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Review Article

A NOVEL ANTIBACTERIAL TARGET: PEPTIDE DEFORMYLASE

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ABSTRACT

PDF catalyzes the formylation-deformylation process which is essential for bacterial protein synthesis, its growth and survival is the major difference between human and bacterial cell. PDF represents most promising bacterial target in the search of novel antibiotics that lack cross-resistance to existing drugs. A number of PDFIs have been introduced till date. Actinonin is the first known PDF inhibitor. Two PDFIs BB-83698 and VIC-104959 (LBM-415; NVP-PDF-713) have entered into clinic trials in humans.

Keywords: Peptide deformylase, PDF inhibitors, Actinonin, Antibacterial.

INTRODUCTION

The PDF inhibitors represent one of the few examples of combining a target-based rational drug design and a medicinal chemistry approach in the field of antibacterial drug discovery. Most of the infections (acute and chronic) are treated by the antibiotics and the emergence of bacterial resistance provides a real challenge to successfully treat bacterial infections making antibiotics[1] a unique class of drugs with a drawback of resistance. This bacterial resistance provides a limited life cycle to these antibacterial agents. Therefore the identification of novel antibiotic classes with activity against resistant strains is critical to ensure future therapeutic success.[2] After a prolonged research for new antibiotics, many effective antibacterial drugs (natural and synthetic) have been developed since the 1940s. However, most of these antibacterial agents share the same target. Many Industrial and academic research labs have been trying to find inhibitors that act on new targets and thus provide a tool in solving the antibiotic resistance problems.[3] Their research includes studies to validate and characterize novel targets by high throughput screening of different libraries for efforts in discovering and developing novel leads. During the screening of novel target, following parameters should be

considered (i) No rapid emergence of bacterial resistance (ii) In humans the molecular target should be absent or sufficiently different (iii) Inhibitors should have high and target related antibacterial activity (iv) Targets should have property easy to control to allow the fine-tuning of additional parameters such as pharmacokinetics, pharmacodynamics and safety. Bacterial peptide deformylase (PDF; EC 3.5.1.88) [4, 5, 6] fulfills the criteria mentioned above and is likely the most attractive bacterial target to deliver the next class of novel antibacterial drugs.

Peptide Deformylase

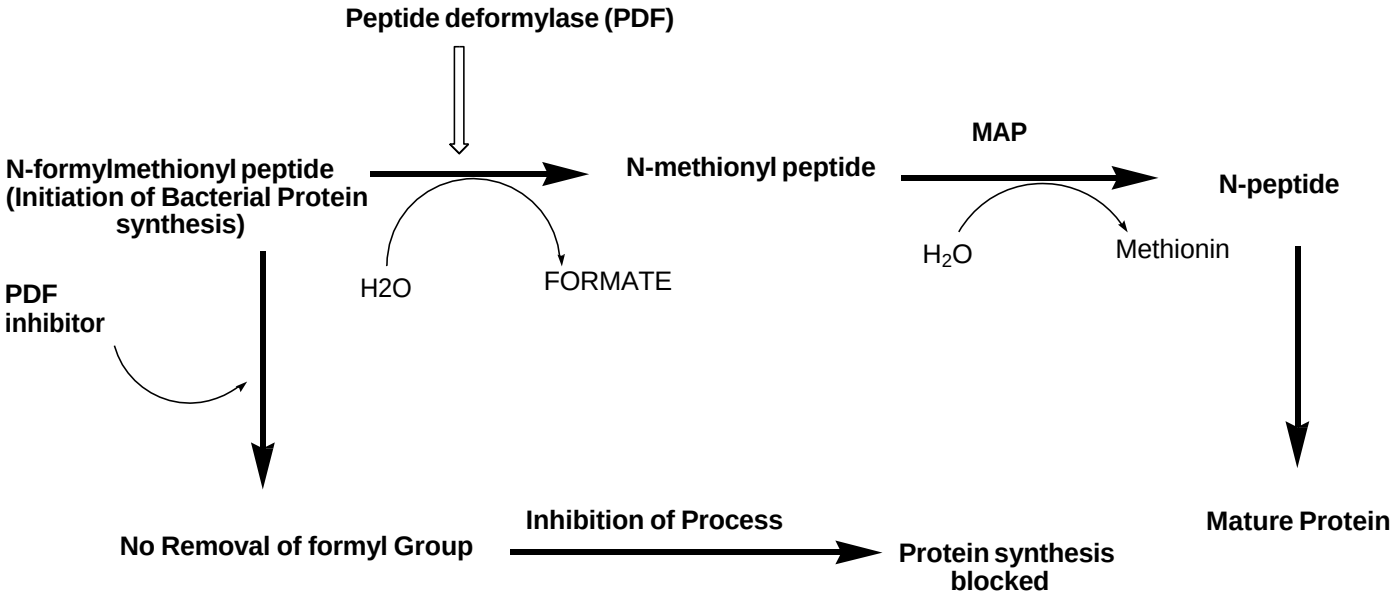
Protein synthesis has proved to be a rich source of targets for antibacterial agents.[7] Many of the currently known antibiotics function by inhibiting one or more steps of this complex process such as the aminoglycosides, macrolides, tetracyclines, lincosamides and oxazolidinones. A major difference in the process of protein synthesis in bacterial and mammalian cells is the transformylation and subsequent deformylation of methionine.[8, 9] PDF is essential in protein synthesis in bacteria, so it is the attractive and new target for next generation of antibiotics.[1,10] PDF is a metalloenzyme which has recently been recognized to utilize iron (Fe^{2+})[7-10] as the catalytic metal involved in protein synthesis.[11,12,13,14] Two bacterial PDF types, PDF1B and PDF2, have been distinguished.[15,16] PDF2 is found only in Gram-positive bacteria. During recent research PDF1A have also came into existence. PDF1A and PDF1B are found in mitochondria and in all Gram negative bacteria respectively.[17] On the basis of various studies the fact was found that bacteria may have one or several functional genes encoding different types of PDF.[15, 16] Gram negative *E.coli* has one PDF1B gene (*def*) only, whereas Gram positive bacteria such as *Bacillus* species have two PDF genes: (*def*, *ykrB*) The human PDF (mPDF) has been classified as a PDF1A.[17]

