination affording an aniline (that remains connected to the tether), followed by a 1,6-elimination of the revealed aniline to release the active drug. For ease of synthesis we chose to adjust the drug release kinetics by incorporating a variety of aryl groups into the β-eliminative "trigger", as these reactions are well characterized and can provide a wide range of reaction rates. This design allowed the use of simple arylthio-substituted ethanols as precursors to the trigger component, with oxidation to the sulfone delayed until the desired compound is assembled, avoiding premature β-elimination. Accordingly, we first synthesized a series of hydroxyethylaryl sulfides in good yield (Scheme 4). These compounds incorporated variously substituted aryl groups (and an ethylene that can be deuterated[14]), providing a range of rates for the β-eliminative trigger removal.

Scheme 4. Preparation of Trigger Alcohols with Various Aryl Substituents[a]



[a]**7a**, Ar = C_6H_5- (84%); **7b**, Ar = 4-$CF_3C_6H_4$- (81%); **7c**, Ar = 4-ClC_6H_4- (98%); **7d**, Ar = 4-$CH_3C_6H_4$- (91%); **7e**, Ar = 4-$CH_3OC_6H_4$- (95%); **7f**, Ar = 2,5-$(CH_3)_2C_6H_3$- (96%); **7g**, Ar = 4-$CH_3C_6H_4$-, d_4, (84%); **7h**, Ar = 4-$CH_3OC_6H_4$-, d_4, (72%).

With the trigger alcohols in hand, the prodrug core was assembled by adding azide-terminated linkers and the various trigger alcohols to a protected 4-aminbenzyl alcohol core. In one approach (Scheme 5A), aniline **9** was alkylated with 6-azidohexyl bromide, and the resulting amine **10** is treated with crude preformed chloroformates **8**, derived from the various trigger alcohols, to afford compounds **12**. In a second, less convergent (but higher-yielding) approach (Scheme 5B), anilines **9** were first converted to carbamates **11** by reaction with crude chloroformates **8**. The resulting carbamates **11** were efficiently alkylated with either a simple alkyl tether or a more hydrophilic tether derived from tetraethylene gylcol. Overall, 12 prodrug core compounds **12** (alkyl tether) and **12′** (hydrophilic tether) were prepared. In preparation for preliminary studies of the sulfone elimination kinetics, the silyl protecting groups of **12** and **12′** were removed (either AcOH or TBAF) and the sulfides oxidized to produce 12 sulfones **13** and **13′**.

The first stage of drug release (β-elimination of the trigger sulfones to afford the parent aniline) was initially evaluated

