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ARTICLE *in* ACS MEDICINAL CHEMISTRY LETTERS · AUGUST 2013

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Design, Synthesis, and Evaluation of Prodrugs of Ertapenem

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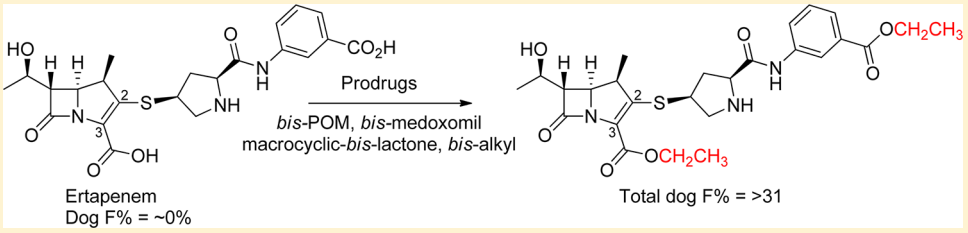
Supporting Information



ABSTRACT: Carbapenems are intravenous lifesaving hospital antibiotics. Once patients leave the hospital, they are sent home with antibiotics other than carbapenems since they cannot be administered orally due to lack of oral absorption primarily because of very highly polarity. A prodrug approach is a bona fide strategy to improve oral absorption of compounds. Design and synthesis, in vitro and in vivo evaluation of diversified prodrugs of ertapenem, one of the only once daily dosed carbapenems is described. Many of the prodrugs prepared for evaluation are rapidly hydrolyzed in rat plasma. Only bis-(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (medoxomil) ester prodrug was rapidly hydrolyzed in most of the plasmas including rat, human, dog, and monkey. Although the rate of conversion of ertapenem diethyl ester prodrug (**6**) was slow in in vitro plasma hydrolysis, it showed the best in vivo pharmacokinetic profile in dog by an intraduodenal dosing giving >31% total oral absorption.

KEYWORDS: *Ertapenem, carbapenem, antibiotics, prodrugs, ertapenem diethyl ester, intraduodenal dosing, ertapenem bis-pivoxyl, ertapenem bis-lactone*

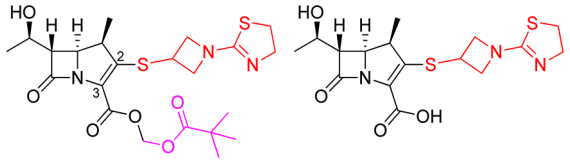
Carbapenems are some of the most effective lifesaving broad-spectrum antibiotics that are in clinical practice.[1] They are administered by intravenous infusion in a hospital setting. Once bacterial burden of a patient is reduced and the symptoms are improved, the patient is generally sent home with a noncarbapenem oral antibiotic. This sometimes causes a challenge in patient compliance and elimination of residual bacteria in patient often causing the patient to return to the hospital. Carbapenem antibiotics are not orally absorbed due to very high polarity. The polarity of these compounds can be reduced by synthesis of lipophilic prodrugs. Surprisingly, not much work has been reported on the prodrugs to allow oral dosing of these antibiotics. Orapenem (tebipenem pivoxyl, **1**) is one exception. It is a pivaloxymethyl ester prodrug of tebipenem (**2**) and is approved for clinical use in Japan.[2−6] Ertapenem (**3**) is a member of the carbapenem class of antibiotics that is broadly used worldwide. This is the only carbapenem antibiotic that is dosed once daily.[1,7,8] While the core structures of ertapenem and tebipenem is common, they are differentiated by the structure of their side chain substituents at C-2. Tebipenem possesses a basic side chain consisting of azetidino-thiazolidine, whereas ertapenem consists of a prolyl-3-aminobenzoic acid. The latter functionalities of ertapenem lead to higher protein binding (92−94%), longer plasma half-life, and the longer duration of action. Therefore, we selected ertapenem for prodrug studies, which could lead to a once daily oral carbapenem. The design, synthesis, and evaluation of selected prodrugs of ertapenem are described herein.

