Indian Discovery Effort in the Quest of Novel Antibiotics

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3.1 Background

India's rise as a major pharmaceutical hub is a result of focused intellectual and financial investments made by several domestic pharmaceutical companies over the past few decades. India continues to manufacture and supply a significant fraction of the global demand for pharmaceutical products. Beginning mid-1970s and until 2005, when India did not accept product patents, the domestic pharmaceutical industry acquired significant expertise in the bulk drug manufacturing (APIs) and formulation processes. Armed with this expertise, India expanded its position as a significant global generic pharmaceutical player. While this is a well-known story, what is not widely recognized is that India quietly prepared itself from 1995 onward for the era post TRIPS, which implemented product patent with effect from January 2005. For the pharmaceutical industry, to remain competitive, this development threw a challenge of taking the path towards innovation. As a result, several domestic companies ventured into the discovery and development of innovative drugs. The chapter provides a brief account of India's contribution to the discovery and development of innovative antibacterial agents and compositions.

3.2 Need for Antibacterial Drug Discovery and Development

Globally, since a long time, bacterial infections have remained a significant cause for morbidity and mortality. Despite several efforts, the human race has registered limited success in its fight against bacteria. Although, structurally, bacteria are a simple living organism, they are also smarter. Bacteria reproduce quickly and in doing so; they often develop sophisticated mechanisms to overcome the effect of

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antibiotics that were earlier effective in killing them. Thus, there is a continual need for developing newer antibiotics to treat infections caused by resistant bacteria (API Synthesis International 2016). An exhaustive study sponsored by the UK Government has estimated that there is a continual need to discover effective antibiotics in coming years. Otherwise, the anticipated burden of deaths from antimicrobial resistance (AMR) could reach ten million lives each year by 2050, implying a cumulative cost of USD 100 trillion to the global economic output (based on a report drafted by Jim O'Neil). The problem in tackling AMR also lies in the fact that many of the major pharmaceutical companies in the US and Europe have abandoned antibacterial research. It is for this reason that companies developing newer antibacterial agents assume importance. As we read this chapter, what brings us solace is that several Indian companies have made their sincere efforts to address the AMR issue by engaging in the discovery of novel antibiotics.

3.3 Antibacterial Discovery and Development in India

Antibacterial research has been actively pursued in India for about 50 years. This consistent long-term interest highlights the fact that India continues to experience a higher burden of infectious diseases. Even during the resource-constrained period of pre-1970s, government entities in India undertook initiatives in antibiotic research. Few of the developed products were meant for domestic consumption and thus did not traverse through high standards of the US and European regulators. Most of that research was limited to publications on newer observations.

The scientific foundation of antibacterial drug discovery in India was genuinely laid in the early 1970s by the German pharmaceutical giant Hoechst, which initiated a well-funded and sustained microbial secondary metabolite screening program at its primary research centre in Mumbai. Post-1990s, several Indian pharmaceutical companies joined the foray of discovering new antibiotics. As observed in other parts of the world, the onus of discovering new antibiotics in India was primarily hinged on pharmaceutical companies, and their programs met with varying level of success. Indian antibiotic research was much helped by the previous contribution of companies in US, Europe and Japan. However, post 2000, these multinational companies did not sustain their discovery programs amid increasing complexity of discovering newer antibiotics effective against multidrug-resistant (MDR) pathogens and low economic returns generated by most new antibacterial drugs. At the same time, widespread AMR kept pounding the healthcare system, compromising its ability to fight infections. In particular, India and China are at a higher risk of a substantial infectious disease burden. Against this background, the narratives given below present a glimpse of 50 years of India's contribution to antibacterial drug discovery and development.

3.3.1 Hindustan Antibiotics Limited

Hindustan Antibiotics Limited, a Government of India owned company, initiated one of the first indigenous antibiotic research in India. This Pune-based firm pursued a fermentation-based antibiotic discovery program, which led to the discovery of several antifungal compounds, including hamycin (Thirumalachar 1966), a polyene antibiotic (Fig. 3.1) structurally close to amphotericin B. Hamycin exhibited an inhibitory concentration of 0.01 mg/L against *Candida albicans*. The drug was

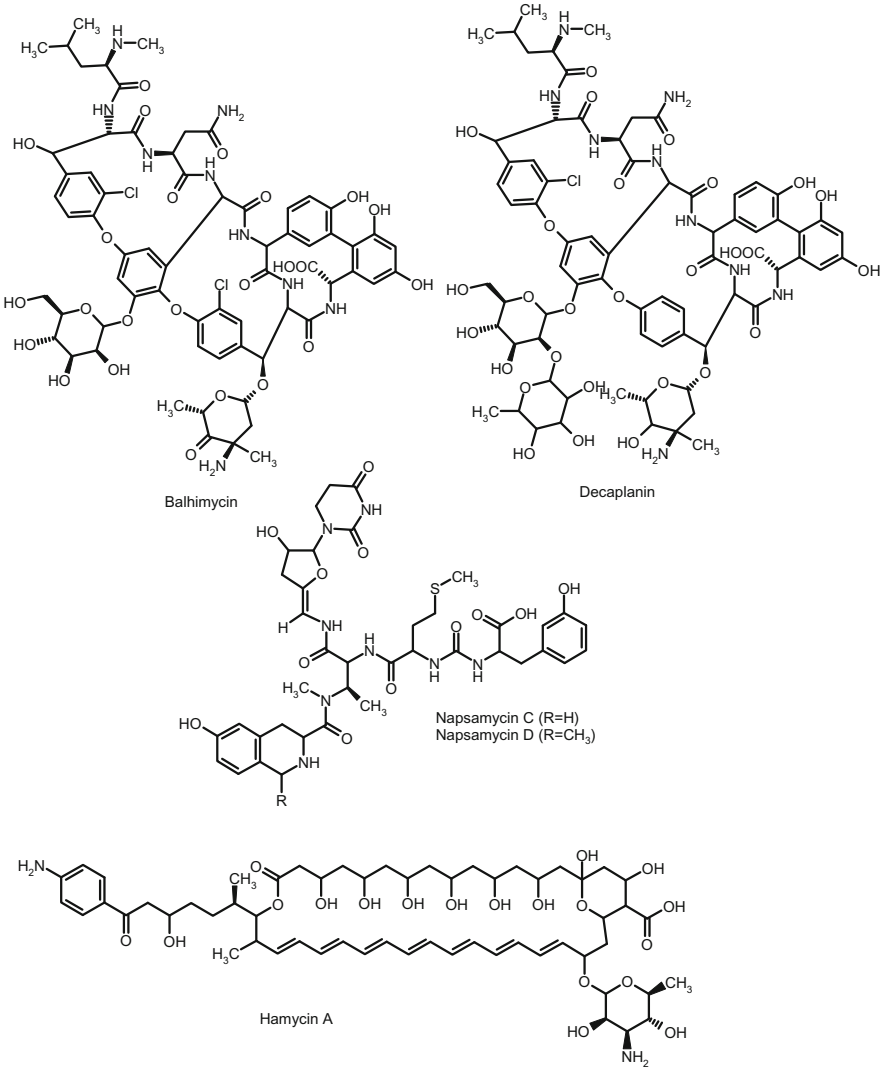


Fig. 3.1 Structures of natural products discovered by Hoechst and Hindustan Antibiotics Ltd

used as a topical antifungal in the form of glycerine suspension for the treatment of oral thrush caused by *C. albicans* and otomycosis incited by *Aspergillus niger*; or in the form of lactose tablets for the treatment of vaginal moniliasis. Hamycin was launched in 1971, but is no longer marketed presently.

3.3.2 Hoechst India Limited

Hoechst, for the first time, brought a systematic natural product discovery culture in India by instituting a sustained antibacterial discovery program in the early 1970s. The German parent Hoechst had long demonstrated its capability of discovering novel antibacterial agents, with the earliest discovery of Salvarsan for treating syphilis in 1910. In India, Hoechst focused on the discovery of microbial fermentation-based novel antibiotics. For nearly 25 years (1972–1998), about 75 scientists at Hoechst's research centre in Mumbai isolated several soil microorganisms from samples collected from different parts of India. It was assumed that India's diverse range of climatic and soil conditions would give rise to diverse microorganisms capable of synthesizing novel antibiotics. Some of the clinically interesting antibiotics discovered were anti-MRSA (*methicillin-resistant Staphylococcus aureus*) agents (Fig. 3.1) such as balhimycin (Nadkarni et al. 1994), decaplanin (Sanchez et al. 1992), napsamycin (Chatterjee et al. 1994) and mersacidin (Chatterjee et al. 1992). Balhimycin and decaplannin were novel glycopeptides similar to the widely used vancomycin, while mersacidin and napsamycin belonged to a new structural class. The striking feature of napsamycin was its specific activity against *Pseudomonas aeruginosa*, a pathogen which is tough to tackle to date.

Even with active support of structural elucidation experts from Hoechst Germany, it took a couple of years for the revelations of complex structures of these novel antibiotics. There were several technical challenges in isolating pure antibiotics from the fermentation broth. One of the issues was that during the fermentation cycle, several closely similar structural analogues were co-produced and co-purified along with major antibiotic of interest. This created a considerable difficulty in establishing the structure of the key active component. Improvement of fermentation yield and the optimization of the downstream process to recover pure antibiotic from the fermentation broth took several months of effort. Structural complexity deterred Hoechst from undertaking further chemical optimization of these antibiotics, although they belonged to a novel class and offered the advantage of a new mechanism of action.