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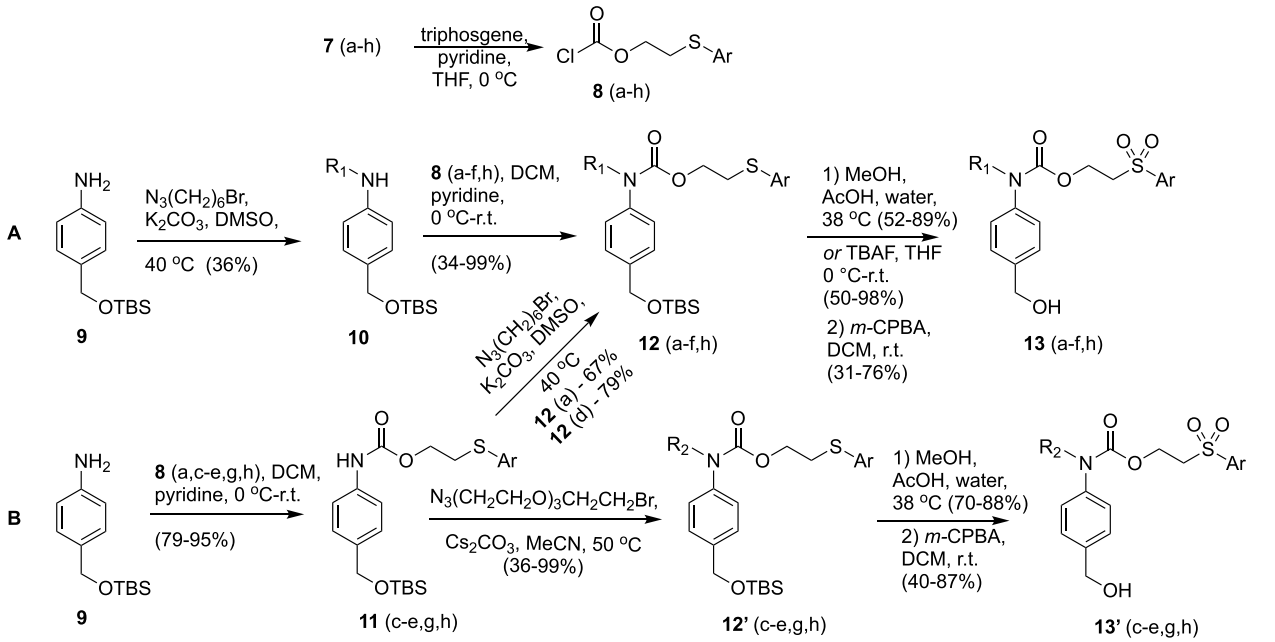
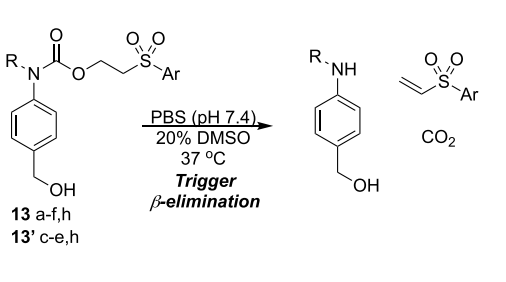
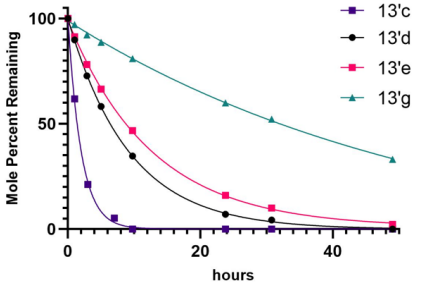
Scheme 5. Assembly of Prodrug Core Incorporating Trigger Sulfones (Overall Yields for Four Steps)[a]



[a]$R_1 = N_3(CH_2)_6$-, $R_2 = N_3(CH_2CH_2O)_3CH_2CH_2$-; **13a** (Ar = C_6H_5-) route A 19%, route B 29%; **13b** (Ar = 4-$CF_3C_6H_4$-) route A 7%; **13c** (Ar = 4-ClC_6H_4-) route A 15%; **13′c** (Ar = 4-ClC_6H_4-) route B 40%; **13d** (Ar = 4-$CH_3C_6H_4$-) route A 8%, route B 18%; **13′d** (Ar = 4-$CH_3C_6H_4$-) route B (22%); **13e** (Ar = 4-$CH_3OC_6H_4$-) route A (19%); **13′e** (Ar = 4-$CH_3OC_6H_4$-) route B (53%); **13f** (Ar = 2,5-$(CH_3)_2C_6H_3$-) route A (21%); **13′g** (Ar = $CH_3C_6H_4$-, d_4) route B (59%); **13h** (Ar = $CH_3OC_6H_4$-, d_4) route A (2%); **13′h** (Ar = $CH_3OC_6H_4$-, d_4) route B (49%).

Scheme 6. Kinetics of Trigger Release from Oxidized Precursors 13′ (R = $N_3(CH_2CH_2O)_3CH_2CH_2$-)[a]

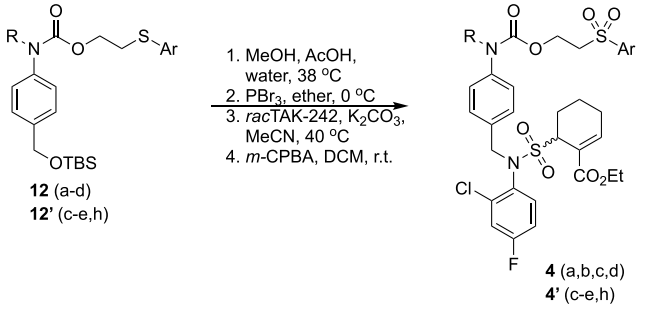




Compound	Ar	$t_{1/2}$ (h)
13'c	4-Cl-C_6H_4-	1.4
13'd	4-CH_3-C_6H_4-	6.3
13'e	4-CH_3O-C_6H_4-	8.8
13'h	4-CH_3O-C_6H_4- (d_4-ethylene)	38.5

[a]PBS (pH 7.4) with 20% DMSO at 37 °C. Data for compounds **13** (R = $N_3(CH_2)_6$-) in Supporting Information Figure S1.

