Exploratory research of novel prodrugs for enhancement of oral absorption of cephalosporin antibiotics

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Introduction : Cephalosporin Antibiotics

A common structure of cephalosporin antibiotics

- Cephalosporin antibiotics have been the mainstay of antibacterial chemotherapy for decades.
- Even though some of them have potent and well balanced antimicrobial activity, they are limited to use for their poor oral absorption as expected from their physicochemical properties.
- In this case, introduction of pivaloyloxymethyl moiety to carboxylic acid of the cephalosporin nucleus is one of the approaches for improvement of oral absorption (e.g. Cefetamet pivoxil (**1**)).
- However, there aren't so many examples of the improvement of oral absorption in the some commercially available cephalosporins as injectable formulation using above methodology.

Cefetamet pivoxil (CEMT-PI, **1**)

- In this study, we conducted two approaches to enhance oral absorption and establish the methodology for the improvement of oral bioavailability of cephalosporins.

1. Novel orally active prodrugs of aminothiazole

Cefetamet pivoxil (CEMT-PI) POM:

2. Novel orally active macrocyclic prodrugs

Ceftriaxone macro-cycle

- In this poster, an approach 1 is shown in below.

* J. R. Koop, U. C. Dubach, R. Brandt, R. Wyss, K. Steckel, Antimicrobial Agents and Chemotherapy 1988, 32, 573.

The Effects of conversions of amino thiazole

- The third generation cephalosporins, such as **1** possess an aminothiazole moiety at the C-7 position of the cephem nucleus.
- In our initial study, we synthesized pivaloyloxymethyl prodrugs (**2**, **4**), a methylthiazole analog (**3**) and *N,N*-dimethylaminothiazole analog (**5**) as Ceftriaxone and Cefcapene derivatives.

Compounds	2	3	4	5
BA* (%)	1.0	14.0	13.6	43.0

* rat 20 mg/kg oral administration

X 14 (from 2 to 3) X 3.1 (from 4 to 5)

- **3** and **5** showed much higher oral absorption compared to **2** and **4**.
- However, methylthiazole and *N,N*-dimethylaminothiazole derivatives didn't show potent antimicrobial activities (data is not shown).

The Conversions of amino thiazole in Cefetamet

- We selected Cefetamet which has aminothiazole moiety at the C-7 position of the cephem nucleus, as an active metabolite in our exploratory study.

Results of *N,N*-dimethylaminothiazole and methylthiazole derivatives

- All of them improved the parameters of membrane permeability (PAMPA, EPSA).
- Compound **8** showed high AUC_{po} than CEMT-PI (**6**).

R	aminothiazole (CEMT-PI, 6)	<i>N,N</i> -dimethylaminothiazole 7	methylthiazole 8
Structure			
AUC _{po} (μg·hr/mL)*	6.5	5.33	8.48
Solubility JP- I (μM)	>50	>50	>50
Solubility JP- II (μM)	>50	>50	>50
CLogP	2.22	3.18	2.95
PAMPA ((10 ⁻⁶)*cm/s)	0.63, middle-high	6.58, high	7.75, high
EPSA**	105.5	75.2	71.2

* rat 20 mg/kg oral administration, **Effective Polar Surface Area. ref. : ACS Med. Chem. Lett. 2014, 5, 1167–1172

Results : Profiles of prodrug compounds

- **13a**, **14** and **15** exhibited low solubility and decreased oral bioavailability compared with **1**.
- **17** showed high solubility but low oral bioavailability.
- **13b** and **13c** exhibited both high solubility, high membrane permeability and oral bioavailability of **13b** and **13c** were comparable to that of **1**.

Compound	CEMT-PI 1	13a	13b	13c	14	15	17
R							
BA* (%)	22.4	16.6	21.2	23.5	4.8	3.7	13.2
Solubility JP- II (μM)	>50	ND***	>50	>50	ND***	ND***	>50
Solution stability JP- II (% , 2hr)	101	98	80	91	96.4	NT****	92.9
PAMPA ((10 ⁻⁶)*cm/s)	0.63 middle	NT****	2.53 high	0.95 high	NT****	NT****	0.00 Low
EPSA**	105.5	75.0	81	79.1	68.7	67.3	129.2

* rat 20 mg/kg oral administration, **Effective Polar Surface Area. ref. : ACS Med. Chem. Lett. 2014, 5, 1167–1172, ***Not detected, ****Not tested

Discussions and Conclusions

- The prodrugs **13a**, **14**, **15** which showed low solubility or low membrane permeability exhibited low oral bioavailability.
- The prodrugs **13b** and **13c** showed high solubility and high permeability but oral bioavailability of **13b** and **13c** remained comparable to **1**.
- We considered the reasons mentioned above were due to gastrointestinal tract instability and/or slow conversion rate to Cefetamet *in vivo* of **13b** and **13c**.
- The prodrugs **17** showed low membrane permeability and oral bioavailability in spite of high solubility.

Future Research Plans

Cefetamet derivatives

Ceftriaxone derivatives

Cefcapene derivatives

1. Conducting the test of the gastrointestinal tract stability and the conversion rate in rat serum to investigate the reasons the oral bioavailability of **13b** and **13c** were comparable to **1**.
2. Validating these modifications using other cephalosporins such as Ceftriaxone and Cefcapene

Contact Us

- Thank you for having a look at our work.
- We would like to discuss about this research with you although ACS Spring 2020 National Meeting was cancelled due to COVID-19.
- If you have questions or comments about this presentation, we are appreciate to receive them by E-mail.
- E-mail address : masayuki.sano@shionogi.co.jp
- I'm looking forward to communicating with you on SciMeetings.