The three-dimensional structure of PDF from various bacterial species has been determined by various groups. In addition to the enzyme structures, several enzyme–inhibitor complex structures were also solved.[18] The structure of Ec-PDF (zinc-containing *E. coli* PDF) was at first solved by NMR methods and by X-ray crystallography.[19, 20] Metal ion of PDF is tetrahedrally coordinated by Cys90, His132, His136 and a H_2O molecule. The Ni-bound PDF has higher specific enzyme activity than the Zn bound PDF.[21] Hye-Jin Yoon *et al.* have determined the crystal structure of SaPDF in complex with its inhibitor actinonin at 1.90 Å resolution.[22]

The three-dimensional structures of the PDF with synthetic inhibitors reveal that the active-site metal ion is pentacoordinated by the metal-binding ligands of the inhibitors.[4, 23]

Function of PDF: Essential Role in Bacteria

PDF activity was first reported by Adams in 1968[24] but the enzyme was not characterized until the early 1990s when the peptide deformylase-encoding gene, *def*, was cloned.[9,25,26] Unlike cytosolic protein synthesis in mammalian cells, bacterial protein synthesis is initiated with *N* formylmethionine and the newly synthesized polypeptide is converted to mature protein through the sequential removal of the *N*-formyl group and methionine by peptide deformylase and methionine amino peptidase, respectively **(Scheme 1)**.[27,28,29] The formylation-deformylation of proteins is a unique property of bacterial metabolism and is not found in mammalian protein biosynthesis, thus making it an attractive target for the discovery of novel antibiotics.[30] The metalloproteinase peptide deformylase (PDF) has the critical role in eubacteria of removing the formyl group in formyl-methione initiated protein synthesis. This is necessary because the methionine aminopeptidase (MAP) cannot hydrolyze N-blocked polypeptides.