Scheme 7. Loading of TAK-242 on Prodrug Cores 12 and 12′



Compound	R	Ar	Yield (4 steps)
4a	$N_3(CH_2)_6$-	C_6H_5-	54%
4b	$N_3(CH_2)_6$-	4-CF_3-C_6H_4-	10%
4c	$N_3(CH_2)_6$-	4-Cl-C_6H_4-	30%
4d	$N_3(CH_2)_6$-	4-CH_3-C_6H_4-	36%
4′c	$N_3(CH_2CH_2O)_3CH_2CH_2$-	4-Cl-C_6H_4-	30%
4′d	$N_3(CH_2CH_2O)_3CH_2CH_2$-	4-CH_3-C_6H_4-	43%
4′e	$N_3(CH_2CH_2O)_3CH_2CH_2$-	4-CH_3O-C_6H_4-	33%
4′h	$N_3(CH_2CH_2O)_3CH_2CH_2$-	4-CH_3O-C_6H_4- (d_4-ethylene)	44%

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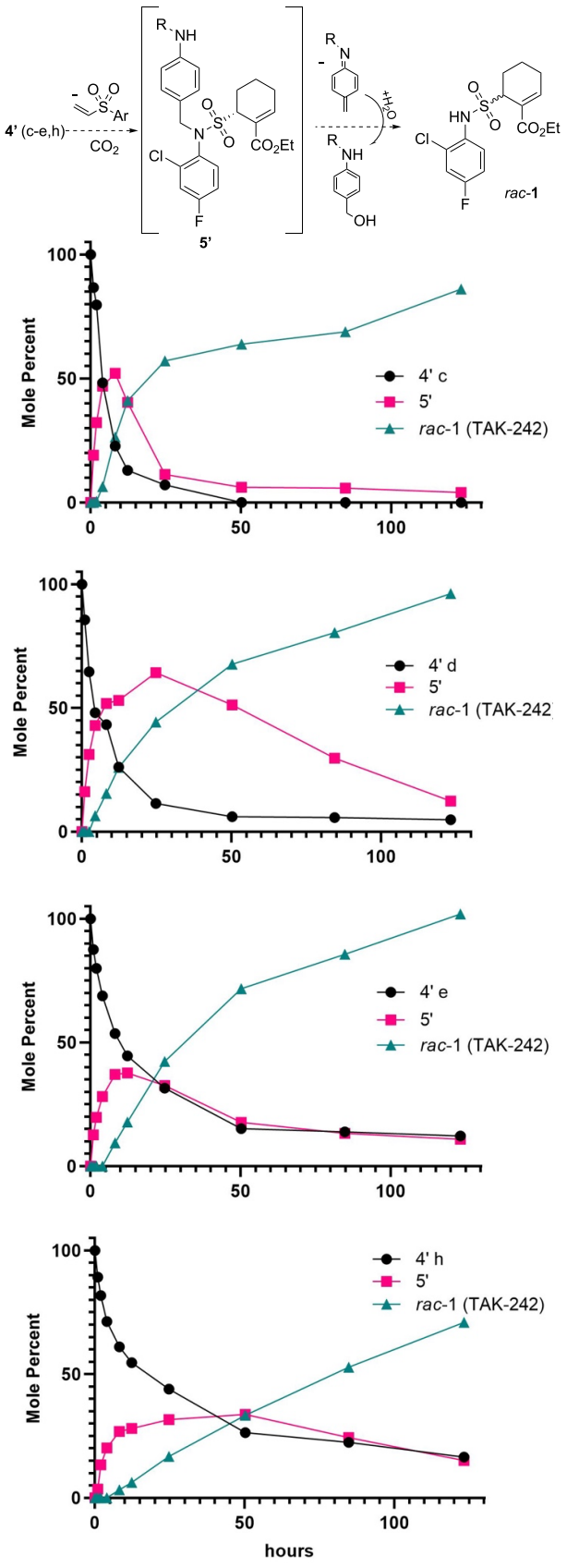
using the simple benzyl alcohols **13** (Scheme 6). Accordingly, compounds **13a–f,h** were incubated at 37 °C in a 9:1 mixture of phosphate buffered saline (PBS; pH 7.4) and DMSO, and the sulfone elimination was monitored by HPLC. As anticipated, simple changes to the aryl substituents provided a broad range of trigger half-lives (Supporting Information Figure S1). Unfortunately, attempts to characterize drug release kinetics for the completed prodrugs **4** were problematic due to poor solubility. We therefore pivoted to the preparation and evaluation of compounds with a more hydrophilic tether, and four intermediates (**13′c–e,h**), providing a range of trigger half-lives, were selected for characterization. Incubation of these compounds (20% DMSO in PBS pH 7.4, 37 °C) revealed trigger half-lives ranging from 1.4 to 38.5 h (Scheme 6).

