Strategic design, synthesis and evaluation of antifungal agents targeting chitin metabolism

A project proposal

Submitted to

Department of Biotechnology
Government of India
New Delhi

by

Dr. M. V. Deshpande
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National Chemical Laboratory, Pune 411008

and

Dr. S. R. Deshpande
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National Chemical Laboratory, Pune 411008

December, 2010
PART I: GENERAL INFORMATION

1. Name of the Institute/University/Organisation submitting the Project Proposal:
   National Chemical Laboratory, Pune-411008

2. State: Maharashtra

3. Status of the Institute: CSIR Institute

4. Name and designation of the Executive Authority of the Institute/University
   forwarding the application:
   The Director, National Chemical Laboratory, Pune - 411008

5. Project Title:
   Strategic design, synthesis and evaluation of antifungal agents targeting chitin metabolism

6. Category of the Project (Please tick): R&D

7. Specific Area: Basic Research in Modern Biology
   Key words/subject area: antifungal agents, organic synthesis, biochemistry

8. Duration: 3 Years

9. Total Cost (Rs.): **33,28,400/-** (Rs. 19,37,200 + 13,91,200)

10. Is the project Single Institutional or Multiple-Institutional (S/M)? : S

11. If the project is multi-institutional, please furnish the following: Not applicable

Name of Project Coordinator:
Affiliation:
Address:

12. **Scope of application indicating anticipated product and processes**

   The research will lead to development of novel target specific and efficient antifungal agents. Promising agents, if proved better than existing antifungal drugs, may pave way for therapeutic drug development.
13. **Project Summary:**

Limited repertoire of antifungal drugs, increasing incidence of opportunistic fungal infections and the emergence of drug resistance in fungal pathogens poses a serious public health concern. Developing improved versions of existing antifungal agents, searching for new compounds and also for new targets or strategies has become a necessity. Chitin is a major structural component of fungal cell wall absent in plants and animals; hence biosynthesis of chitin is a promising target for development of antifungal agents.

Main objective of the project is to develop new antifungal agents with specific inhibitory activity against enzymes of chitin synthesis pathway. The objective will be achieved by strategic design of substrate analogues and their derivatives for two enzymes namely chitin synthase (CS) and glucosamine-6-phosphate synthase (GlcN-6-P synthase), synthesis of these molecules and demonstration of antifungal activity. In accordance with two active site mechanism of CS, dimeric molecules of CS inhibiting monomers with different linkers will be synthesized to get more efficient inhibitors. In order to tackle the problem of resistance development, hybrid molecules with dual inhibitory action against both the enzymes will be developed. For this, effective inhibitors of CS and GlcN-6-P synthase will be coupled together and tested for their antifungal potential.
PART II: PARTICULARS OF INVESTIGATORS

Principal Investigator:
14. Name: Dr. M. V. Deshpande
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   Institute/University: National Chemical Laboratory
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   Number of research projects being handled at present: Five

Co-Investigator
15. Name: Dr. Mrs. S. R. Deshpande
   Date of Birth: 12-2-1952   Sex (M/F): F
   Designation: Scientist EII
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   Institute/University: National Chemical Laboratory, Pune
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   Pune
   PIN: 411008
   Telephone: 020-25902574   Fax: 020-25902629
   E-mail: sr.deshpande@ncl.res.in
   Number of Research projects being handled at present: -
PART III: TECHNICAL DETAILS OF PROJECT

16. Introduction

16.1 Origin of the proposal

The incidence of fungal infections and associated mortality rates has dramatically increased during the last few decades. Rapidly changing climatic conditions and natural disasters also contribute to the increase in fungal diseases. For instance, online journal mBio of American Society for Microbiology (April 2010) issue suggests the possibility of new fungal diseases in mammals due to global warming. Earlier, New Scientist (2005) reported that Tsunami survivors were at risk of fungal infections.

This year’s ‘SMYTE’ (28th) Small Meeting on Yeast Transporters and Energetics was held in New Delhi, India during 23-27th September 2010. Ernst J., Milewski S., Morschhauser J., Prasad R., Sanglard D., Sychrova H. and many other eminent researchers from all over the world were present for the meeting. The main concern expressed was of multidrug resistance in fungal pathogens. One of the approaches suggested to combat the situation is the development of antifungal agents using novel strategies and targets.

