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Review Article

BIOLOGICAL ACTIVITY OF RECENT DEVELOPMENT ON β-LACTAM DERIVATIVES: A REVIEW

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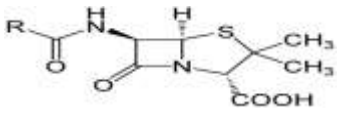
ABSTRACT

β-lactam antibiotics are the most frequently prescribed antibiotics due to its antimicrobial activity. Beta-lactam antibiotics are the broad class of antibiotics which contain a β-lactam ring in their molecular structure, including penicillin derivatives (penams), cephalosporin (cephems), monobactams and carbapenems. The Beta-Lactam nucleus, 6-aminopenicillanic acid proved to be the key in penicillin synthesis and modification. The Beta-Lactam nucleus opened up the floodgate where novel beta-lactam agents could be proved by unusual side chains to 6-APA. Bacteria often develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the beta lactam ring. To overcome this resistance, beta lactam antibiotics are often given with β-lactamase inhibitors such as clavulanic acid. Semi-synthetic beta-lactam compounds have been developed continuously and systematically. This article aims to review the research on beta-lactam derivatives in recent years.

Keywords: *β-lactam; antibiotic; penicillin; antibacterial.*

INTRODUCTION

β-lactam composed of a four-membered ring which is formed by an intramolecular condensation of an amino acid in which the amino group is located at beta position or any compound containing this group. The first synthetic β–lactam was prepared by Hermann Staudinger in 1907 by reaction of aniline and benzaldehyde with diphenylketone in a [2+2] cycloaddition [1]. Any substance which can destroy or inhibit the growth of bacteria or microorganism is known as antibiotic. The term antibiotic was first used in 1942 by Selman-Waksman and his collaborators in journal articles to describe any substance produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution [2]. With advances in medicinal chemistry, most modern antibacterials are semi-synthetic modifications of various natural compounds [3]. Beta lactam are the broadly used antibiotic and worked by inhibit the cell wall biosynthesis of the bacterial organism [4]. These include, for example, the beta-lactam antibiotics, which include the penicillins (produced by fungi in the genus Penicillium), carbapenems (Primaxin), cephalosporins (cefotaxime), and monobactams (Aztreonam).



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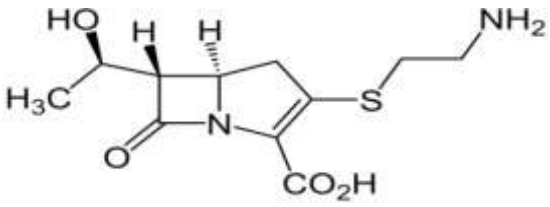
Pharmacological Activity and structure

On the basis of various literature surveys β-lactam derivative are:

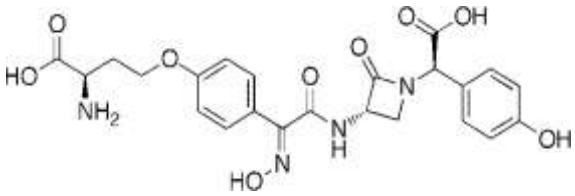
- **Thienamycin**

In 1976, the family of carbapenem antibiotics was isolated from fermentation broth of *Streptomyces cattleya* (NRRL 8057). Thienamycin is one of the most potent naturally produced antibiotics [5]. Thienamycin has excellent activity against both Gram-positive and Gram-negative bacteria and is resistant to bacterial β-lactamase enzyme. In vitro, thienamycin employs a similar mode of action as penicillin through disrupting the cell wall synthesis (peptidoglycan biosynthesis) of various Gram-positive and Gram-negative bacteria (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis* to name a few).



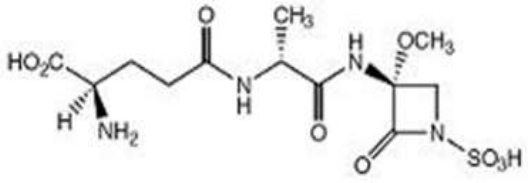
- **Nocardicin**

In 1970, researchers of Fujisawa Pharmaceuticals a new antibiotic was isolated from the fermentation broth of an actinomycete [6] , Nocardia uniformis subsp. Tsuyamanensis; it shows moderate activity against a broad spectrum of Gram-negative bacteria. Nocardicin A is a new monocyclic beta-lactam antibiotic, it is a subclass of monobactum.