With the prodrug cores and trigger kinetics in hand, full TAK-242 prodrugs were prepared (Scheme 7). Starting with a selection of eight compounds **12** and **12′**, benzyl alcohol protecting groups were removed and the resulting alcohols converted to bromides by treatment with PBr_3. These crude benzyl bromides were reacted with the racemic sulfonamide drug *rac*TAK-242 under weakly basic conditions, and the trigger sulfides were oxidized to sulfones in a final step. This oxidation was saved for last in order to avoid premature β-elimination of the trigger moieties. Eight representative *rac*TAK-242 prodrugs **4a–d** and **4′c–e,h** were prepared by this route in reasonable yields from the prodrug cores, providing candidates with a range of trigger half-lives as well as containing tethers of varying hydrophilicity (Scheme 7).

As noted above, while the limited aqueous solubility of prodrugs **4** precluded an effective analysis of the overall kinetics of drug release, the more hydrophilic prodrugs **4′** could be thoroughly evaluated in buffer containing 20% DMSO. Under these conditions compounds **4′** and all intermediates and products remained soluble over the course of the HPLC analysis. This allowed both the initial trigger removal (forming intermediate **5′**) and the subsequent 1,6-elimination (releasing free *rac*TAK-242) to be monitored (Scheme 8). Compound **4′c** exhibited a rapid loss of the starting prodrug (anticipated trigger half-life of ∼1.4 h) with a rapid accumulation of the aniline intermediate **5′**, followed by a slow 1,6-elimination releasing free TAK-242 (*rac*-**1**). On the other hand, the less reactive prodrug **4′h** (anticipated trigger half-life of ∼38.5 h) slowly built up and sustained an accumulation of the aniline intermediate **5′** which steadily released the free drug. Compounds **4′d** and **4′e** provided intermediate drug release rates.

Overall, we were pleased to find that these new prodrugs functioned as desired; they released TAK-242 cleanly, with no sulfonamide hydrolysis or other side reactions observed in the kinetics experiments. Additionally, while the two-step kinetics were more complex, drug-release could be modulated by selecting different β-elimination triggers, providing a range of half-lives. Further tuning of release kinetics could potentially be approached by modifying the aniline linker to adjust the 1,6-elimination kinetics. For bioconjugation applications, the tether linkage to the aniline core ensures that the prodrug remains immobilized until final release of the active component. Current studies are examining the use of these novel prodrugs in various transplantation models, optimizing the prodrug solubility, and evaluating this strategy for the development of slow-release TAK-242 derivatives suitable for systemic application.

Scheme 8. HPLC Analysis of Kinetics of Two-Step TAK-242 Release in PBS (pH 7.4) with 20% DMSO at 37 °C (R = $N_3(CH_2CH_2O)_3CH_2CH_2$-)



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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.2c00492.

Full experimental details for the synthesis of compounds **4**−**16** and HPLC analyses of prodrug hydrolysis and release of parent drug; preparation of several related compounds; pH studies of β-elimination for **4′d** (PDF)

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Author Contributions

J.H.K. synthesized and characterized the prodrugs, performed the kinetic analyses, and produced the manuscript. R.R.K. guided the experimentation and edited the manuscript. A.T.L., C.A.S., and M.R.S. assisted with compound syntheses and characterizations. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Ii, M.; Matsunaga, N.; Hazeki, K.; Nakamura, K.; Takashima, K.; Seya, T.; Hazeki, O.; Kitazaki, T.; Iizawa, Y. A novel cyclohexene derivative, ethyl (6R)-6-[N-(2-Chloro-4-fluorophenyl)sulfamoyl]-cyclohex-1-ene-1-carboxylate (TAK-242), selectively inhibits toll-like receptor 4-mediated cytokine production through suppression of intracellular signaling. *Mol. Pharmacol.* **2006**, *69* (4), 1288−1295. (b) Yamada, M.; Ichikawa, T.; Ii, M.; Sunamoto, M.; Itoh, K.; Tamura, N.; Kitazaki, T. Discovery of Novel and Potent Small-Molecule Inhibitors of NO and Cytokine Production as Antisepsis Agents: Synthesis and Biological Activity of Alkyl 6-(N-Substituted sulfamoyl)cyclohex-1-ene-1-carboxylate. *J. Med. Chem.* **2005**, *48* (23), 7457−7467.