16.2 (a) Rationale of the study supported by cited literature (b) Hypothesis (c) Key questions.

a) Rationale of the study

Despite the increasing importance of fungal pathogens, the number of effective antifungal agents remains limited, with resistance compromising the effectiveness of most antifungals. Treatment of deep-seated mycoses is complicated by the limited choice and spectra of existing antifungal agents as well as the toxicity often associated with antifungal chemotherapy. The majority of invasive mycoses are caused by Cryptococcus neoformans and species of Candida and Aspergillus. Currently, five classes of compounds are used clinically to treat systemic mycoses. The classes, their targets and mode of action are given in Table 1. Limitations of these compounds as mentioned in the table demands search for better antifungal agents. Although the treatment of fungal infections is progressing steadily, currently available agents act on targets that are also found in mammalian cells. The discovery of antifungal agents that possess selective toxicity against the eukaryotic fungal cell remains an important scientific challenge.
<table>
<thead>
<tr>
<th>Class of antifungals</th>
<th>Target</th>
<th>Mode of action</th>
<th>Antibiotic</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyenes</td>
<td>Ergosterol biosynthesis</td>
<td>Polyenes complex with ergosterol in the fungal cell membrane and compromise the integrity of the cell membrane.</td>
<td>Amphotericin B</td>
<td>Sometimes acute and chronic side effects</td>
</tr>
<tr>
<td>Azoles</td>
<td>Ergosterol biosynthesis</td>
<td>Inhibition of lanosterol demethylase (cytochrome P450 dependent) enzyme leading to ergosterol depletion and accumulation of intermediates in the pathway. It disrupts the structure of the cell membrane, alters the activities of several membrane-bound enzymes.</td>
<td>Imidazoles (e.g. ketoconazole, miconazole), Triazoles (e.g., fluconazole, itraconazole and voriconazole)</td>
<td>Systemic azoles are well tolerated and are generally free of serious host toxicities. In some cases mammalian cytochrome P-450-dependent enzymes that synthesize steroid hormones were reported to be affected.</td>
</tr>
<tr>
<td>Allylamines</td>
<td>Ergosterol biosynthesis</td>
<td>Inhibit the enzyme squalene epoxidase in the ergosterol biosynthesis pathway</td>
<td>Terbinafine</td>
<td>Limited clinical efficacy owing to poor pharmacokinetics.</td>
</tr>
<tr>
<td>Fluoropyrimidines</td>
<td>Nucleic acid synthesis</td>
<td>Inhibit DNA and RNA synthesis</td>
<td>5-fluorocytosine (5-FC)</td>
<td>Possible effect on other non-targeted cells is a major concern.</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Glucan synthesis</td>
<td>Inhibit (1,3)-glucan synthesis resulting in disruption of the fungal cell wall</td>
<td>Caspofungin</td>
<td>Only compound in this class approved for clinical use and is fungicidal with minimal host toxicity.</td>
</tr>
</tbody>
</table>
Ideally, a selectively toxic antifungal agent should be developed that interacts with a fungal target not found in other eukaryotic cells. This strategy involves selective inhibition of the biosynthesis of important structural elements in the fungal cell. The fungal cell wall is such a therapeutic target. Apart from resistance, toxicity and low efficacy are other problems associated with antifungal use in human infections. To tackle these problems and satiate the demand, attempts can be made to develop cell wall target specific novel antifungal agents using strategic design and organic synthesis approach.

With greater knowledge of fungal metabolism efforts are being made to inhibit specific enzymes in different metabolic pathways of the fungus. One of the important targets for antifungal agents is fungal cell wall. Fungal cell walls are primarily composed of polysaccharides namely chitin, glucan, mannan and glycoproteins (Fig. 1).

![Fig. 1 Fungal cell wall](image)

Chitin is main structural component of fungal cell wall which is absent in plants and mammals, and thus its metabolism presents an attractive target for the control of pathogenic fungi (Deshpande, 1998). Glucosamine-6-phosphate synthase (GlcN-6-P synthase, EC 2.6.1.16) enzyme brings together carbon and nitrogen metabolism pathways to initiate chitin synthesis. While in the final step of chitin synthesis the enzyme involved is chitin synthase (CS, EC 2.4.1.16). These two enzymes are considered as prime targets for the development of antifungal agents.

Nikkomycin (Dahn et al., 1976) and Polyoxin (Isono et al., 1969) are naturally occurring CS inhibitors produced by *Streptomyces sp.* In NCL active CS inhibitors 1,2,3-triazolyl uridine derivatives as modified analogues of nikkomycin have been synthesized (Chaudhary et al., 2009).
(b) Hypothesis

It was suggested that CS possessed two active sites with alternating orientation of the N-acetyl-D-glucosamine (GlcNAc) residues within the chitin chain, and dimeric inhibitor molecules have been shown to be more effective (Yeager and Finney, 2004a). Therefore, it can be an effective strategy to develop new dimeric molecules having 1,2,3-triazolyl uridine as a core structure. Secondly, hybrid molecules with dual inhibitory action against the two enzymes may resolve the problem of resistance development against one molecule. Therefore, targeting GlcN-6-P synthase and CS can be the promising way for the development of new antifungal agent.