In subsequent years, several companies focused on natural products or fermentation-based antibacterial discovery. However, these efforts did not lead to success due to complexities associated with the development of natural products such as the lack of appropriate infrastructure, a dearth of scientific skills and heightened quality/analytical standards dictating the evaluation of highly purified preparation in clinical studies. Therefore, despite the initial excitement, natural product-based antibiotic discovery research met with a disappointing outcome. The challenge of transforming a natural product into a '*drugable antibiotic*' persists

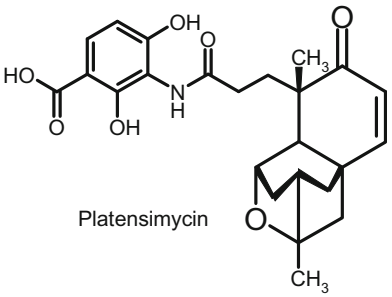


Fig. 3.2 Platensimycin by Merck

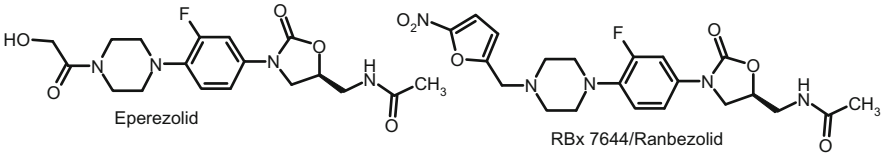


Fig. 3.3 Modification of eperezolid by Ranbaxy

even in twenty-first century; a stark reality evident from the example of platensimycin discovered by Merck (Fig. 3.2), which ultimately remained merely a subject of scientifically interesting publication. Given the inherent pharmacological limitations linked with natural products, in recent years, not even a handful of clinically viable natural product-based antibiotics could be developed.

Taking a cue from this, in the 1990s, many global and Indian companies focused their discovery program on medicinal chemistry-based antibacterial drug discovery. These include Ranbaxy Laboratory, Dr Reddy's Laboratory, Wockhardt Limited, Orchid Pharmaceuticals, Zydus Cadila, Aurigene, Vyome Biosciences, Panacea Biotech, Bug Works and Vitas Pharma.

3.3.3 Ranbaxy Laboratories

For over 15 years, antibacterial research at Ranbaxy focused on fluoroquinolones, oxazolidinones and macrolide/ketolide class of agents. Ranbaxy's oxazolidinone research program optimized Pharmacia's lead compound eperezolid (PNU-100592, a backup clinical candidate for highly successful anti-MRSA drug linezolid). The company discovered an equipotent bio-isosteric replacement at piperazine ring of eperezolid in the form of substituted methyl-*N*-piperidine. Various five-member rings were attached with or without methylene bridge on to the piperazinyl-phenyl-oxazolidinone core, to provide potent oxazolidinone NCEs (Mehta 2001). The research produced two candidates for clinical development, MRSA-active ranbezolid (Fig. 3.3; RBX 7644) and MDR-TB-active RBX 8700.

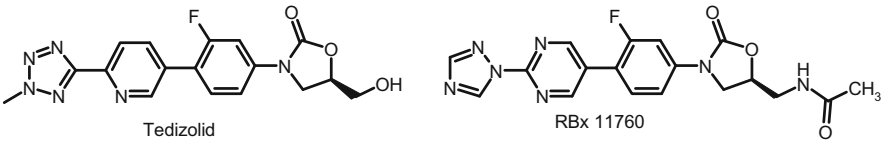


Fig. 3.4 Modification of tedizolid by Ranbaxy

Ranbezolid showed in vitro MICs similar or slightly superior to linezolid (PNU-100766 Zyvox). Ranbezolid displayed activity against all anaerobes (Gram-positive and Gram-negative) (Das et al. 2005). Anti-anaerobes activity of ranbezolid was ascribed to not being a substrate of the efflux pump. Importantly, unlike other nitrofuran compounds, ranbezolid was reported to be free of DNA damaging activity in the Ames test, micronucleus test, chromosomal aberration test, and macromolecular synthesis in anaerobes test. Ranbezolid exhibited favourable pharmacokinetic and safety profile in the preclinical studies. The ranbezolid development progressed up to phase 1; however, further clinical development was not pursued.

Another biaryl oxazolidinone from Ranbaxy, RBX 11760 (Fig. 3.4) was inspired by a recently marketed compound tedizolid. RBX 11760 exhibited 2–4× lower MICs than linezolid which were comparable to that of tedizolid. It showed good oral bioavailability (60% and 72% in mouse and rat, respectively), with low plasma clearance and low to moderate volume of distribution in mouse and rat. It also displayed higher in vivo efficacy compared to tedizolid in the infection model (Barman et al. 2016).

RBX 11760 was also investigated for the possibility of treating *Clostridium difficile* infections, as it exhibited good MICs against *C. difficile* isolates, in the range of 0.5–1 mg/L. The drug showed concentration-dependent killing of *C. difficile* ATCC 43255 and *C. difficile* 6387 up to 2–4 × MIC (1–2 mg/L). However, further development of RBX 11760 was not pursued (Mathur et al. 2011).

Ranbaxy's macrolide research ended up identifying 2-fluoro-ketolide compounds. RBX 14255 (Fig. 3.5) was active against erythromycin- and clarithromycin-resistant *C. difficile* strains, including the epidemic BI/NAP1/027 strain. It exhibited better efficacy than metronidazole and vancomycin in the Golden Syrian hamster animal model, against *C. difficile* infection (Kumar et al. 2012). However, the development of RBX 14255 was halted in 2008, after the preclinical stage.

3.3.4 Dr Reddy's Laboratory

Dr Reddy's Laboratory (DRL) discovery activities focused on tetracycline and oxazolidinone class of antibacterial compounds. A methylthiocarbamate analogue of oxazolidinone, DRF 8417 (Fig. 3.6) progressed to preclinical studies. As an antibacterial agent, DRF 8417 was 2–4× more active than linezolid and its in vivo efficacy in Swiss albino mice was comparable to linezolid (Sreenivas et al. 2007).

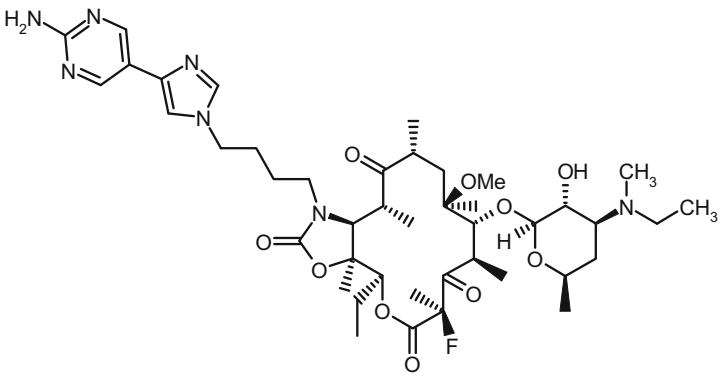


Fig. 3.5 2-Fluoroketolide by Ranbaxy

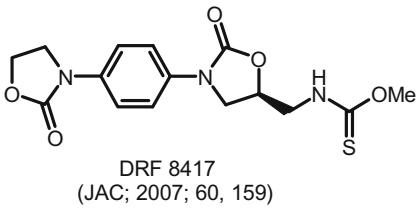


Fig. 3.6 Non-fluoro-phenyl thioacetamide by Dr Reddy's Laboratories

Additional reports on the progress of DRF 8417 are not available. As per company's website, from the oxazolidinone and 1,2,3-triazole program, four other compounds progressed up to preclinical stage: DRF 11057, DRF 13792, DRF 16048 and DRF 19440. Structures of these compounds are not available in the public domain as none of them progressed beyond preclinical studies.

3.3.5 Nicholas Piramal

In 1999, Nicholas Piramal acquired Hoechst's research centre in Mumbai and continued natural product-based antibacterial discovery program until 2015–2016. During this period, a novel antibiotic PM 181104 (Fig. 3.7) was developed jointly with the National Institute of Oceanography, Goa. PM 181104 has a complex structure and exhibited potent activity against MRSA and vancomycin-resistant enterococci (Mahajan 2009). It is a 23-member macrocyclic peptide isolated from bacterial species *Kocuria* (ZMA B1/MTCC 2569) fermented broth. The compound displayed extremely high potency against MRSA and *S. epidermidis* with MICs ranging from 0.00781 to 0.0625 mg/L.

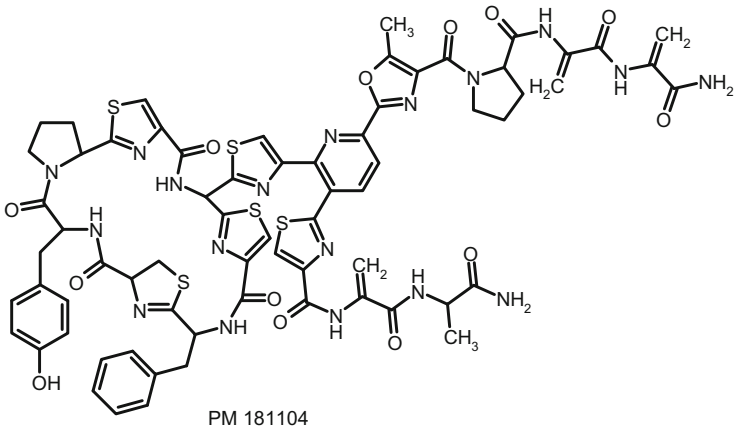


Fig. 3.7 Macrocyclic peptide by Nicholus Piramal

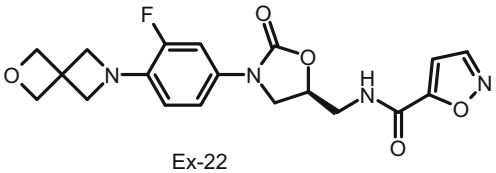
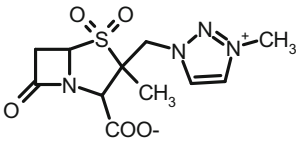


Fig. 3.8 Spiro-oxazolidinone by Nicholus Piramal

In a systemic infection animal model of *S. aureus* E7 (MRSA), PM 181104 showed PD_{100} at a dose of 5 mg/mL as compared to linezolid 25 mg/mL (EP 2010202). PM 181104 progressed up to the preclinical stage, after which no progress was reported.