(2) (a) Wu, H.; Chen, G.; Wyburn, K. R.; Yin, J.; Bertolino, P.; Eris, J. M.; Alexander, S. I.; Sharland, A. F.; Chadban, S. J. TLR4 activation mediates kidney ischemia/reperfusion injury. *J. Clin. Invest.* **2007**, *117* (10), 2847−2859. (b) Krüger, B.; Krick, S.; Dhillon, N.; Lerner, S. M.; Ames, S.; Bromberg, J. S.; Lin, M.; Walsh, L.; Vella, J.; Fischereder, M.; Krämer, B. K.; Colvin, R. B.; Heeger, P. S.; Murphy, B. T.; Schröppel, B. Donor Toll-like receptor 4 contributes to ischemia and reperfusion injury following human kidney transplantation. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106* (9), 3390−3395.

(3) Chong, A. J.; Shimamoto, A.; Hampton, C. R.; Takayama, H.; Spring, D. J.; Rothnie, C. L.; Yada, M.; Pohlman, T. H.; Verrier, E. D. Toll-like receptor 4 mediates ischemia/reperfusion injury of the heart. *J. Thorac. Cardiovasc. Surg.* **2004**, *128* (2), 170−179.

(4) (a) Prakash, A.; Mesa, K. R.; Wilhelmsen, K.; Xu, F.; Dodd-o, J. M.; Hellman, J. Alveolar Macrophages and Toll-like Receptor 4 Mediate Ventilated Lung Ischemia Reperfusion Injury in Mice. *Anesthesiology* **2012**, *117* (4), 822−835. (b) Merry, H. E.; Phelan, P.; Doak, M. R.; Zhao, M.; Hwang, B.; Mulligan, M. S. Role of Toll-Like Receptor-4 in Lung Ischemia-Reperfusion Injury. *Ann. Thorac. Surg.* **2015**, *99* (4), 1193−1199.

(5) Hsieh, J.-L.; Shen, P.-C.; Wu, P.-T.; Jou, I. M.; Wu, C.-L.; Shiau, A.-L.; Wang, C.-R.; Chong, H.-E.; Chuang, S.-H.; Peng, J.-S.; Chen, S.-Y. Knockdown of toll-like receptor 4 signaling pathways ameliorate bone graft rejection in a mouse model of allograft transplantation. *Sci. Rep.* **2017**, *7*, 46050.

(6) (a) Gao, Q.; Ma, L. L.; Gao, X.; Yan, W.; Williams, P.; Yin, D. P. TLR4 Mediates Early Graft Failure After Intraportal Islet Transplantation. *Am. J. Transplant.* **2010**, *10* (7), 1588−1596. (b) Krueger, B.; Yin, N.; Zhang, N.; Yadav, A.; Coward, W.; Lal, G.; Zang, W.; Heeger, P. S.; Bromberg, J. S.; Murphy, B.; Schroeppel, B. Islet-expressed TLR2 and TLR4 sense injury and mediate early graft failure after transplantation. *Eur. J. Immunol.* **2010**, *40* (10), 2914−2924. (c) Ro, H.; Hong, J.; Kim, B. S.; Lee, E. W.; Kim, M.-G.; Han, K. H.; Yeom, H.-J.; Lee, E. M.; Jeong, J. C.; Oh, K.-H.; Ahn, C.; Yang, J. Roles of Toll-Like Receptors in Allogeneic Islet Transplantation. *Transplantation* **2012**, *94* (10), 1005−1012. (d) Wang, D.; Jiang, L.; Liang, Y.; Hao, X.; Chen, C.; Xia, W.; Zhuang, R.; Su, Y.; Guo, S. COMP-Ang1 promotes long-term survival of allogeneic islet grafts in a bioinert perforated chamber by inhibiting inflammation via inhibition of the TLR4 signaling pathway. *Biotechnol. Lett.* **2016**, *38* (6), 1033−1042.