- **Sulfazecin and isosulfazecin**

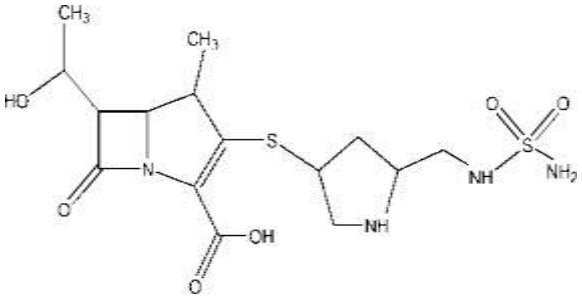
In the long history of antibiotic screening, actinomycetes and fungi have been the meer producers of beta-lactam antibiotics although several phytopathogenic bacteria have been reported to produce toxins with a beta-lactam structure. Sulfazecin is a new water soluble acidic antibiotic and it is active against Gram-negative bacteria, was isolated from the culture broth of Pseudomonas acidophila G-6302 by use of anion exchange resin and activated charcoal [7].



- **Doripenem**

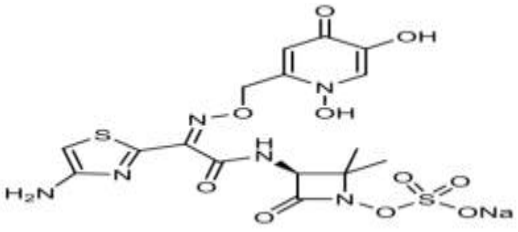
Doripenem (formerly S-4661), a parenteral 1-beta-methyl carbapenem, is the newest agent in the family, and it received approval by the US food and drug administration (FDA) in 2007 for the treatment of complicated intra-abdominal infections (IAIs) and complicated urinary tract infections (UTIs). Doripenem has a spectrum of activity similar to that of imipenem/cilastatin and meropenem8 and is effective in treating both gram-negative and gram-positive pathogens, including

Pseudomonas aeruginosa and anaerobes and it is a bactericidal agent.



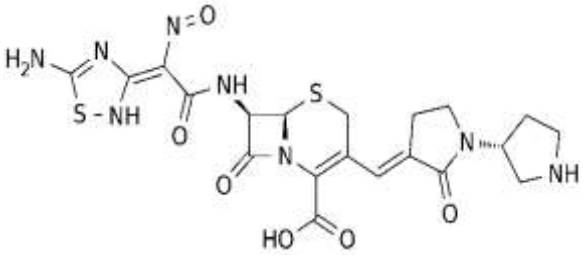
- **BAL30072**

BAL30072 is a monobactam which developed by Basilea Pharmaceutical AG and currently in Phase I trials. BAL30072 is stable towards metallo-β-lactamases and has some inhibitory activity towards class C β-lactamases, whereas the latter is unlikely to change into clinical efficacy against most Amp C-producing pathogens. BAL30072 was active against multidrug-resistant (P. aeruginosa, Acinetobacter spp., Burkholderia sp. and Stenotrophomonas maltophilia). It was active against 70% of the carbapenem-resistant Enterobacteriaceae strains tested [8].



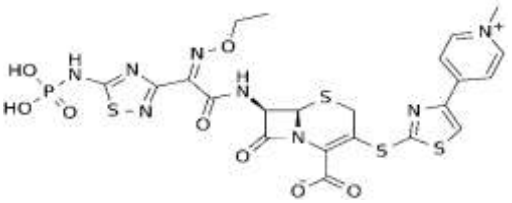
- **Ceftobiprole**

Ceftobiprole (Zeftera/Zevtera) is a fifth-generation cephalosporin antibiotic with activity against methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, and *Enterococci* [9, 10, 11]. Ceftobiprole inhibits the 2a penicillin-binding protein (PBP) of methicillin-resistant *Staphylococcus aureus*.