Scheme 1: Role of PDF and its inhibitors in bacterial protein synthesis

PDF is potentially an attractive target for antibacterial drug design due to following properties (a) gene (*def*) associated with PDF activity is vital to bacterial growth (*in vitro*)[9,31] (b) it has broad spectrum activity as offered by various studies[32] (c) the methionine formylation and deformylation cycle is not involved in eukaryotic cytoplasmic protein synthesis[28] (d) various well-studied metallo hydrolases, including thermolysin and matrilysin etc. have similar active center as in PDF which thus provide etiquette for antibacterial design.[20,21,22,33,34] Essentiality of PDF for bacterial survival has been shown by genetic studies.[35] Both PDF and MAP are essential for growth in *Escherichia coli*.[29,36] PDF inhibitors have two different effects for bacterial growth, a direct bacteriostatic or bactericidal effect and an indirect proinflammatory effect by the production of proinflammatory peptides.[37]

PDF Inhibitors: An Antibacterial Agent

David R P Guay divided PDFIs into two categories (a) peptide PDFIs and (b) non peptide PDFIs. Non-peptidic PDF inhibitors are not included in this article due to their insufficient antibacterial activity. They have been previously reviewed by Clements, J. M. *et.al.*[38] Classification of PDFIs as given by David R P Guay as shown in table1.

Actinonin

Actinonin (Figure 1), was the first reported potent PDF inhibitor.[33] It was first obtained from the culture filtrates of a *Streptomyces* species and was the first known naturally occurring hydroxamic acid (R-CO-NHOH).[39] It is a hydroxamate containing PDF inhibitor. The hydroxamate-containing compounds are very potent inhibitors against PDF and most of them are currently in clinical trials.[40] Although several different chelating groups have been reported in the literature, but hydroxamate remains the preferred group. The hydroxamate group of actinonin evidently acts as the chelating group to bind the metal ion of the enzyme and has been described as a potent, competitive, and reversible inhibitor of PDF.[41] Actinonin has been shown to be active against Gram positive bacteria, with some evidence of activity against Gram negative bacteria. The biological activity coupled with its chemical stability and low toxicity makes actinonin an interesting antibiotic.[42] Actinonin has slow dissociation rate from EI (Enzyme-Inhibitor) complex that can extend the efficacy of the molecule further than its clearance rate from systemic circulation. This slow off-rate of

actinonin makes it beneficial for drug development.[43] IC50 values for actinonin were found 90, 3, 0.8 and 11 nM for Zn-PDF (*E. coli*), Ni-PDF (*E. coli*), Fe-PDF (*E. coli*), and Ni-PDF (*S. aureus*), respectively. Most of the PDFIs have the same generic structure as actinonin but in contrast to actinonin, some of the newly described PDF inhibitors are also active *in vivo* when administered both intravenously and orally.[44] Phase I clinical studies were recently completed for two such potent peptide deformylase inhibitors (BB-83698 and VIC-104959 (LBM-415; NVP-PDF-713) derived from actinonin which have now gone on to phase II and III trials.[18, 45]

Different biologically active derivatives of actinonin

LBM41

LBM415 (Figure 2) is a new antibacterial agent belonging to the peptide deformylase inhibitor class. The compound exhibited potent *in vitro* antibacterial activity against a wide spectrum of important pathogens, including Gram-positive, particular Gram-negative and intracellular bacteria. LBM415 demonstrated potent activity against clinical strains of *Staphylococci, Streptococci, Enterococci, Haemophilus influenzae* when evaluated previously in comparison with other antibiotics. Amongst various PDFIs, LBM415 (NVP PDF-713)[46] is one of the first compounds advanced to clinical trials for the oral and parenteral treatment of respiratory tract and skin infections caused by susceptible Gram positive and Gram negative organisms. *Osborne, CS et al.*[42] showed that LBM415 is active *in vivo* against systemic infections caused by susceptible and resistant strains of *S. aureus* and *S. pneumoniae*. The pharmacokinetics of VIC-104959 is characterized by rapid oral absorption with an oral bioavailability of 62% and 22 – 101% in mice and rats, respectively.[47]

BB-83698

BB-83698 (Figure 3) has progressed to Phase I clinical trials. BB-83698 displays excellent *in vitro* potency against *S. pneumoniae* (MIC90=0.25 – 0.5 μg/ml), however, the compound was found less potent against *H. influenza* (MIC90 = 16 – 64 μg/ml). BB-83698 was also very susceptible to other *Streptococci*, such as *S. pyogenes* and *S. agalactiae*.[48] Pharmacokinetic studies point out that BB-83698 has well oral absorption with 55 – 88% oral bioavailability in mice.[49] Chikhi A and Bensegueni A showed that indol-group and its derivatives can represent a novel class of inhibitors specifically active on bacterial PDFs.[46]

Sch-382583

Schering-Plough group described the isolation and structure of Sch-382583(figure 4) from *Streptomyces*[50] with a *K*i of 60 nM, this piperazic acid-containing pseudopeptide is the most potent carboxylic acid inhibitor of PDF reported to date.