(7) (a) Shao, Z.; Jiao, B.; Liu, T.; Cheng, Y.; Liu, H.; Liu, Y. TAK-242 treatment ameliorates liver ischemia/reperfusion injury by inhibiting TLR4 signaling pathway in a swine model of Maastricht-category-III cardiac death. *Biomedecine & pharmacotherapie* **2016**, *84*, 495−501. (b) Shen, X.-D.; Ke, B.; Zhai, Y.; Gao, F.; Tsuchihashi, S.-I.; Lassman, C. R.; Busuttil, R. W.; Kupiec-Weglinski, J. W. Absence of toll-like receptor 4 (TLR4) signaling in the donor organ reduces ischemia and reperfusion injury in a murine liver transplantation model. *Liver Transpl.* **2007**, *13* (10), 1435−1443. (c) Oetting, W. S.; Guan, W.; Schladt, D. P.; Leduc, R. E.; Jacobson, P. A.; Matas, A. J.; Chinnakotla, S.; Schröppel, B.; Murphy, B. T.; Israni, A. K. Donor Polymorphisms of TLR4 Associated with Graft Failure in Liver Transplant Recipients. *Liver Transpl.* **2012**, *18* (12), 1399−1405. (d) Howell, J.; Gow, P.; Angus, P.; Visvanathan, K. Role of toll-like receptors in liver transplantation. *Liver Transpl.* **2014**, *20* (3), 270−280.

(8) (a) Zhao, Y.; Liu, Q.; Yang, L.; He, D.; Wang, L.; Tian, J.; Li, Y.; Zi, F.; Bao, H.; Yang, Y.; Zheng, Y.; Shi, J.; Xue, X.; Cai, Z. TLR4 inactivation protects from graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Cellular and Molecular Immunology* **2013**, *10* (2), 165−175. (b) Brennan, T. V.; Rendell, V. R.; Yang, Y. Innate Immune Activation by Tissue Injury and Cell Death in the Setting of Hematopoietic Stem Cell Transplantation. *Front. Immunol.* **2015**, *6*, 101.

(9) Chang, C. A.; Murphy, K.; Kane, R. R.; Lawrence, M. C.; Naziruddin, B. Early TLR4 Blockade Attenuates Sterile Inflammation-mediated Stress in Islets During Isolation and Promotes Successful Transplant Outcomes. *Transplantation* **2018**, *102* (9), 1505−1513.

(10) Chang, C. A.; Akinbobuyi, B.; Quintana, J. M.; Yoshimatsu, G.; Naziruddin, B.; Kane, R. R. Ex-vivo generation of drug-eluting islets improves transplant outcomes by inhibiting TLR4-Mediated NFkB upregulation. *Biomaterials* **2018**, *159*, 13−24.

(11) (a) Santi, D. V.; Schneider, E. L.; Reid, R.; Robinson, L.; Ashley, G. W. Predictable and tunable half-life extension of therapeutic agents by controlled chemical release from macromolecular conjugates. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109* (16), 6211−6216. (b) Ashley, G. W.; Henise, J.; Reid, R.; Santi, D. V. Hydrogel drug delivery system with predictable and tunable drug release and degradation rates. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110* (6), 2318−2323.
(12) (a) Kim, E.; Koo, H. Biomedical applications of copper-free click chemistry: in vitro, in vivo, and ex vivo. *Chemical Science* **2019**, *10* (34), 7835−7851. (b) Jewett, J. C.; Sletten, E. M.; Bertozzi, C. R. Rapid Cu-Free Click Chemistry with Readily Synthesized Biarylazacyclooctynones. *J. Am. Chem. Soc.* **2010**, *132* (11), 3688−3690.
(13) Plunk, M. A.; Alaniz, A.; Olademehin, O. P.; Ellington, T. L.; Shuford, K. L.; Kane, R. R. Design and Catalyzed Activation of Tak-242 Prodrugs for Localized Inhibition of TLR4-Induced Inflammation. *ACS Med. Chem. Lett.* **2020**, *11* (2), 141−146.
(14) Hearn, B. R.; Fontaine, S. D.; Pfaff, S. J.; Schneider, E. L.; Henise, J.; Ashley, G. W.; Santi, D. V. Primary deuterium kinetic isotope effects prolong drug release and polymer biodegradation in a drug delivery system. *J. Controlled Release* **2018**, *278*, 74−79.

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This paper was originall published ASAP on December 9, 2022. Due to a production error, parts of Scheme 6 were missing. The corrected version was reposted on December 12, 2022.

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