- **Ceftaroline**

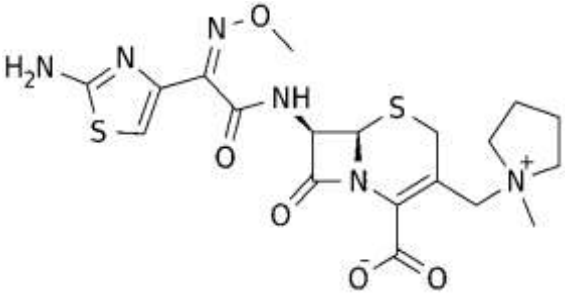
Ceftaroline fosamil (INN), brand name Teflaro in the US and Zinforo in Europe, is an advanced-generation [12]. Ceftaroline fosamil is a new β-lactam antibiotic with an altered 3' side chain that allows it to interact with penicillin-binding protein, ensuing in lower MIC values for methicillin-resistant Staphylococcus aureus. Ceftaroline fosamil at a dose of 600 mg administered intravenously every 12 h is highly likely to be successful in clinical practice for treatment of complicated skin and skin structure infections [13].



- **Cefepime**

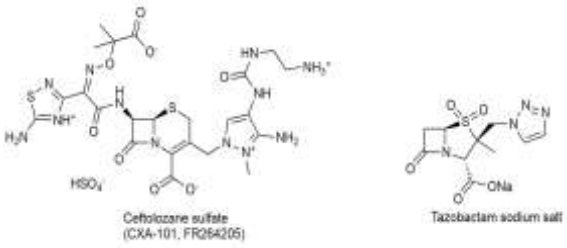
Cefepime is a fourth-generation cephalosporin antibiotic established in 1994. Cefepime has an broad spectrum of activity against Gram-positive and Gram-

negative bacteria, with greater activity against both organisms than 3rd generation agents. Cefepime is usually used to treat moderate to severe pneumonia and other infections caused by multiple drug-resistant microorganisms (e.g. Pseudomonas aeruginosa) and empirical treatment of febrile neutropenia [14].



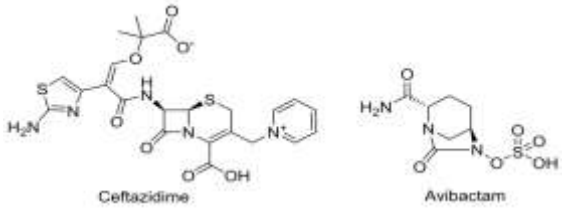
- **CXA-101**

CXA-101 (ceftolozane) is a cephalosporin which is particularly active against *P. aeruginosa*, including isolates from chronically-infected cystic fibrosis patients, due to enhanced affinity of the β-lactam for the PBPs of this species [15-18]. It also has (relatively) poor activity towards other Gram-negative microrganism, and also towards multidrug-resistant Gram-positive cocci and anaerobes. Tazobactam could not lower MICs, for Enterobacteriaceae producing KPCs, and CXA-101 does not show better activity than ceftolozane against P. aeruginosa. Cubist has recently filed a patent covering use of ceftolozane/tazobactam (2:1) for treating pulmonary infections [19].



- **CAZ104**

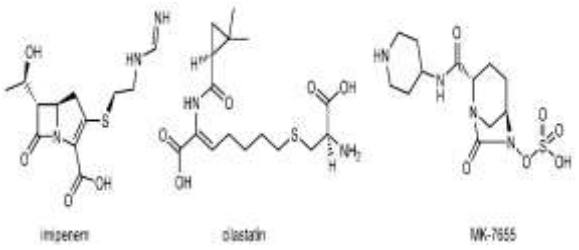
Ceftazidime is a third-generation cephalosporin with generally good activity against Gram-negative microorganisms, together with *P. aeruginosa* and Enterobacteriaceae. Ceftazidime currently is being developed in combination with avibactam, a diazabicyclooctane (a non-β-lactam β-lactamase inhibitor) which inhibits preferentially class A β-lactamases, including ESBLs and KPCs [20]. It is not effective against P. Aeruginosa strains producing OXA ESBLs or VEB-1 [21].



- **Imipenem/Cilastatin/MK-7655**

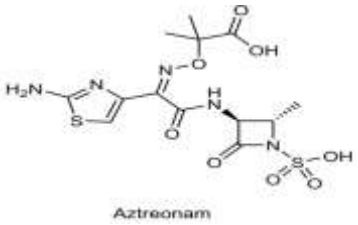
Imipenem, the first carbapenem to reach the market, is a potent, broad-spectrum β-lactam with antipseudomonas activity. MK-7655 is a diazabicyclooctanes (DBO) β-lactamase inhibitor that, combined with imipenem, showed good activity against imipenem-resistant Gram-negative isolates in vitro [22]. Imipenem acts as an antimicrobial through inhibiting cell wall synthesis of various Gram-positive as well as Gram-negative bacteria. It remains very

constant in the presence of β-lactamase (both penicillinase and cephalosporinase), and is very a strong inhibitor of β-lactamases from some Gram-negative bacteria that are resistant to most β-lactam antibiotics.