Ertapenem possesses four polar groups that could be derivatized for prodrugs. We primarily focused our attention on the ester prodrugs of the two carboxyl groups. We selected prodrug moieties that are well precedented and are part of approved drugs. One of the key attributes required for the prodrugs was to have no or significantly attenuated antibacterial activity. This could be accomplished by esterification of the C-3 carboxyl group. Thus, we chose to synthesize only diester and bis-lactone prodrugs. The prodrug moieties that fit these criteria are pivaloxymethyl (e.g., drug, adefovir dipivoxyl, cefetamet pivoxil),[9,10] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (e.g., lomesartan medoxomil, olmesartan medoxomil),[9,11] ethyl (e.g., xemilofiban),[12] and lactone (e.g., lovastatin).[13] We incorporated concepts of these prodrug moieties and prepared

Received: March 5, 2013
Accepted: July 3, 2013
Published: July 3, 2013

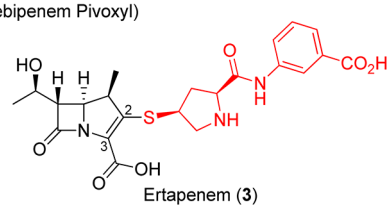
   dx.doi.org/10.1021/ml400092n | ACS Med. Chem. Lett. 2013, 4, 715−719

a series of prodrugs. Four of these prodrugs (bis-pivaloxymethyl (POM) ester (**4**), bis-(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) (medoxomil) ester (**5**), diethyl ester (**6**), and propyl-bis-lacone (**7**)) are described herein.



Orapenem (**1**)
(Tebipenem Pivoxyl)

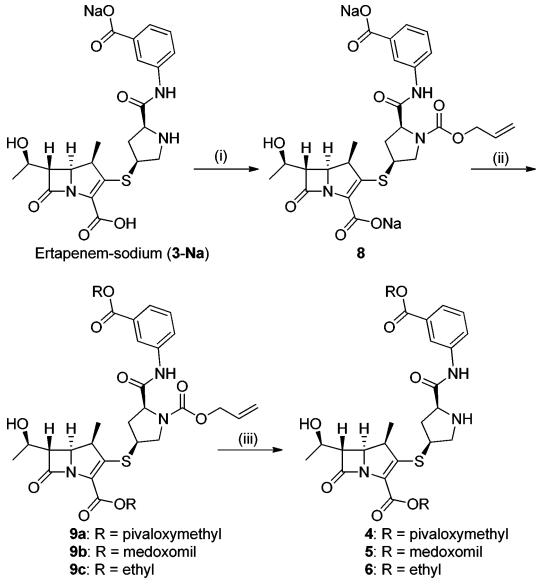
Tebipenem (**2**)



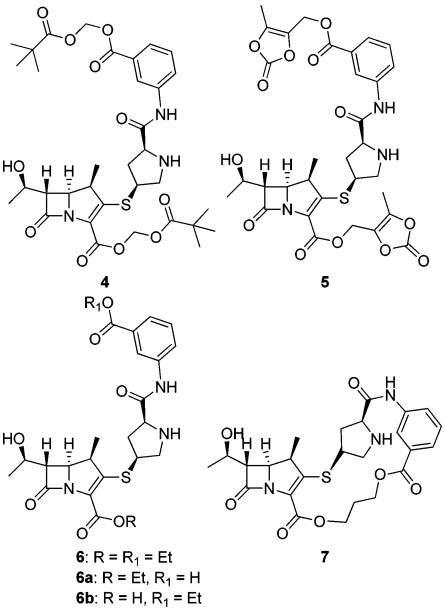
Ertapenem (**3**)

The synthesis of bis-esters started with the protection of the basic amine of the ertapenem by reacting ertapenem-sodium (**3**-Na) with allyl chloroformate at a neutral pH to produce allyloxycarbonyl intermediate **8**, which was lyophilized as a sodium salt and used without further purification. The reaction pH was tightly controlled to neutral levels and the product was used directly for the next step to prevent decomposition. The disodium salt of **8** was bis-alkylated by reaction of two equivalents of appropriate alkyl iodides to afford diesters **9a**–**9c**. The allyloxy carbamate protecting group was removed by reacting **9** with phenylsilane catalyzed by tetrakis-(triphenylphosphine) palladium (Scheme 1). The final prodrug diesters were purified by reversed phase HPLC. These bis-esters were synthesized in ∼20% overall yields and >96% purity.