As part of academia-industry collaborative research, Piramal and three other institutes, VIT University (Vellore), NMIMS (Mumbai), and National Chemical Laboratory (Pune), identified spiro analogues of oxazolidinone by replacing morpholine moiety of linezolid with a spiro ring: 2-oxa-6-aza spiro[3.3]heptane (Gadekar et al. 2016). This modification was aimed at minimizing the liability of oxidative metabolism associated with morpholine moiety in linezolid. Various further modifications at C5 oxazolidinone site displayed both antibacterial and antitubercular activity. The most potent compound was example-22 (Fig. 3.8), which was less active than linezolid.



OCID101
Ex-1
(US 7687488)

Fig. 3.9 Zwitterionic analogue of tazobactam by Orchid

3.3.6 Orchid Pharma

The discovery program at Orchid also started with oxazolidinone (OCID0050) class and then moved to the carbapenem-based discovery program, in collaboration with Merck Sharp Dohme. From publications and conference posters, it appears that Orchid's oxazolidinone NCE OCID0050 was once a promising candidate for development. Although the chemical structure of OCID0050 is not disclosed, the publication states that OCID0050 was a piperazinyl thioacetamide oxazolidinone (Paul-Satyaseela et al. 2009), two- to fourfold more active than linezolid, with activity even against resistant strains. There is no further information on the development of this compound.

Orchid's well-recognized strength in manufacturing the β-lactam class of drugs was leveraged in the discovery of novel β-lactamase inhibitor OCID 5090 (Fig. 3.9). A combination of β-lactam antibiotic cefepime and OCID101 [recently named as AAI 101 or enmetazobactam] entered global phase 3 clinical trial. The combination is being developed by Allecra, Germany which in-licensed the molecule from Orchid. OCID 5090 was described in US patents (Palanisamy 2010), along with various *N*-alkyl quaternary salts of tazobactam's 1,2,3-triazole. OCID 5090 is 2–8× more effective than tazobactam in lowering MIC of piperacillin against several class A β-lactamases producing *Enterobacteriaceae*. Its superior β-lactamase inhibitory activity reflected well in vivo, as 4:1 combination of piperacillin and OCID 5090 was 2–3× superior in terms of ED_{50} than 4:1 piperacillin and tazobactam combination (Palanisamy 2014).

In a yet another in vitro study, MICs of piperacillin in combination with OCID 5090, at 1 mg/L concentration of OCID101, were found to be 1.0–4.0 mg/L against *E. coli* ($n = 6$); 2.0–8.0 mg/L against *K. pneumoniae* ($n = 6$); 2.0 mg/L against *E. cloacae* ($n = 2$); and 16.0–32.0 mg/L against *P. aeruginosa*.

In the in vivo mice infection model, a combination of piperacillin and OCID 5090 (4:1) was 2–2.5× superior to piperacillin and tazobactam (4:1) combination. For instance, ED_{50} values were 22.62 (mg/kg b.w.) as compared with 37.22 (mg/kg b.w.) for *E. coli* MRO 10006; 24.88 (mg/kg b.w.) versus 58.81 (mg/kg b.w.) for *E. coli* MRO 10007, and 34.89 (mg/kg b.w.) versus 99.48 (mg/kg b.w.) for *K. pneumoniae* MRO 11008 (Paul-Satyaseela et al. 2014).

Rodent PK of OCID 5090 showed $AUC_{0\text{-}4}$ of 5.3 μg h/mL as compared with tazobactam AUC of 2.138 μg h/mL. However, the elimination half-life was almost the same for two β-lactamase inhibitors (0.272 h versus 0.269 h).

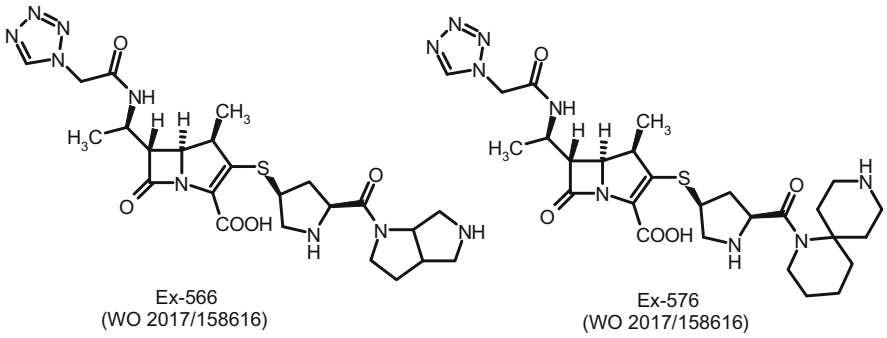


Fig. 3.10 Carbapenem analogues by Orchid and Merck

OCID 5090 was also studied in combination with carbapenem such as imipenem. The US patent application (Palanisamy 2014) describes in vivo efficacy in mice systemic infection model involving KPC2 harbouring *K. pneumoniae*, where ED_{50} of imipenem + OCID 5090 combination was 2.2 mg/kg (OCID 5090 at 64 mg/kg) while the same for the imipenem and tazobactam combination was 4 mg/kg (tazobactam at 64 mg/kg). Standalone imipenem provided ED_{50} value of 8.9 mg/kg. The same patent also claims the use of OCID 5090 for the detection of β-lactamases, including KPC.

Merck & Co, in collaboration with Orchid, entered into the antibacterial discovery program with the objective of modifying the meropenem nucleus. Their collaborative work is published in patent application (Balasubramanian 2017), which lists the examples where the traditional hydroxyl ethyl substituent is replaced with a substituted aminoethyl group. Many compounds exhibited potent antibacterial activity against *P. aeruginosa* ATCC 27853 (meropenem susceptible strain), with MICs being in the range of 0.25–2.0 mg/L. The representative noteworthy examples are 566 and 576 (Fig. 3.10). These compounds showed MIC of 0.5 mg/L against *S. aureus* ATCC 29213, 0.5 mg/L against *K. pneumoniae* ATCC BAA 1705 expressing KPC2, 0.06 mg/L against *E. coli* ATCC 25922, and 0.25 mg/L against *P. aeruginosa*. No further development is reported for Merck-Orchid carbapenems.

A joint publication by Manipal College of Pharmaceutical Sciences and Orchid (Aaramadaka et al. 2007) described a series of urea-oxazolidinones, where piperazinyl nitrogen is a part of urea and thiourea.

3.3.7 Aurigene

Aurigene, a contract research laboratory established by Dr Reddy's Laboratories, explored the area of FAB1 [bacterial Fatty Acid Biosynthesis 1] inhibitors. Based on the literature disclosure, all Aurigene's FAB1 inhibitors appear to be modifications of aromatic α,β-unsaturated ketone nucleus of AFN-1252 [Korean company Affinium's lead compound, which was once the compound under detailed

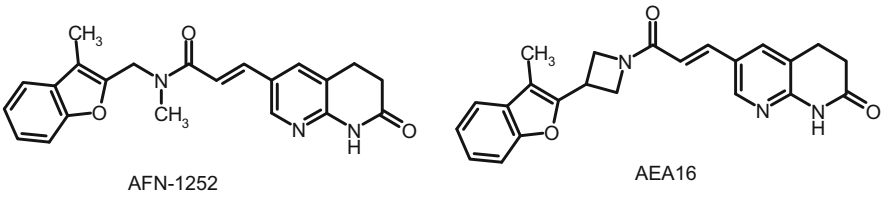


Fig. 3.11 FAB1 inhibitor AEA16 by Aurigene

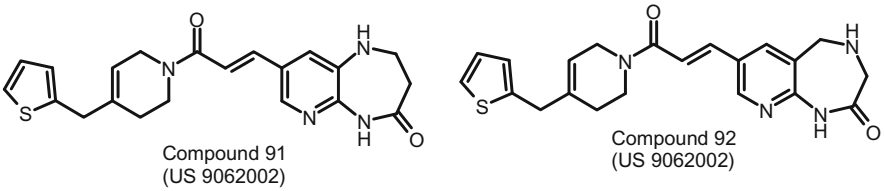


Fig. 3.12 FAB1 inhibitors by Aurigene and Pharmauji Sdn.BHD

investigation]. Aurigene's AEA16 (Fig. 3.11) progressed up to preclinical studies, and was structurally very close to AFN-1252. AEA16 showed improved mouse liver microsomal stability and PK properties as compared to AFN-1252. This property was ascribed to the closed ring structure in the form of azetidine present in AEA16, as compared to open *N*-methyl structure in AFN-1252 (Takhi et al. 2014). Extensive nonclinical studies have been published with AEA16. Cell-free FABI enzyme inhibition in *S. aureus* (IC_{50}) was reported to be 0.141 μM and MICs were in the range of 0.06–0.5 mg/L. In the murine systemic MRSA infection model, ED_{50} of AEA16 was 0.90 mg/kg/day, while the corresponding value for the reference agent AFN-1252 was 2.3 mg/kg/day. However, the development of AEA16 was discontinued in 2015. In addition, a US patent (Takhi 2015) filed jointly by Aurigene and Pharmauji Sdn.BHD, Kuala Lumpur described piperdi-3-ene analogues. Many compounds from this series were fairly active-based on their IC_{50}s and MICs. For example, compound 91 (Fig. 3.12) showed MICs of 0.25–0.5 mg/L against *S. aureus*. No further progress on any of these compounds is reported.