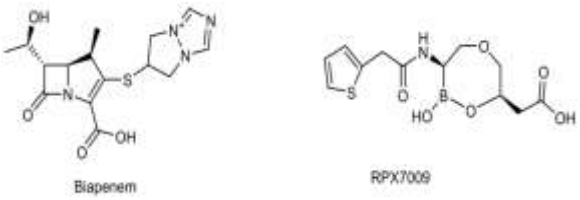
- **ATM-AVI**

ATM-AVI is a combination [23] of aztreonam & avibactam, a monobactam launched in 1984. Aztreonam inhibits mucopeptide synthesis in the bacterial cell wall and hence blocking peptidoglycan crosslinking. It has mild affinity for penicillin-binding protein-1a and high affinity for penicillin-binding protein-3.



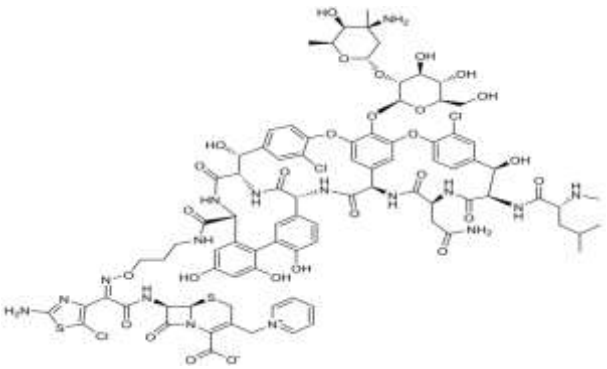
- **Biapenem/RPX7009**

Biapenem is a broad-spectrum carbapenem with good activity against S. pneumoniae, methicillin-susceptible Staphylococcus aureus, A. baumannii, ESBL-producing Enterobacteriaceae and P. Aeruginosa [24]. RPX7009 also gave a weak potentiation of biapenem against Enterobacteriaceae with combinations of AmpC or extended-spectrum β-lactamase activity and impermeability. *A. carbapenemases*.



- **TD-1792**

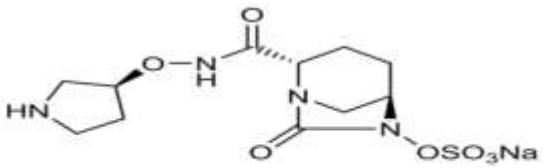
TD-1792 is a highly potent, bactericidal, once-daily antibiotic discovered by Theravance. In Phase 2 clinical study evaluating the safety and efficacy of TD-1792 in the treatment of complicated skin and skin structure infections (cSSSI) caused by Gram-positive bacteria. TD-1792 was designed to allow the molecule to interact and inhibit simultaneously two molecular targets involved in murein biosynthesis that are in close proximity to one another, with the expectation that such a strategy would raise significantly the statistical barrier to resistance development[25].



- **FPI-1465**

FPI-1465 is a DBO β-lactamase inhibitor, which differs from avibactam only by the presence of a (3S)-pyrrolidin-3-yl oxycarbamate moiety. The compound

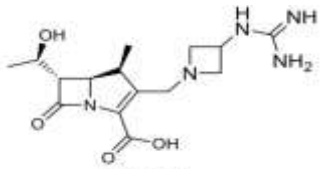
presently is undergoing preclinical testing [26]. FPI-1465 is inhibitory towards ESBL enzymes produced by Enterobacteriaceae species, such as CTX-Ms, it showed synergistic effects when combined with aztreonam and with ceftazidime [26].



FPI-1465

- **FSI-1671**

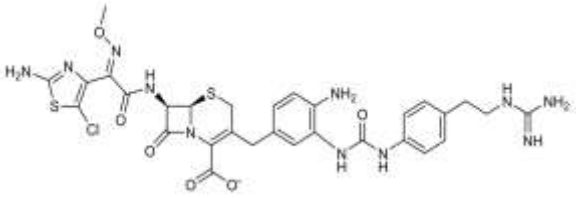
FSI-1671 is a new carbapenem, with enhanced in vitro activity against A. baumannii, including MDR strains. Joo et al. have observed synergism for FSI-1671 in combination with sulbactam, a β-lactamase inhibitor with intrinsic activity against *Acinetobacter spp.* towards MDR strains of *A. baumannii*. [27].