Scheme 1. Synthesis of Diester Prodrugs of Ertapenem[a]

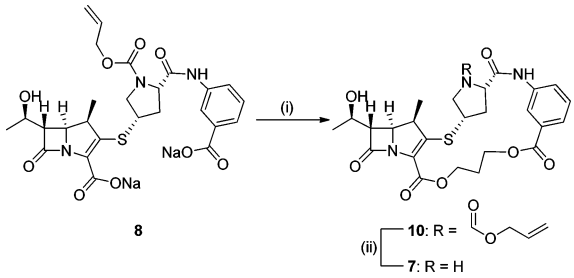


[a]Reagents: (i) allyl chloroformate, water, acetone, phosphate buffer (pH 7), room temperature, 30 min; (ii) benzyltriethylammonium chloride, DIEA, DMF, 40 °C, 4–18 h; (a) iodomethyl pivalate; (b) (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (medoxomil) iodide; (c) ethyl iodide; (iii) $Pd(PPh_3)_4$, phenylsilane, DMF, room temperature, 10–30 min.



For the synthesis of ertapenem-propyl-bis-lactone (**7**), allylcarbamate disodium salt of ertapenem (**8**) was reacted with one equivalent of 1,3-diiodopropane to afford the protected macrocyclic lactone **10**, which was deprotected with phenylsilane to furnish the final bis-lactone **7** (Scheme 2) after reversed phase HPLC purification (∼15% yield and 97% purity).

Scheme 2. Synthesis of Macrocyclic Ester Prodrugs of Ertapenem[a]



[a]Reagents: (i) $ICH_2CH_2CH_2I$, benzyltriethylammonium chloride, DIEA, DMF, 40 °C, 4–18 h; (ii) $Pd(PPh_3)_4$, phenylsilane, DMF, room temperature, 60 min.

All four compounds were tested for their stability in phosphate buffer (pH 7), simulated gastric fluid (SGF) (pH 2.0), and simulated gastrointestinal fluid (FaSSIF, pH 6.5). Samples were analyzed by LC–MS/MS. All four compounds were stable in phosphate buffer and FaSSIF at 50 μM for greater than 3 h. All prodrugs were unstable in SGF producing over 25% β-lactam ring open decomposition products in 60 min.

All prodrugs were evaluated for the hydrolysis by rat, human, dog, and monkey plasma to produce ertapenem. It is well-known that rat plasma has additional esterases (e.g., carboxylesterases and cholinesterases) compared to higher species.[14] Higher mammalian species including humans express many of these esterases in liver.[15] It is expected that in vitro hydrolysis of the prodrugs in the rat plasma may be more pronounced than corresponding hydrolysis in the plasma of other mammalian species. Therefore, any prodrug that is stable

dx.doi.org/10.1021/ml400092n | ACS Med. Chem. Lett. 2013, 4, 715–719

in the rat plasma may not be suitable for further studies. For the plasma hydrolysis experiments, the prodrugs (50 μM) were incubated for 60 min, and the hydrolytic rate was determined by measurement of the disappearance of the prodrug and appearance of the ertapenem by sampling at 5, 15, 30, and 60 min. The analysis was performed by quantitative LC−MS/MS, and the results are summarized in Table 1. Ertapenem was stable in all plasmas tested.