Other actinonin derivatives

These are two another derivatives of actinonin. (Fig.5 & 6)

SAR of PDF Inhibitors (PDFIs)

British Biotech (now Vernalis) and Versicor (now Vicuron) [1] are the groups who are playing advanced role in study of PDFIs. The work done by these and other groups ultimately led to the understanding of basic requirements for PDF inhibitors as drug candidates. The different functionalities responsible for biological activity are outlined below in figure 7.

P1 side chain

Linear aliphatic chains of 4 or 5 atoms and cycloalkylmethyl groups are optimal for activity as examined on analogs of BB-3497.[51]

P2 side chain

t-Butyl group have shown the best activity. This *t*-butyl group provides improved stability and oral bioavailability due to sterically shielding the neighboring amide bonds. In another study of optimization for P2 side chain in VRC-3375

produced excellent inhibitory action when L-proline is attached with this side.[52]

P3 side chain

P3' served as ideal group for balanced properties including pharmacokinetic properties, physico-chemical properties such as solubility, balance of antibacterial spectrum, *in vivo* efficacy and tolerability. Partial studies with analogs of BB-3497 indicated that amines such as pyrrolidine, morpholine or substituted piperazines to be optimal for PDF inhibition and antibacterial activity[51]. By using 22 building blocks by combinatorial approach to VRC- 3375 on P3 site pyrrolidine was the best group reported by the authors regarding antibacterial potency, cytotoxicity and selectivity.[53]

Metal binding site

The comparative research noticed that hydroxamates are the best groups for this metal binding site. N-formyl-hydroxylamines (reversed hydroxamic acids) have also been tested but were found less potent while hydroxamic acids (hydroxamates) were found to be the most potent enzyme inhibitors.[54] Replacement of hydroxamic acid by carboxylate has a negative impact on enzyme inhibition by roughly three orders of magnitude resulting in loss of antibacterial activity.

Activity of Actinonin and Different Selected PDFIs against Various Species

The activity of actinonin and its selected derivatives is summarized in Table 2.

CONCLUSION

The PDF inhibitors represent one of the few examples of combining a target-based rational drug design and a medicinal chemistry approach in the field of antibacterial drug discovery. Only the peptide deformylase inhibitors (PDIs) have shown any real promise, with some advancing to phase I human trials. Lead PDF inhibitors possess a broad spectrum of activity, and the most promising data are the equal efficacy of the PDF inhibitors against susceptible and multiple drug-resistant bacteria *in vivo*. Metalloprotease have a spectrum of activity consistent with treatment of respiratory tract infections (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and atypical respiratory pathogens. Additionally, these inhibitors can be bactericidal against *S. pneumoniae* and *H. influenzae*. They are active against *Streptococci* but their activity against *Staphylococci* and *Enterococci* is variable.

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Table 1: Classification of PDFIs

Name of Class	Examples
Peptide Inhibitors	Actinonin BB-83698(British Biotech) BB-3497 (British Biotech) VRC 3375 VRC 4887 (NVP PDF 386) LBM-415 (NVP PDF 713)
Non peptide Inhibitors	β-sulfonylhydroxamic acid β-sulfinylhydroxamic acid 2 Bicyclic hydroxamic acids

Table 2: Activity of actinonin and different selected PDFIs against various species

ORGANISM	CLINICAL CANDIDATE	MIC [µg/ml]	ORGANISM	CLINICAL CANDIDATE	MIC [µg/ml]
S. pneumonia	Actinonin[33]	8	*H. influenza*	Actinonin[33]	1 – 2
	BB-83698[55]	0.06 – 1		BB-83698[55]	0.06 – 128
	BB-3497[56]	2 - >8		BB-3497[56]	0.06 – 8
	VRC-3997[57]	1 – 2		VRC-3997[57]	2 – 8
	VRC-3375[53]	8 – 32		VRC-3375[53]	2 – 4
S. aureus	Actinonin[33]	8 – 16	*E. coli*	Actinonin[33]	>64
	BB-83698[55]	1 – 256			
	BB-3497[56]	4 – 16		BB-3497[56]	8
	VRC-3997[57]	0.5 – 2		VRC-3997[57]	>64
	VRC-3375[53]	1 – 4		VRC-3375[53]	>64
S. pyogenes	Actinonin[33]	8	*Enterococcus* spp.	Actinonin[33]	32 – 64
	BB-83698[55]	0.015-0.25		BB-3497[56]	8 – 32
	VRC-3375[53]	64		VRC-3375[53]	32 – 64