(c) Key questions

- Can dimeric/multimeric molecules be more effective in vitro and in vivo?
- Can dual inhibitors be broad spectrum and less toxic?

16.5 Current status of research and development in the subject (both international and national status)

International Status:

Exploitation of novel targets, like CS and GlcN-6-P synthase, offers an attractive option for antifungal agent development. GlcN-6-P synthase catalyses complex reaction involving ammonia transfer from L-glutamine to fructosamine-6-phosphate (Fru-6-P), followed by isomerisation of the formed Fru-6-P to glucosamine-6-phosphate (Fig 2). This is the first committed step in a pathway which provides GlcNAc for biosynthesis of chitin in fungi, insects and crustaceans; as well as glycoproteins, glycosaminoglycans and mucopolysaccharides in mammals.

In fungi and bacteria, deletion of the respective gene encoding the enzyme could be lethal (Whelan and Ballou, 1975; Sarvas, 1971). In mammals, a temporary depletion of enzyme activity is acceptable, due to the slow turnover of aminosugar-containing macromolecules and a rapid turnover of the mammalian gene encoding the enzyme, known as glutamine fructose-6-phosphate amidotransferase (GFAT) (Bates et al., 1966; Marshall et al., 1991). These features make GlcN-6-P synthase a potential target for antifungal agents (Borowski, 2000). On the other hand, CS can be a good target as it is absent in plants and mammals.

GlcN-6-P synthase of eukaryotic origin is a homotetramer but the complete spatial arrangement of the subunits is not well understood. A single enzyme subunit contains two
domains: the N-terminal and the C-terminal one, catalyzing glutamine hydrolysis and sugar-phosphate isomerisation, respectively. The structures of these domains were overexpressed and crystallised separately (Isupv et al., 1996).

So far several GlcN-6-P inhibitors were reported, of both natural and synthetic origin, which exhibited fungicidal activity. Most of them were glutamine analogs acting as active site-directed alkylating agents. Tetaine was the first recognised selective inhibitor of GlcN-6-P synthase (Chmara et al., 1984a; Milewski et al. 1986). Later on a series of potent selective inhibitors of GlcN-6-P synthase were designed and synthesized (Chmara et al., 1984b; Andruszkiewicz et al., 1986 and 2000; Milewski et al., 1992). The most studied of these compounds, namely \(N^2\)-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid (FMDP), a glutamine analog, acts as an active-site-directed
inactivator, blocking the N-terminal, a glutamine binding domain of the enzyme (Fig 3).

FMDP was reported to inactivate the enzyme due to formation of a covalent bond with the sulphydryl group of its N-terminal cysteine residue (Chmara et al., 1985; Badet et al., 1988; Kucharczyk et al., 1990). Incorporation of FMDP into peptide structure allowed effective internalization of the enzyme inhibitor by the way of peptide permeases (Milewski et al., 1988a, b). Another compound, 2-amino-2-deoxy-D-glucitol-6-phosphate (ADGP) is an analog of the putative transition state of the catalyzed sugar conversion reaction and is a strong inhibitor of the C-terminal domain of the GlcN-6-P synthase subunit. The molecular modeling studies for GlcN-6-P synthase inhibition by different inhibitors (Tarnowska et al., 1992; Tempczyk et al., 1989) and to synthesize novel ligands with better activity were also reported (Milewski et al., 2004; Janiak et al., 2004).

Another target enzyme, CS produces chitin which is a (1-4)-β-linked homopolymer of GlcNAc according to the following reaction (Fig 2):

\[ 2n \text{UDP-GlcNAc} \rightarrow (\text{GlcNAc-β-(1-4)-GlcNAc})_n + 2n \text{UDP} \]

Two classes of antifungal antibiotics, namely polyoxins and nikkomycins were isolated from streptomycetous cultures (Fig 4) (Dahn et al., 1976; Isono et al., 1969).