3.3.8 Bugworks

Bugworks is a startup, established by the ex-employees of AstraZeneca India at Bengaluru. Its molecule BWC0977 is ready to enter full-fledged preclinical studies. Aimed at overcoming multidrug resistance and minimizing resistance development, BWC0977 targets bacterial topoisomerases—gyrase and topoisomerase IV with novel interactions. Two posters (Michael et al. 2019; Hameed et al. 2018a) describe the features of BWC0977; however, the exact structure is not available.

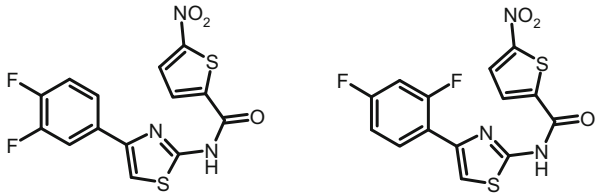


Fig. 3.13 Nitrothiophene carboxamides by Bugworks

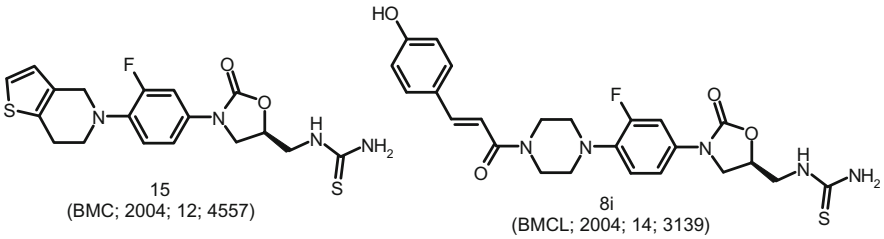
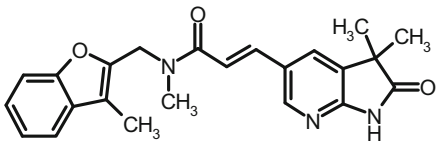


Fig. 3.14 Thiacetamide oxazolidinones by Zydus Cadila

A separate publication (Hameed et al. 2018b) describes a novel narrow-spectrum nitrothiophene carboxamide (Fig. 3.13) series derived by using a structure-based design. These compounds were optimized to overcome efflux pump mediated resistance. Moreover, the compounds were claimed to be pro-drugs that require activation in *E. coli* by specific bacterial nitroreductases NfsA and NfsB. They were active against wild-type and multidrug-resistant clinical isolates of *E. coli*, *Shigella* spp., and *Salmonella* spp. The incorporation of nitro moieties in the structure of novel antibiotic, as exemplified by ranbezolid and more recently by nitrothiophene carboxamides, is indicative of the desperation of medicinal chemists for potency optimization at the cost of potential drugability concern.

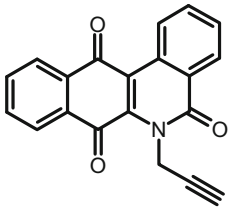
3.3.9 Zydus Cadila

Zydus also worked in the oxazolidinone antibacterial class, for a brief period. According to publications, modifications were explored in the C5 position of oxazolidinone ring such as thioacetamide and thiourea and the morpholine/pierazinyl ring of linezolid/eperezolid analogues. Thienotetrahydropyridine oxazolidinone analogues (Lohray et al. 2004a) and substituted cinnamoyl piperazinyl oxazolidinone analogues (Lohray et al. 2004b) were synthesized and compared with linezolid and eperezolid for antibacterial activities. The most active compounds from both publications were 15 and 8i (Fig. 3.14). No further progress has been reported by Zydus Cadila.



VT-02-00068
(US 9115149)

Fig. 3.15 FAB1 inhibitor by Vitas Pharma



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(ACS Med. Chem Lett.)

Fig. 3.16 MRSA active compound acting through novel mechanism by Vitas Pharma and IISER

3.3.10 Vitas Pharma

Vitas Pharma, a company based in Hyderabad, in collaboration with Cambridge University, reported another FABI inhibitor compound VT-02-00068 (Fig. 3.15), which is currently in the preclinical stage. An US patent (Rangarajan 2012) describes the features of this bacteriostatic compound, which is a modification of AFN-1252.

VT-02-00068 was studied extensively in preclinical studies. MICs of VT-02-00068 were reported to be in the range of 0.015–0.25 mg/L against several Gram-positive organisms. The compound was inactive against *E. faecalis*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis,* and *E. coli*. Metabolic stability in mouse liver microsome was established and a systemic infection model in mice with MRSA 33591 VT-02-00068 provided survival rates of 100%, 100% and 65% at intravenous doses of 30 mg/kg/body weight, 10 mg/kg/body weight and 3 mg/kg/body weight, respectively. Mutation prevention concentration was found to be 0.5 mg/L. Oral mouse PK properties were also characterized. As per Vitas Pharma's website, this compound is still in the preclinical toxicological evaluation.

Indian Institute for Scientific Education and Research (IISER), Pune and Vitas Pharma jointly reported natural product inspired redox active small molecule to overcome drug resistance in MRSA. From the publication (Khodade et al. 2014), compound 1f (Fig. 3.16) appears to be a potent MRSA inhibitor with a unique mode of action that involves enhancement of reactive oxygen species (ROS) levels in bacterial cell, thereby damaging DNA and causing cell death. The compound 1f has comparable or superior MICs than that of vancomycin. MICs against several MRSA strains are reported.

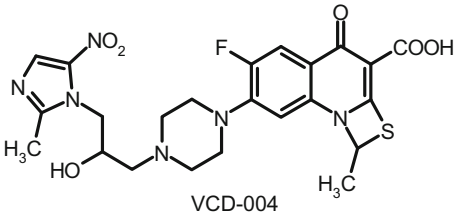


Fig. 3.17 Fluoroquinolone analogue by Vyome Bioscience

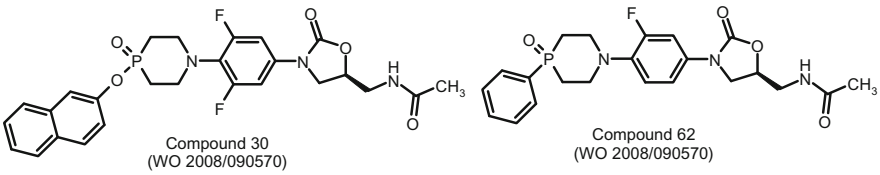


Fig. 3.18 Phosphorus analogues of oxazolidinone by Panacea Biotech

3.3.11 Vyome Bioscience

As per Vyome Bioscience's website, four molecules as topical antibacterial agents are at the advanced stage of development, including: VB-1953 in the clinical phase 2 for resistant acne; VB-6395 at the preclinical stage for facial Gram-negative folliculitis; VB-9333 (Dual Action Rational Therapeutics NCE) at the preclinical stage for treating skin pathogen-mediated implant infection; and VB-9450 (Dual Action Rational Therapeutics NCE) at the preclinical stage for treating infections caused by antibiotic-resistant acne. The structures of these NCEs are not known. Vyome's research is mainly focused on catering to unmet needs in dermatology. The recent publication (Ghosh et al. 2018) describes VCD-004 (Fig. 3.17) and four other similar compounds. These are fluoroquinolones with 2-methyl-5-nitro-imidazole structure. Such chemical moieties are generally not considered suitable for systemic use of a compound to treat disseminated infections. VCD-004 shows high potency against resistant *P. acnes*, along with excellent in vivo efficacy. VCD-004 has improved mode of DNA gyrase binding and additional binding with QBP, which could translate in lowering the resistance development propensity (as indicated by low MPC/MIC ratio) as compared to clindamycin, the currently used drug. It has optimal skin penetration and a potent anti-inflammatory impact via the reduction of pro-inflammatory cytokine (IL-6), independent of its antibacterial action.

3.3.12 Panacea Biotech

Panacea worked in the area of oxazolidinones. PBL 2270 oxazolidinone was in the preclinical developmental stage, but the exact structure of this compound is not

known. A patent application (Jain 2008) by Panacea describes modifications of linezolid at morpholine ring and by incorporating phosphorus atom in place of oxygen of morpholine. In vitro MICs of 15 compounds are reported to be comparable or superior to linezolid. The MIC of compounds 30 and 62 (Fig. 3.18) is one-fold lower than that of the linezolid in MSSA and MRSA strains and 4x lower in *E. faecalis* (susceptible) and *E. faecium* (vancomycin-resistant).