FSI-1671

- **CB-027**

CB-027 is reported by Cubist to be an ultra-broad spectrum cephalosporin with invitro activity against both MRSA and P. aeruginosa. This compound is claimed to have invivo activity against MRSA analogous to that of vancomycin and of ceftaroline, and against ceftazidime-resistant P. aeruginosa and K. Pneumonia [28].



Conclusion

It is believable that the recognition of antibiotics marks one of the most important milestones in human history. The use of antibiotics has brought upon in endless benefits to medicine, physiology and biology. With the assorted chemical structure of Beta-lactam molecules and their respective antibacterial activity, chemists are keen to look beyond what nature had supplied and how science could contribute and substituted. Though the generation of semi-synthetic compounds presented a great prospect, natural sources continued to be explored. Cephalosporin C was isolated by Abraham and Newton from a strain of Cephalosporium acremonium. This compound generated an entirely new family of β-lactam antibiotics because as a replacement for of 6-APA, it possesses a nucleus of 7-aminocephalosporinic acid (7-ACA). Using 7-ACA as the precursor, several generations of cephalosporins with potent broad-spectrum activity have been synthesized. However, as a community we should proceed with caution because misuse and the abuse of these substance will led to unwanted consequences including the return of multi-drug resistant bacteria.

Reference

1. Hermann Staudinger (1907); Zur Kenntniss der Ketene. Diphenylketen; Justus Liebigs Ann. Chem; 356 (1-2):51-123.

2. Astrid Zervosen, Eric Sauvage, Jean-Marie Frère, Paulette Charlier, André Luxen; Development of New Drugs for an Old Target — The Penicillin Binding Proteins; MOLECULES; 2012 Oct 24; 12478-505.

3. Pratt, Frére, J.-M., Ed.; R.F. Beta-lactamase inhibitors: Non-beta-lactams. In Beta-lactamases; Nova Science Publisher; 2012; pp. 259–292.

4. Elander, R.P.; Industrial production of beta-lactam antibiotics; Applied microbiology and biotechnology; 2003; 61(5-6); pp. 385-392.

5. G.H.Wagman, R.Cooper; Natural product Isolation:Seperation methods for antimicrobial.

6. H. Aoki, H.Sakai, M.Kohsaka, T.Konomi, J.Hosoda

7. Nocardicin A, a new monocyclic beta-lactam antibiotic. I. Discovery, isolation and characterization

8. J. Antibiot.; 1976; Volume 29; pp. 492-500.

9. Asai. M., Haibara. K., Muroi. M., Kintaka, K., Kishi.; Sulfazecin, a novel beta lactam antibiotic of bacterial origin, Isolation and chemical characterization; T. J. Antibiot. (1981)

10. Page, M.G.; Dantier, C.; Desarbre, E. In vitro properties of bal30072, a novel siderophore sulfactam with activity against multiresistant gram-negative bacilli. Antimicrob. Agents Chemother; 2010, Volume 54,pp. 2291–2302.

11. Yun HC, Ellis MW, Jorgensen JH; Activity of ceftobiprole against community-associated methicillin-resistant Staphylococcus aureus isolates recently recovered from US military trainees; Diagnostic Microbiology and Infectious Disease; 2007;Volume 59 (4); pp. 463.

12. Widmer A; Ceftobiprole: A new option for treatment of skin and soft-tissue infections due to methicillin-resistant Staphylococcus aureus; Clin Infect Dis; 2008; Volume 46 (5): 656–8.

13. Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS; A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections; Clin Infect Dis; 2008; Volume 46 (5):647–55.

14. Kollef MH; New antimicrobial agents for methicillin-resistant Staphylococcus aureus; Crit Care Resusc; December 2009; Volume 11 (4): 282–6

15. Talbot GH, Thye D, Das A, Ge Y; Phase 2 study of ceftaroline versus standard therapy in treatment of complicated skin and skin structure infections; Antimicrobial Agents and Chemotherapy; October 2007; Vol. 51 (10): 3612–6.

16. Chapman TM, Perry CM; Cefepime: a review of its use in the management of hospitalized patients with pneumonia; Am J Respir Med;2003; 2 (1): 75–107.