Table 1. Results of the Plasma Hydrolysis of the Prodrugs (4−7)[a]

	% remaining prodrug and % conversion to the parent carbapenem after 60 min							
	rat		human		dog		monkey	
compd #	%R	%C	%R	%C	%R	%C	%R	%C
1	0	95	0	95	25	75	0	95
4	2	46	36	1	37	1	NT	NT
5	1	89	1	98	3	43	2	58
6	0	2	5	0	75	0	77	0
7	0	0	17	0	79	0	49	0

[a]S = stable, R = remaining, C = conversion to ertapenem from 4-7 and tebipenem from 3, and NT = not tested.

All four compounds rapidly disappeared in rat plasma within 5 min of incubation. However, only bis-medoxomil (**5**) quantitatively produced ertapenem in 60 min. Bis-pivaloxymethyl ester (**4**) produced 46% ertapenem in 60 min in rat plasma. Diethyl ester (**6**) and bis-lactone (**7**) did not produce any ertapenem after 60 min incubation in the rat plasma. Prodrug **5** was completely hydrolyzed by human plasma affording quantitative conversion to ertapenem in 60 min. The prodrug **5** was completely consumed in dog and monkey plasma but formation of the ertapenem was only 43% and 58%, respectively, in 60 min, while 95% diethyl ester **6** disappeared by incubation in the human plasma after 60 min but no ertapenem was formed. Compounds **6** and **7** showed significant stability in dog and monkey plasma. Incubation of tebipenem pivoxyl (**1**) in all four plasmas quantitatively produced tebipenem in less than 15 min indicating significant C-2 substitution (ertapenem vs tebipenem) selectivity for the hydrolysis by various plasma esterases.

Since many esterases are expressed only in the liver in the higher species, it was important to complement plasma hydrolysis studies of the selected compounds for hydrolysis in the liver microsomal preparations and hepatocytes. Incubation of the diethyl ester **6** in rat, human, dog, and monkey liver microsomal preparations with or without NADPH produced a mixture of 5−10% each of the ertapenem (**3**) and mono benzoate ethyl ester (**6b**) and about 50% of the C-3 ethyl ester (**6a**) in about 15 min. The rate of the hydrolysis of **6** by human and dog hepatocytes was slower but most of the parent was consumed in 60 min with major (25−30%) production of C-3 ethyl ester (**6a**). The rate of the hydrolysis in rat and monkey hepatocytes was not only slower but also the formation of any products including C-3 ethyl ester (**6a**) was minimal (<5%). The hydrolysis of the tebipenem pivoxyl (**1**) in the liver microsomal preparations and hepatocytes from all the species was rapid (<15 min) providing quantitative production of tebipenem (**2**).

Carbapenems in general and ertapenem (**3**) in particular have very low absorption due to high polar surface area, high polarity, and low logD (Table 2). This class of compound is known to be highly unstable at low pH as evidenced by

Table 2. Calculated and Measured Properties of Tebipenem Pivoxyl, Ertapenem, and Its Prodrugs

compd #	MW	cPSA	clogD[a]	cPapp[b]	Papp[b,c]
1	497.6	109	2	12	10.1
2	383.5	93	2.4	5.2	0.7
3	475.5	156	−5.9	1.8	0.5
4	703.8	187	3	7.2	
5	699.7	205	−0.7	6.7	
6	531.6	134	2.9	6.9	13
7	515.6	134	1.1	8.2	

[a]ACD + clogP at pH 7.4. [b]10^{-6} cm/s. [c]LLC-PK1 cell line.