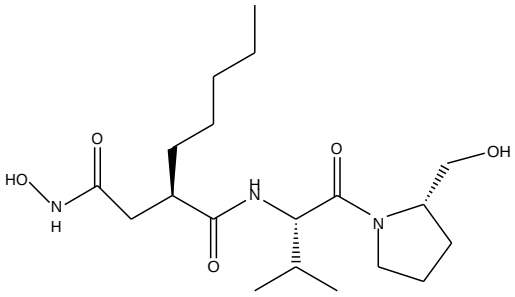

Figure1: Structure of Actinonin

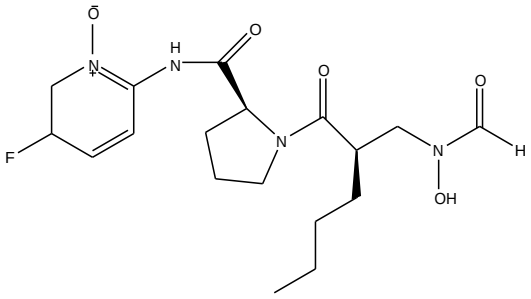

Figure2: NVP LBM-415

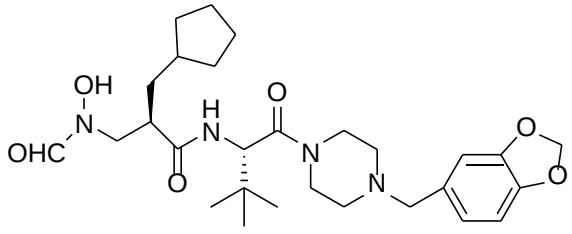

Figure3: BB-83698

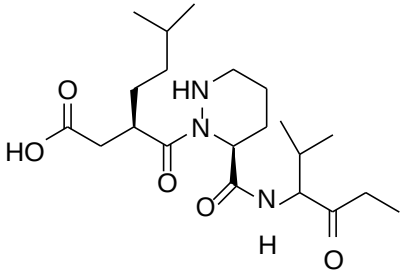

Figure4: Sch-382583

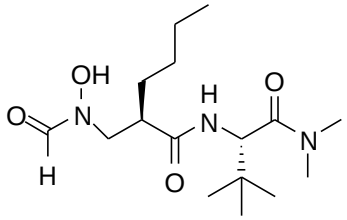

Figure5: BB-3497

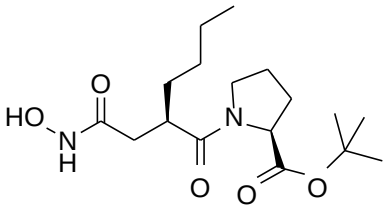

Figure6: VRC-3375

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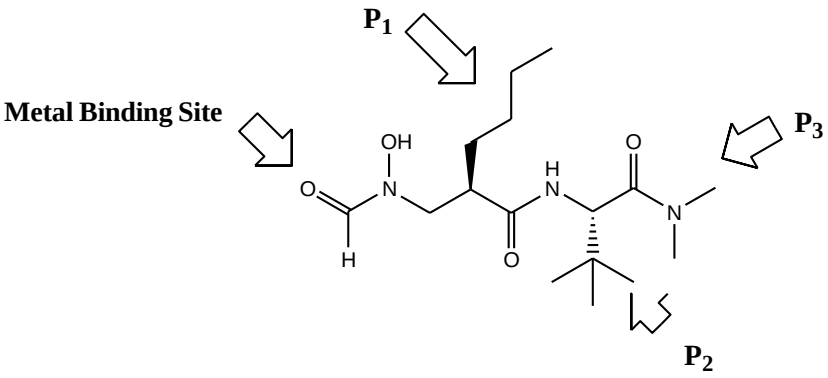

Figure7: General SAR of PDF inhibitors

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