17. Moyá, B., Zamorano, L., Juan, C., Ge, Y., Oliver, A.; Affinity of the new cephalosporin CXA-101 to penicillin-binding proteins of Pseudomonas aeruginosa; Antimicrob. Agents Chemother; 2010; 54, pp. 3933–3937.

18. Livermore, D.M.; Mushtaq, S.; Ge. Y.; Warner, M.; Activity of cephalosporin CXA-101 (FR264205) against Pseudomonas aeruginosa and Burkholderia cepacia group strains and isolates; Int. J. Antimicrob. Agents; 2009; 34; pp. 402–406.

19. Juan. C., Zamorano. L., Pérez. J.L., Ge. Y., Oliver. A.; Activity of a new antipseudomonal cephalosporin, CXA-101 (FR264205), against carbapenem-resistant and multidrug-resistant Pseudomonas aeruginosa clinical strains; Antimicrob. Agents Chemother; 2010; 54; pp. 846–851.

20. Takeda, S., Ishii, Y., Hatano, K., Tateda, K., Yamaguchi, K.; Stability of fr 264205 against ampc β-lactamase of Pseudomonas aeruginosa; Int. J. Antimicrob. Agents; 2007; 30; 443–445.

21. Chandorkar. G., Huntington. J., Parsons. T., Umeh. O.; Methods for treating intrapulmonary infections; WO 2,013,036,783, 2013.

22. Livermore D.M., Blaser M., Carrs O., Cassell. G., Fishman N., Guidos R., Levy S., Powers J., Norrby R., Tillotson G.; Discovery research: The scientific challenge of finding new antibiotics; J. Antimicrob. Chemother. ; 2011; 66; 1941–1944.

23. Walkty A., DeCorby M., Lagacé -Wiens P., Karlowsky J., Hoban D., Zhanel G.; In vitro activity of ceftazidime combined with nxl104 versus Pseudomonas aeruginosa isolates obtained from patients in canadian hospitals. Antimicrob. Agents Chemother.; 2011; 55; 2992–2994.

24. Hirsch E.B., Ledesma K.R., Chang K.-T., Schwartz M.S., Motyl M.R., Tam. V.H.; In vitro activity of mk-7655, a novel β-lactamase inhibitor, in combination with imipenem against carbapenem-resistant gram-negative bacteria; Antimicrob. Agents Chemother. ; 2012; 56; 3753–3757.

25. Crandon. J.L., Nicolau D.P.; Human simulated studies of aztreonam and aztreonam-avibactam to evaluate activity against challenging gram-negative organisms, including metallo-β-lactamase producers; Antimicrob. Agents Chemother. ; 2013; 57; 3299–3306.

26. Pallett A., Hand K.; Complicated urinary tract infections: Practical solutions for the treatment of multiresistant gram-negative bacteria; J. Antimicrob. Chemother; 2010; 65; iii25–iii33.

27. Blais J., Lewis S.R., Krause K.M., Benton B.M. Antistaphylococcal activity of TD-1792, a multivalent glycopeptide-

cephalosporin antibiotic; Antimicrob. Agents Chemother; 2012; 56; 1584–1587.

28. Fedora pharmaceutical demonstrates that FPI-1465 increases activity of certain antibiotics against drug-resistant bacteri. Avaliable online: http://www.fedorapharma.com/instantedit/files/ Fedora _ICAAC_data_091213.pdf (Accessed on 12 September 2013).

29. Joo H., Choi W.-B., Kim D.-I., Kowalik E., Hager M.W., Mao S., Li Y., Liu S. In Fsi-1671, a novel anti-acinetobacter carbapenem; in vivo efficacy against carbapenem-resistance gram-negative bacterial infection. In Proceedings of the 53rd International Interscience Conference on Antimicrobial Agents and Chemotherapy, Denver, CO, USA, 2013, 11 September; p. F-1201.

30. Zhang S., Chuong L.I.M.C., Khang I.C., Alsup A., Li T., Arya A., He Y., Yin N., Rock J., Abel C.; et al. In vivo efficacy of cb-027 against methicillin-resistant Staphylococcus aureus, and ceftazidime-resistant Pseudomonas aeruginosa and Klebsiella pneumoniae infections in mice. In Proceedings of the 52nd International Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, USA, 10 September 2012; p. F-846.