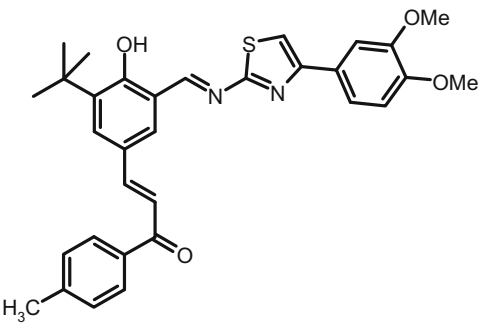
3.3.13 Central Drug Research Institute

Central Drug Research Institute (CDRI), a leading government research laboratory, is also active in the development of antibacterial agents. Publications (Sashidhara et al. 2015) from CDRI described a new class of hybrids synthesized using a pharmacophore hybridization approach. A series of novel hybrids possessing chalcone and thiazole moieties were synthesized and evaluated for their antibacterial activities. This class of agents exhibited potency against *S. aureus* and in particular compound 27 (Fig. 3.19) exhibited potent inhibitory activity relative to other synthesized hybrids.

Furthermore, the haemolytic and toxicity data demonstrated that compound 27 was non-haemolytic and nontoxic to mammalian cells. The in vivo studies utilizing the *S. aureus* septicaemia model, demonstrated that compound 27 was as potent as vancomycin (Sashidhara et al. 2015). Another publication (Yadav et al. 2015) from CDRI describes tricyclic dihydrobenzoxazepine and tetracyclic indole derivatives, which specifically target bacterial DNA ligases without cross pharmacological interaction with human DNA ligase. Unfortunately, no further systematic development of these compounds is reported to date.

3.3.14 Wockhardt Limited

For over 20 years, Wockhardt has focused on developing end-to-end antibacterial drug discovery capability to discover novel antibacterial agents; to address several



Compound 27

Fig. 3.19 Chalcone and thiazole hybrid by CDRI

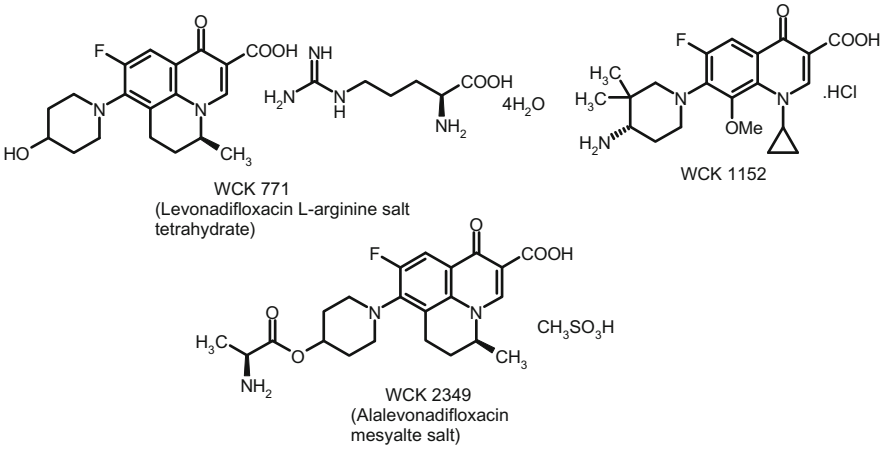


Fig. 3.20 Fluoroquinolones by Wockhardt

unmet medical needs; and progress them to advance stages of clinical development. A discovery team of 125+ scientists at Wockhardt has invested its resources and efforts in designing new chemical entities (NCEs) aiming at clinically validated bacterial targets. This approach was guided by the fact that it ensures a reasonable level of *drugability* for a new drug candidate. Accordingly, discovery program at Wockhardt focused on targets such as bacterial DNA gyrase/topo IV inhibitors (fluoroquinolones), protein synthesis inhibitors (oxazolidinones and macrolide/ketolide), β-lactam β-lactamase inhibitor and non-β-lactam enhancers of β-lactam antibiotics in addition to β-lactamase inhibitors belonging to 1,6-diaza-bicycly-spiro [3.2.1] octanes class (DBO). Remarkably, from each class, the team was able to identify clinical candidates, with two of them gaining market approval and others progressing to the final Phase III stage of clinical development.

The salient chemical features of Wockhardt's NCEs are chiral molecules synthesized from noncommercial synthons. These molecules were put through discriminating biological tests at an early stage, instead of the sequential battery of traditional tests. The efforts have yielded six drug candidates; WCK 771/WCK 2349 (Fig. 3.20; for acute bacterial skin structure and soft tissue infections, Indian NDA approved); WCK 1152 (Fig. 3.20; for respiratory tract infections, development halted midway of phase 1); WCK 4873 (Fig. 3.22; for community-acquired pneumonia, global phase 2 completed successfully and slated to enter Phase III in India); WCK 4282 (for contemporary widely encountered MDR Gram-negative infections, global Phase III study to commence in second half of 2021) and WCK 5222 (for severe life-threatening XDR\MDR Gram-negative infections, Phase 3 scheduled in 2021). All the clinical phase NCEs of Wockhardt have been designated as QIDP (qualified infectious disease product) by the US FDA (Preston et al. 2019), based on their potential to treat a range of clinically important resistant pathogens.

Wockhardt's first clinical candidate WCK 771 (INN: levonadifloxacin; Fig. 3.20) represents a serendipitous find resulting from a quest for a safe broad-spectrum anti-MRSA drug with bactericidal action to address the gaps in the then prevailing well-established MRSA drugs—vancomycin/teicoplanin and daptomycin (de Souza et al. 2005). The major limitation perceived by the clinicians in the treatment of MRSA infections is the lack of oral therapy option and suboptimal performance (reported rates of clinical efficacy ~60%) of marketed anti-MRSA agents in the treatment of MRSA-caused pneumonia and blood stream infections. During 1999–2000, Wockhardt's investigations on a topical anti-acne cream, developed by the Japanese company Otsuka, based on a racemic mixture of nadifloxacin, revealed that its levorotatory isomer S-(-)-nadifloxacin shows excellent anti-MRSA activity and good tolerability in rodents when injected intravenously at relatively higher doses. Further research over the next 5 years led to the identification of injectable drug WCK 771, which is the first ever antibacterial agent in the form of amino acid arginine salt of S-(-)-nadifloxacin, designated as levonadifloxacin by WHO. WCK 771 was selected as a clinical candidate based on its superior injection site tolerability and safety at high intravenous doses. More than 3 years (2002–2006) of intensive prodrug-based research, involving the designing of >50 prodrugs, led to the discovery of the first ever antibacterial oral prodrug (alalevonadifloxacin, WCK 2349) (Patel 2007), which employs amino acid L-alanine as a prodrug moiety.

Another clinical candidate identified at Wockhardt was WCK 1152 (Fig. 3.20), 'S' enantiomer of racemic NCE 8-methoxy quinolone WCK 919. This compound showed potent activity against levofloxacin resistant *S. pneumoniae* strains (Al-Lahham et al. 2005) and progressed up to Phase-1 human clinical studies. On the other hand, 'R' enantiomer WCK 1153 showed unacceptable genotoxicity in preclinical studies. Even, the 'S' enantiomer WCK 1152 did not progress further because it caused unacceptable side effect of dose-dependent reversible visual disturbance, an uncommon adverse effect unlike that of the classical cardiac toxicity linked QT interval prolongation, usually associated with 8-methoxy fluoroquinolones.

To harness the advantage of anti-MRSA activity of levonadifloxacin and overcome vein irritation (phlebitis) at injection site observed with sodium salt, several amino acid salts such as L-lysine salt and L-arginine salt of levonadifloxacin (WCK 771) were prepared. The phlebitis free L-arginine salt of levonadifloxacin was selected as a clinical candidate. As an intravenous infusion, WCK 771 has undergone several Phase-1 and clinical pharmacology studies in the USA and Phase 2 and Phase 3 clinical trials in India. Based on successful completion of ABSSSI (acute bacterial skin structure and soft tissue infection) Phase 3 study in India, an NDA was filed with DCGI. In January 2020, Wockhardt received approval for manufacturing and marketing of levonadifloxacin and alalevonadifloxacin under the brand name EMROK.

Since levonadilfloxacin was not orally bioavailable due to its poor aqueous solubility and inefficient absorption, a prodrug approach was contemplated. Thus, amino acid ester-linked prodrugs of levonadifloxacin were explored for their improved oral administration potential, measured on the basis of oral bioavailability

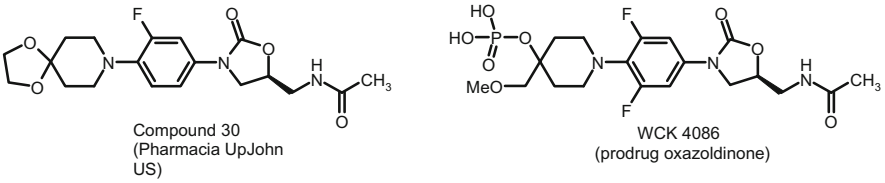


Fig. 3.21 Oxazolidinones by Wockhardt

(% of the orally-administered drug appearing in blood vs. injectable drug). Methane sulfonic acid salt of L-alanine ester of levonadifloxacin (WCK 2349) emerged as a prodrug of choice for oral delivery. It has >200 mg/mL aqueous solubility across the pH range encountered in the alimentary tract. L-alanine ester moiety helps for active absorption via intestinal amino acid receptors, and the ubiquitous presence of esterase enzymes efficiently releases the parent levonadifloxacin in the bloodstream. WCK 2349 has completed the Phase 1 clinical trial in the USA and Phase 2 and Phase 3 studies in India. Based on multiple nonclinical and clinical safety studies, both WCK 771 and WCK 2349 have emerged as safest fluoroquinolone known to date. (Bhagwat et al. 2019a, b; Appalaraju et al. 2020; Tellis et al. 2019).