significant instability of ertapenem and prodrugs in SGF. Therefore, in order to develop a viable prodrug, the compounds have to be dosed in a way that bypasses the stomach acid. This can be achieved by enteric coated tablets/capsules. However, it is rather difficult to enteric coat each compound in the discovery phase not least because of the high amount of compound requirement but also due to high formulation investment. Therefore, an alternative dosing regimen that bypasses the stomach was sought. Intraduodenal (ID) dosing accomplishes this goal. Therefore, this approach was adopted for the PK studies of ertapenem prodrugs in rats and dogs. First, male Sprague−Dawley rats were ID dosed with ertapenem (**3**), tebipenem (**2**), and tebipenem pivoxyl (**1**), and data was compared with the data from IV and PO dosing. While ertapenem showed dismal absorption by ID and PO dosing (Table 3), the absorption was marginally better by ID dosing. Surprisingly, no absorption difference was observed for tebipenem pivoxyl whether dosed ID or PO (data not shown). The comparison of calculated physical properties of ertapenem (**3**), its prodrugs (**4**−**7**), tebipenem (**2**), and tebipenem pivoxyl (**1**) are presented in Table 2. Tebipenem showed better properties for oral absorption than ertapenem as defined by lower molecular weight, lower polar surface area, and better permeability (Table 2). These properties for tebipenem pivoxyl appear to be more favorable for absorption and was reflected by observed higher bioavailability (40−73%) in various species including human.[16] The calculated properties of the ertapenem prodrugs (**4**−**7**) showed improvement over corresponding properties of ertapenem but none of the prodrugs appears to be as good as tebipenem pivoxyl, which proved to be the case with dismal observed GI absorption in SD rats (Table 3). After dosing of ertapenem prodrugs, we analyzed the plasma for AUC of the dosed prodrug, ertapenem, and the two monoesters as listed. The bioavailability (F%) was calculated for ertapenem alone as well as for all ertapenem metabolites and ertapenem, which is expressed as total absorption. The total absorption was calculated by adding the AUC of ertapenem, prodrug intermediates, and parent prodrugs. ID dosing of prodrugs **4** and **5** in SD rats resulted in only 0.37% and 0.77% ertapenem, respectively, in plasma indicative of poor absorption of these compounds in rat and not due to poor hydrolysis since no parent prodrug was detected. ID dosing of the diethyl ester (**6**) in SD rats showed 4.98% ertapenem and 0.63% of 1:6 ratio of C-3 (**6a**) and benzoate (**6b**) monoesters in the plasma.

In order to test whether the poor absorption observed in rats was species dependent, we studied the PK of compounds **4** and

dx.doi.org/10.1021/ml400092n | ACS Med. Chem. Lett. 2013, 4, 715−719

Table 3. Sprague-Dawley Rat (Fasted) Pharmacokinetics Measurement of Prodrugs by Intraduodenal (ID) Infusion Dosing[a]

parameters	3 (IV, 1 mpk)[b]	3 (ID, 10 mpk)[c]	3 (PO, 10 mpk)[c]	4 (ID, 10 mpk)[d]	5 (ID, 10 mpk)[d]	6 (ID, 4.4 mpk)[e]
prodrug $AUC_{(0-8)}$ μM·h	NA	NA	NA	NQ[h]	NQ[h]	0.06
3 $AUC_{(0-8)}$ μM·h	7.84	0.48	0.39	0.20	0.30	1.54
C-3 ester $AUC_{(0-8)}$ μM·h	NA	NA	NA	NQ[h]	ND	0.07
benzoate ester $AUC_{(0-8)}$ μM·h	NA	NA	NA	NQ[h]	ND	0.42
F% (3)[f]	NA	0.65	0.53	0.37	0.77	4.98
F% (Total)[g]	NA	0.65	0.53	0.37	0.77	6.56

[a]NA, not applicable; ND, not determined. [b]Dosing vehicle (30% captisol, clear solution). [c]Dosing vehicle (0.5% methyl cellulose [MC] clear solution). [d]Dosing vehicle (0.5% MC, homogeneous suspension). [e]Dosing vehicle (0.5% MC, nearly clear solution). [f]Calculated by dividing normalized AUC of ertapenem formed from prodrug/normalized AUC of ertapenem dosed IV. [g]Calculated by dividing normalized AUC of circulating parent prodrug, ertapenem, and two monoesters formed from prodrug/normalized AUC of ertapenem dosed IV. [h]Not quantifiable; absolute data was below level of quantitation, 5 nM. The difference between $AUC_{(0-\infty)}$ vs $AUC_{(0-8)}$ was ±20%.