Wockhardt's oxazolidinone program was aimed at inventing an NCE with a safety advantage over linezolid and PK commensurate to once-a-day dosing. A spiro ketal oxazolidinone series was explored to attain a better PK profile. This research was based on furthering a lead compound 30 reported by Pharmacia Upjohn (Yamada 1995). Compound 30 was less potent but exhibited good in vivo efficacy as an indication of good oral PK profile. The outcome of this oxazolidinone research was a phosphate ester prodrug of 4-hydroxy-4-methoxymethyl-piperidine oxazolidinone (PatilS 2007) (Fig. 3.21; WCK 4086) that exhibited superior PK, safety and tolerability over linezolid.

Wockhardt also worked in ketolide and 2-fluoroketolide antibacterial class, which was ridden with oral bioavailability, safety and tolerability issues. This was evident by the failure of several big pharma companies such as Johnson & Johnson, Aventis, GSK and Pfizer to progress their macrolide/ketolide lead candidates to Phase 3 or gain regulatory approval thereof. Wockhardt attempted to address these challenges by SAR driven improvement in potency, using hydrophilic moieties, without deploying 2-fluorine substituent. This approach was followed to minimize hepatic liability, which was ultimately achieved by introducing chiral methyl substituent in the side chain. This not only enabled adequate hepatic safety but also improved affinity to additional target in ribosomal domain II. Thus, a potent ketolide WCK 4873 (Fig. 3.22) active against high-level macrolide-resistant strains was identified (Deshpande et al. 2016a; Flamm et al. 2017; Rodvold et al. 2017; Takalkar 2016; Bader 2016). One of the salient features of Wockhardt ketolides is the replacement of traditional carbamate ring with chiral lactone ring, along with hydrophilic amidoxime arm in place of a conventional lipophilic *n*-butyl arm. The extra chiral centre arising from lactone arm adds specific direction and additional 'Z' stereo-chemistry of double bond of amidoxine function restricts free rotation. The overall

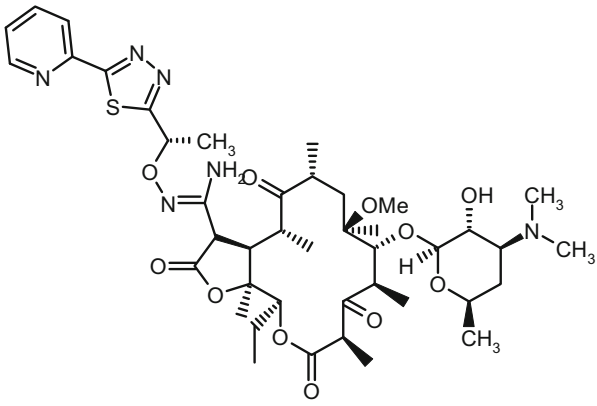


Fig. 3.22 Ketolide (Nafithromycin) by Wockhardt

hydrophilic character of the molecule provides a benefit of urinary elimination, which avoids excessive accumulation of the drug in the liver.

3.3.14.1 1,6-Diaza-Bicycly-spiro[3.2.1] Octanes β-Lactam Enhancers

Aiming at overcoming MDR resistance in Gram-negative bacteria, the team at Wockhardt conceived two programs: (1) discovery of novel β-lactamase inhibitors targeting recently evolved β-lactamases, which are not inhibited by classical β-lactamase inhibitors (clavulanic acid, tazobactam, sulbactam and avibactam); and (2) finding compounds which could synergize with existing β-lactams without relying on β-lactamase inhibition, an approach based on novel β-lactam enhancer mechanism. Selection of novel β-lactamase inhibitors was contingent on the ability of NCEs to inhibit class D β-lactamases, specifically associated with newly emerged pathogen—*Acinetobacter baumannii*. On the other hand, to be designated as an enhancer, the β-lactamases stable non-β-lactam compounds were screened for PBP2 binding activity, which was later demonstrated to synergistically boosts the bactericidal effect of established β-lactam antibiotics primarily binding to PBP3. The non-β-lactam high-affinity PBP 2 binders (Fig. 3.23; based on DBO pharmacophore) represent the first ever completely man-made compounds selectively recognizing bacterial PBPs. Figure 3.24 depicts diverse naturally derived and semisynthetic PBP binding compounds and the year of their discovery, with non-β-lactam PBP binders shown in the centre.

Wockhardt's β-lactamase inhibitor program successfully identified two candidates: WCK 4234 and WCK 5061 (Bhagwat 2012). Both of these β-lactamase inhibitors are more potent than the marketed β-lactamase inhibitors, with regards to inhibition of serine-β-lactamases such as class C β-lactamases, which are widely prevalent in contemporary Gram-negative pathogens. It is noteworthy that WCK 4234 provided protection even against *Acinetobacter baumannii* associated serine-β-lactamases such as class D OXA carbapenemases and

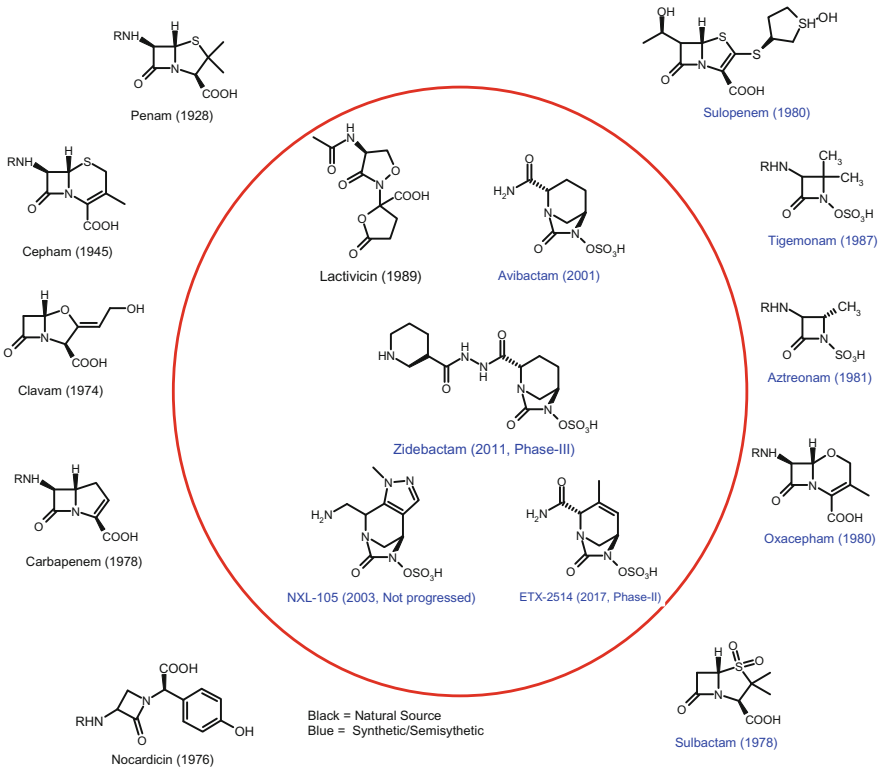


Fig. 3.23 PBP binding β-lactam and non β-lactam pharmacophores

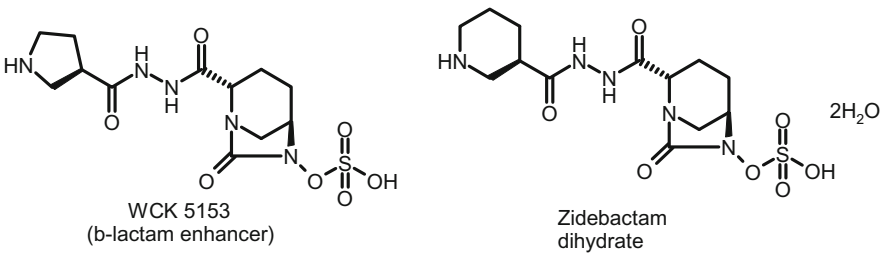


Fig. 3.24 β-lactam enhancers by Wockhardt

Enterobacteriaceae associated class A and class D carbapenemases such as KPCs and OXA 48/181. However, these inhibitors were unable to inhibit metallo-β-lactamases (class B β-lactamase) due to the latter's significant structural and functional differences as compared to serine-β-lactamases. The combination of WCK 4234 with carbapenem antibiotics such as imipenem and meropenem provided in vivo efficacy against MDR *A. baumannii* infection (Patil 2014), not realizable with any of the marketed BL-BLI combination.

The second approach of identifying novel β-lactam enhancers emanated as an outcome of the team's realization that it would be a herculean task, if not impossible, to discover a β-lactamase inhibitor with an ability to inhibit all the four classes of β-lactamases. Unique in vitro and in vivo screening tactics employed in microbiology laboratories helped identify DBO-based NCEs showing high-affinity binding to Gram-negative PBP2. The medicinal chemistry team efficiently designed and synthesized several analogues to optimize their PBP 2 affinity, which reflected in terms of their standalone antibacterial activity. This led to the discovery of β-lactam enhancers WCK 5107 (zidebactam) and WCK 5153, both of which showed potent activity against a range of pathogens belonging to Enterobacteriaceae and *P. aeruginosa* (Deshpande et al. 2016b). The combination of PBP 3 binding diverse β-lactam antibiotics (such as penicillin, cephalosporin and monobactams) with PBP 2 binding β-lactam enhancers proved remarkably bactericidal to Gram-negative pathogens, irrespective of them expressing all four classes of β-lactamases and other non-enzymatic resistance mechanisms such as efflux and impermeability. The combination of zidebactam with fourth-generation cephalosporin cefepime was coded as WCK 5222. By now, several international publications describe the fascinating and ever-evolving antibacterial profile and safety features of WCK 5222 (Almarzoky Abuhussain et al. 2019; Avery et al. 2018, 2020; Kidd et al. 2020; Lepak et al. 2019; Livermore et al. 2017; Monogue et al. 2019; Mullane et al. 2019; Preston et al. 2019; Sader et al. 2017a, b).

The broadest spectrum of coverage of WCK 5222 is achieved through zidebactam-mediated pharmacodynamic enhancement (manifested as augmented bacterial killing in vitro and in vivo) of cefepime (Bhagwat et al. 2019c; Moya et al. 2019). In Gram-negative pathogens, WCK 5222 rapidly saturates all the essential PBPs such as PBP 1a/b, 2 and 3, leading to complete cessation of bacterial cell wall synthesis, causing pronounced bactericidal effect which is not possible with either cefepime alone or zidebactam alone or any other BL-BLI combinations. The rapidity of killing action of WCK 5222 parallels to that of carbapenems, the most powerful β-lactam antibiotics discovered to date. Studies demonstrating the rapid binding of cefepime and zidebactam to their respective PBP targets amid the presence of potent β-lactamases, explain the role of enhancer mechanism in surmounting multidrug resistance in diverse Gram-negative pathogens. Major drug regulatory authorities, US FDA, EMEA (Europe) and NMPA (China), have recognized the potential of WCK 5222 in addressing several toughest unmet needs, and have accordingly granted abridged development path involving the bypassing of conventional clinical Phase 2 study and directly undertaking clinical Phase 3 study. The enabling stand by regulatory agencies is a reflection of urgency caused by the worrying spread of AMR among Gram-negative pathogens and the inadequacy of current armamentarium.

Generally not highlighted, the development of a novel drug throws enormous challenges in API and formulation scale-up, which are required to be overcome efficiently to support time-bound clinical development. As an example, it took Wockhardt scientists more than a year to address multiple challenges involved in scaling up the manufacturing of sterile zidebactam with physical attributes such as a

free-flowing nature and the absence of a tendency to form agglomerates. Such physical features were mandated by high-speed split-filling technology employed for manufacturing of WCK 5222 vials for Phase 3 study.

The highlights of antibacterial discovery programs undertaken in India over the past 50-odd years reveal that only a few molecules discovered could move to the clinical stage of development and even fewer novel antibacterial drugs progressed to an advanced stage of clinical development beyond India. The issue is no different at the international level, which is evident from the dwindling number of Phase 3 projects targeting MDR/XDR pathogens. Some of the discovery efforts were marred by a short-term and fragmented/patchy approach, which typically ended in reporting of sketchy in vitro data. Such a scenario highlights the issues of the clinical viability of the selected projects and the discovery team's ability to critically scrutinize the selected leads at every stage for go-no-go decision.

The successes of discovery programs critically rely on the scientific freedom bestowed to the team and the intra-team dynamics manifested in terms of good coordination in a spirit of harmony. Moreover, the attainment of discovery goals is dependent on access to resources provided by management. Wockhardt's remarkable success in antibacterial discovery is a result of several enabling elements that helped shape these discoveries. A few of these factors are discussed below:

3.4 Elements of Success in Wockhardt's Discovery Program

3.4.1 Scientific Freedom, Access to Resources and Organizational Capabilities

The discovery team was given complete scientific freedom on major issues and direction of the discovery program. This developed a trust between scientific leadership and management. Discovery core teams were assembled and an in-house animal housing facility was created to minimize the dependence on external sources. Existing organizational capabilities: scale-up team and a formulation research team (including respective GMP manufacturing teams) supported late-stage developmental activity such as large-scale synthesis of NCEs and NCE formulation development.

3.4.2 Team Building and Right Sizing

Discovery team was organized in two major sub-teams of chemistry and biology, to minimize hierarchy and create a free flow of information among scientist belonging to different disciplines. To sharpen in-house skills, relatively young and inexperienced scientists were encouraged to conduct experiments with drugs from known classes of antibiotics, to understand their features and compare findings with literature reports. Failed experiments were analyzed openly, which sometimes led to unexpected clues. A practice of sharing findings among teams was followed. This

exercise led to a deeper understanding of the therapeutic area and generated a conducive milieu, which helped retain talent.

3.4.3 Understanding Gold Standard Antibiotics

The team undertook focused extensive experimentation on marketed gold standard drugs and newer agents in the global development pipeline. This imparted strength/weakness/opportunity analysis of standard drugs and developed experimental and interpretative skills, along with identifying an emerging unmet medical need. One of clinical candidate WCK 4282 (2 g cefepime combined with 2 g tazobactam in 1:1 proportion) is based on a finding that resistance mechanism of KPC can be neutralized by adding higher quantity of tazobactam to cefepime, but not with other injectable cephalosporins, while well-established marketed combination based on piperacillin employs tazobactam in a much lower 8:1 proportion.

3.4.4 Dynamics Between Classes of Antibiotics and Territorial Preference

Understanding about territorial preferences for certain classes of drugs was considered for the selection of antibacterial classes. For instance, as per market trend, fluoroquinolones are more prescribed in Japan, China and India for their wider indication profile and the dosing convenience (oral and injectable), compared to Europe or the USA. In Europe, carbapenems are preferred over cephalosporins while it is reverse in the USA. Some of the territorial preferences are due to differences in regulatory judgments of country-specific regulatory agencies. Considering the above dynamics, fluoroquinolone, oxazolidinone, macrolide and diazabicyclo octane classes were selected for the antibacterial research.

3.4.5 Differentiating Product Profile for Unmet Medical Needs

Unmet medical needs were identified for inventing newer agents with differentiating product profiles compared to existing products. For example, lack of bactericidal anti-MRSA agent, with IV to oral switchable option was identified as an unmet medical need. Fluoroquinolone class was selected for being bactericidal. Taking a clue from a Japanese publication, where unaffected MICs of (±)-nadifloxacin for Staphylococcal/MRSA isolates in light of increased MICs of other quinolones, WCK 771 and WCK 2349 projects were evolved deriving inspiration from nadifloxacin pharmacophore. The study revealed that affected quinolones such as ciprofloxacin and gatifloxacin were: (a) substrate of NorA+ efflux pump; and (b) preferentially bound to DNA topoisomerase IV, prone to mutation, whereas (±)-nadifloxacin and S-(-)-nadifloxacin are: (a) not a substrate of NorA+ efflux pump and; (b) prefer critical enzyme DNA gyrase as target over topoisomerase

IV. As a result, WCK 771 [L-arginine salt of (S)-nadifloxacin] was realized as the bactericidal intravenous anti-MRSA drug.

With a prodrug approach, taking a clue from marketed prodrug valacylovir, WCK 2349 [L-alanine ester of (S)-nadifloxacin mesylate] was identified as an oral anti-MRSA drug candidate. WCK 2349 did not generate any safety signal even at higher doses in animals and patients. Thus, the unmet medical need of IV plus oral bactericidal anti-MRSA agent was addressed.

Oxazolidinone class was also explored to evolve an anti-MRSA agent, as this class offered a novel mechanism of action leading to marketing success of linezolid. The unmet medical need identified was to overcome its class-specific limitations, such as toxicity arising from myelosuppression and MAO inhibition. To reduce toxicity, the research goals were identified as: (a) removing/reducing myelosuppression; and (b) optimizing PK profile to render once-a-day dose thereby reducing the daily drug load. For this, a specific toxicity screening model was developed and linezolid doses were identified to judge bone marrow safety of newer agents from this class. Simultaneously, in-house 'in vivo efficacious oxazolidinones' were screened through this model, ensuring exposures comparable to linezolid's 'bone marrow suppression inducing exposures'. The related impact on peripheral blood cell counts and bone marrow was examined and a structure-toxicity relationship was developed. The oxazolidinone WCK 4086 (phosphate prodrug of WCK 3023) was identified with features like linezolid comparable efficacy, good oral bioavailability, once-a-day dosing potential, metabolic stability in rat, dog and in human liver microsomes, and promising bone marrow safety.

For discovery program aimed at identifying respiratory antibiotics based on macrolide class, the mandatory differentiating attributes for a new product were identified as: (a) a new product must cover all types of resistances in respiratory pathogens; and (b) should minimize class-specific hepatotoxicity. Ketolide subclass of macrolide was chosen for research, as it is known to overcome the efflux mediated resistance mechanism. For other resistances, a screening test based on high potency against 'telithromycin-resistant pneumococci' was developed as an indicator of higher affinity towards the alternate binding site in domain II of ribosomal RNA. To ensure hepatic safety, a hepatotoxic dose of telithromycin was identified in rats based on a 7-day repeat dose toxicity study, while in parallel, liver and lung accumulations were measured. Potent ketolides with acceptable PK profile underwent this hepatic safety screening model. A comprehensive structure-toxicity relationship led to the identification of WCK 4873 (nafithromycin), which is active against the *ermB* gene harbouring *S. pneumoniae* that expresses a high level of macrolide resistance. Moreover, extensive preclinical PK studies helped establish a higher lung penetration of nafithromycin compared to the liver. The hepatic load was found to reduce further, as the drug has a renal elimination pathway ascribed to its hydrophilic character. Nafithromycin generates safe metabolites compared to telithromycin and solithromycin. In clinical studies, most of the attributes of nafithromycin were well realized.