Table 4. Beagle Dog (Fasted) Pharmacokinetics Measurement of Prodrugs by Intraduodenal (ID) Infusion Dosing[a]

parameters	3 (IV,1 mpk)[b]	4 (ID, 10 mpk)[c]	6 (ID, 10 mpk)[d]	7 (ID, 10 mpk)[e]
prodrug $AUC_{(0-8)}$ μM·h	NA	NQ[h]	4.99	0.10
3 $AUC_{(0-8)}$ μM·h	8.90	1.81	14.3	0.44
C-3 ester $AUC_{(0-8)}$ μM·h	NA	0.04	2.17	ND
benzoate ester $AUC_{(0-8)}$ μM·h	NA	NQ[h]	3.34	ND
F% (3)[f]	NA	3.00	18.1	0.53
F% (Total)[g]	NA	3.07	31.3	>0.65

[a]NA, not applicable; ND, not determined. [b]Dosing vehicle (30% captisol, clear solution). [c]Dosing vehicle (0.5% MC, homogeneous opaque suspension). [d]Dosing vehicle (10% Tween, nearly clear solution). [e]Dosing vehicle (PEG400, hazy suspension). [f]Calculated by dividing normalized AUC of ertapenem formed from prodrug/normalized AUC of ertapenem dosed IV. [g]Calculated by dividing normalized AUC of circulating parent prodrug, ertapenem, and two monoesters formed from prodrug/normalized AUC of ertapenem dosed IV. [h]Not quantifiable; absolute data was below level of quantitation, 5 nM. The difference between $AUC_{(0-\infty)}$ vs $AUC_{(0-8)}$ was ±20%.

6 in Beagle dogs by ID dosing. The absorption of compound **4** was only slightly improved in dogs showing 3% ertapenem in plasma (Table 4). The results were significantly better for the diethyl ester despite poor in vitro hydrolysis of the esters in the dog plasma. Dosing of diethyl ester by ID route to dogs showed about 18.1% absorption as measured in the form of ertapenem and a total absorption of over 31.3% when the levels of both monoesters (**6a** and **6b**) and parent diethyl ester **6** and ertapenem were combined (Table 4 and Figure 1). It is

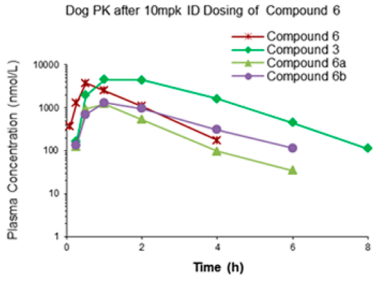


Figure 1. Dog PK profile of diethyl ester (**6**).

interesting to note that compound performed better in vivo than in vitro conditions. More than 70% of the parent prodrug was remaining after 60 min incubation in the in vitro hydrolysis reaction in the dog plasma without producing any ertapenem. The rate of the hydrolysis in liver microsomal preparations and hepatocytes were also slower indicating that the hydrolysis in vivo is far more efficient compared to in vitro. Encouraged by this result, we tested the bis-lactone **7** for the dog PK by ID dosing. It showed poor absorption, and only about 0.53% ertapenem was present in the plasma. The intact prodrug (**7**) was circulating in a ratio of 1:4 compared to ertapenem.

Synthesis of ester prodrugs helped selection of compounds with improved absorption of ertapenem leading to identification of the diethyl ester prodrug (**6**). It showed total absorption of over 31%, which is in the range of a number of clinically used cephalosporin prodrugs (e.g., ceftditoren pivoxil, 20%, cefcapene pivoxil, 27%).[16,17] While the diethyl ester prodrug established that noteworthy improvements in bioavailability were achievable for this sensitive class of compounds, robust clinical utility would require both greater absorption and rapid liberation of the parent and will be the focus of future efforts.

■ ASSOCIATED CONTENT

Supporting Information

Graphical representation of time-dependent plasma hydrolysis profile of **1** and **4**−**7**, and syntheses and characterization of **4**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge technical assistance from Wuxi chemistry, DMPK, and pharmaceutical sciences teams.

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