While dealing with Gram-negative pathogens, since combinations based on novel β-lactamase inhibitors and β-lactam antibiotic have limitations of not protecting

partner β-lactam antibiotic against β-lactamases of class B and D, treating pathogens harbouring all the four classes β-lactamases was identified as an unmet medical need. Designing novel universal β-lactamase inhibitor is fairly challenging and unrealizable in a reasonable period, because of the diversity of β-lactamase enzymes and varied mechanisms for hydrolysis of partner β-lactam antibiotics.

This problem was dealt with β-lactamase stable 'synergy driving NCE', which overcomes resistance through complementary PBP binding when combined with a suitable β-lactam antibiotic. A β-lactamase inhibitor, avibactam, belonging to diazabicyclo octane (DBO) class, was reported to have a weak affinity to Gram-negative PBP 2. Conceptually, it was thought that, if its PBP 2 affinity can be enhanced by 100× and then combined with a β-lactam antibiotic that binds to PBP 3, the combination could produce a potent synergy. Thus, novel DBO derivatives were tested for antibacterial activity against *E. coli* and Klebsiella strains. Standalone antibacterially active NCEs were further screened for concentration-dependent cell morphological changes for judging the extent of PBP 2 affinity. Among tested compounds, WCK 5107 (zidebactam) was identified as a potent selective PBP 2 binding agent. It displayed an antimicrobial spectrum that extended up to *P. aeruginosa*. The powerful affinity of the drug to PBP 2 was evident from its ability to promptly induce spheroplast formation (from characteristic rod form to oval spheroplasts) even at sub-MIC. Zidebactam synergized with a majority of penicillins, cephalosporins and monobactam aztreonam. Some of these combinations overcame all the known resistance mechanisms impacting β-lactam class of antibiotics. Its combination with cefepime (WCK 5222) became a novel mechanism-based clinical candidate. Another DBO analogue WCK 5153 showing features comparable to zidebactam with 2–4× improved potency against *P. aeruginosa* became a backup for WCK 5107.

3.4.6 Blending the Role of Experts and CROs with Internal Expertise

At various stages of drug development, specialized technical expertise is required. For instance, GLP toxicology studies need to be undertaken for IND/NDA filing as a regulatory requirement; independent microbiological studies are needed to confirm internal observations; radio-labelled drug synthesis, mass balance study, drug–drug interaction study are required at various stages of clinical development. Leading international experts are required for confirming the PK-PD adequacy of selected therapeutic dose for Phase 2 and Phase 3, and justifying breakpoints to regulatory bodies such as CLSI (USA) or EUCAST (Europe). At times, CROs and experts design their studies and interpret the results differently. Therefore, the role of the internal team leaders is to communicate constantly with external CROs/experts and harmonize the study findings to address critical data gaps. This collaborative aspect was handled successfully, which helped avoid regulatory delays.

3.4.7 The Role of Discovery Team in Supporting Clinical Development

Multidimensional understanding generated on a clinical candidate in preclinical development was leveraged in support of clinical development. For instance, safety, tolerability and metabolism-related observations helped in designing clinical study protocols. Similarly, blood-sampling time points and therapeutic dose to be employed for Phase 2/3 studies were identified on the basis of nonclinical PK-PD studies. The analytical team contributed to developing bio-analytical methods for plasma and body fluid samples collected to assemble human PK profile for the new drug.

3.4.8 Long-Term Engagement by Top Management

Some of the factors discouraging long-term commitments to antibacterial discovery are the increased cost of clinical development, complex regulatory requirements mandating indication-specific trials, and post-launch slower revenue growth for the first 4–5 years. Despite being aware of these factors, the long-term commitment showed by the top management contributed to the successful and meaningful outcome of the research.

3.4.9 De-risking Projects

Intending to minimize the probability of failures at the clinical developmental stage, certain de-risking approaches were an integral part of the Wockhardt discovery programs. The de-risking was ensured by focusing on time-tested, well-established antibacterial classes with known liabilities and developmental history providing clues for risk mitigation, rather than researching an entirely new class. The known classes have well-understood developmental path based on familiar PK/PD patterns, toxicity issues and difficulties encountered during development. The solutions to these issues were often known. Further de-risking comes from an approach of firmly relying on the outcome of laboratory-based experiments rather than theoretical predictions. Detailed in vitro and in vivo pharmacology helped in unravelling the finer aspects of development. For example, NCEs with higher MICs were evaluated in secondary and tertiary screens for unravelling other interesting features and generating multi-parametric SARs. Such an approach helped in understanding the dynamics between potency, PK and in vivo efficacy. Additional de-risking measures included avoiding over-reliance on cell-free screening assays (IC_{50}) and in-silico modelling rather than emphasis was put on efficacy, PK-PD investigations and safety assessment based on in vivo tests.

3.5 Urgency to Expand Antibiotic Discovery Initiatives in India

The combination of India centric and international factors contributes to the urgency for creating an efficient R&D based mechanism in India, to effectively deal with the threat posed by AMR. India ranks high on the charts of the infectious disease burden, and the judicious use of effective antibiotics is warranted. Bill and Melinda Gates Foundation surveillance has shown that India has one of the highest levels of resistance to all antibiotics (including carbapenems) and there is an alarming spread of multidrug-resistant organisms.

Taking note of the impact of AMR on health care, the WHO has identified AMR as a major healthcare threat. It has also identified several pathogens for which newer antibacterial agents are required urgently. As major pharmaceutical companies close their antibacterial discovery programs due to the unattractive business model as compared to other therapeutic areas, the pace of introduction of new antibiotics addressing unmet needs is quite slow. This situation calls for urgent measures to invigorate antibiotic discovery research capability within India, so that it would propel the country into the league of major antibiotic discovery hub, an area in which even China has yet to demonstrate the significant capability of progressing discoveries to an advanced stage of international development.

3.6 The Way Forward

The country must create self-sufficiency of safe and effective antibacterial agents. For this, high-calibre antibacterial discovery and development programs need to be supported by enabling national incentives/funding. It should be possible to identify projects worthy of national-level funding by employing objective criteria. The scrutiny of objective parameters such as clinical viability of the project, independent studies supporting the project concept, favourable review by international regulatory agencies and the safety outcomes from phase 1 study, serve as reliable tools to identify projects worthy of funding. These parameters would ensure that only high-impact projects are qualified for national funding. In this context, it is worth noting that the initiatives such as DST extending financial loans for undertaking clinical studies approved by DCGI provide the much-needed push incentive for antibiotic development.

As a longer-term strategy, two or three dedicated antibacterial research institutions competing with each other could be set up in India. This strategy would generate a competent national pool of scientists that would sustain and refine the art and science of antibiotic discovery and development.

Another area that needs careful attention pertains to building a dedicated competent regulatory mechanism for the evaluation and approval of novel antibiotics relevant to India. The regulatory team should have adequate representation of: (a) clinical microbiologists with a thorough background of diverse resistance mechanisms and pathogen-specific epidemiology; (b) clinicians with a deeper insight of management of infectious disease; and (c) PK/PD experts to judge the

adequacy of selected clinical doses for a novel antimicrobial agent. A high-quality regulatory guidance would act as nudging force for the competing discovery teams, and would also help in implementing the course correction, as and when needed, during the transition of a new drug from nonclinical to clinical stage. Through these long-term measures, India would continue to serve its own need for antibiotics on an on-going basis while aspiring to become a global hub of antibiotic discovery and development.

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Mahesh V. Patel is involved in antibiotic discovery research since more than 45 years, including 21 years at Hoechst Research Centre, Mumbai, 4 years at Ranbaxy Laboratories, New Delhi and 22 years at Wockhardt Research Center, Aurangabad in Mumbai. His work at Hoechst led to the discovery of four novel antibiotics. Over the past 22 years (1998-till date), he has been leading the antibiotic discovery team at Wockhardt, Aurangabad culminating in to six clinical candidates for which US INDs have been accepted and QIDP (Qualified Infectious Disease Product) awarded for all of them. Discovery team recently gained first time ever market approval for two novel antibiotics in India. Dr. Patel is the inventor/co-inventor of more than 50 granted US Patents. He earned his Ph.D. degree from the University of Bombay in 1985 and postdoctoral research focused on HIV interaction with cell surface cofactors.

Sachin S. Bhagwat has 25 years of experience in the discovery and development of novel antibiotics. He began his discovery research career at Ranbaxy Laboratories, New Delhi (1995–1998) and later joined antibiotic discovery team at Wockhardt Research Center, Aurangabad (1998–till date) eventually leading the antibiotic pharmacology function. Dr. Bhagwat's research interest includes, historical discovery approaches, unmet need in bacterial infections, mechanism of action and resistance, Phase III dose identifying PK/PD studies, and international collaborative research. Dr. Bhagwat is the inventor/co-inventor in 40 + granted US/EU patents covering five major classes, fluoroquinolones, oxazolidinones, macrolide/ketolides, β-lactams and diazabicycloctane and has authored several research articles. He earned his Ph.D. degree in 2002 (Bhopal University) on pharmacodynamic efficacy determinants of quinolone antibacterials.

Prasad K. Deshpande obtained his Ph.D. in 1993 from Indian Institute of Chemical Technology, Hyderabad, India, in synthetic organic chemistry and later on postdoctoral research at North Dakota State University, USA (1993–1996). Having gained experience in optimizing manufacturing of active pharmaceutical ingredients, he led Wockhardt medicinal chemistry efforts in designing and synthesis of NCEs which culminated in various international patents, publications as well as clinical stage novel antibiotics.