Both of these compounds are structurally very similar to UDP-GlcNAc, an active monomer of chitin. Since they are structurally similar, the antibiotic mimics the action of UDP-GlcNAc and binds to CS. This causes blocking of the active site and subsequent inhibition of chitin synthesis. In case of fungi, the observed effect on species exposed to polyoxins and nikkomycins was swelling and bursting of growing hyphae (Deshpande et al., 1998).
Compounds such as pseurotin A and 8-O-demethylpseurotin A were isolated from a fungus *Aspergillus fumigatus*, which showed inhibition of CS activity. However, these compounds could not enter into the fungal cell without a facilitating compound. Therefore, a combination of Amphotericin B was used to overcome this problem and to render CS accessible to pseurotins (Wenke et al., 1993).

Earlier, rational drug design proceeded only on the basis of existing inhibitors, because the structure of CS was unknown. The novel 1,3,4-oxadiazolines derivatives C1–10 and C11–20 designed as potential antifungal reagents were shown to interfere with chitin biosynthesis (Ke et al., 2009). Yeager and Finney observed that two simple uridine-derived dimeric inhibitors exhibited 10-fold greater CS inhibition than their monomeric equivalents. Based on the results, they proposed that CS possessed two active sites with alternating orientation of the GlcNAc residues within the chitin chain (Yeager et al., 2004b). Recently, two compounds obovatol (Hwang et al., 1976) and phellinsin A (Lee et al., 2007) were isolated from plant extract of *Magnolia obovata* and cultured broth of *Phellinus* sp. PL3 respectively, which found to possess better antifungal activity than nikkomycin Z and Polyoxin D respectively (Fig 5).

![Phellinsin A and Obovatol](image)

Fig. 5 naturally occurring chitin synthase inhibitors

Antifungals with single-site mode of action are at relatively high risk for resistance development compared to those with multi-side mode of action. At present conjugated approach is an emerging strategy which involves the combination of two separate pharmacological agents into a single molecule having dual activity. Similar approach was reported to form hybrid molecules of two known antimalarial drugs, chloroquine (CQ) and the non-sedating H1 antagonist astemizole (Musonda et al., 2009). While Stevens et al. (2000) studied synergistic effect of the fungicidal activity of glucan synthase inhibitor (LY 303366) and a CS inhibitor (Nikkomycin Z). Babic et al. (2008)
synthesised 1-C-linked diphosphate analogues of UDP-N-Ac-glucosamine and UDP-N-Ac-muramic acid as new inhibitors of the bacterial cell wall biosynthesis.

**National status**

Recently, in NCL, 14 modified nucleosides by click reaction were synthesized and their CS inhibitory activity was demonstrated (Chaudhary et al., 2009). In another attempt, antifungal pyrimidines targeting CS were successfully synthesized by Suzuki cross-coupling reaction (Gholap et al., 2008). A series of 2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile and various analogues were synthesized. Five of these compounds showed comparable activity to nikkomycin Z (Gholap et al., 2007). In another study, tetrapeptides derived from glycine and β-alanine were hooked at the C-3b position of the modified cholic acid to realize novel linear tetrapeptide-linked cholic acid derivatives. While relatively inactive by themselves, these compounds interacted synergistically with antibiotics such as fluconazole and erythromycin to inhibit growth of fungi and bacteria (Bavikar et al., 2008). The bile acid dimers linked through 1,2,3-triazole and bis-β-lactam showing significant antifungal as well as antibacterial activity against all the tested fungal and bacterial strains were also synthesized (Vatmurge et al., 2008a). Synthesis of novel 1,2,3-triazole-linked β-lactam–bile acid conjugates using 1,3-dipolar cycloaddition reaction of azido β-lactam and terminal alkyne of bile acids in the presence of Cu(I) catalyst (click chemistry) was done. These molecules exhibited significant antifungal and moderate antibacterial activity against all the tested strains (Vatmurge et al., 2008b). Another kind of inhibitors steroidal dimers with antifungal and antiproliferative activity have been synthesized successfully in our laboratory (Salunke et al., 2004).

Antibiotics polyoxins and nikkomycins are peptidyl nucleosides containing carbohydrate moiety. Srivastava et al. (2007) synthesized similar compounds by coupling thiadiazoly1 thiohydantoin and glucopyranose rings. Few of these 3-(5-aryl-1,3,4-thiadiazol-2-yl)-1-(β-D-glucopyranosyl)-5-alkyl-2-thio-4-midazolidinones showed good antifungal activity. During intensive search for more effective and safer non-nucleoside chitin synthesis inhibitors, Vijaykumar et al. (1996) isolated a depsipeptide Arthrichitin from the fermentation broth of *Arthrinium phaeospermum* (HIL Y-903022). Sarojini et al. carried out synthesis, characterization, *in vitro* and molecular docking studies of new 2,5-dichloro thienyl substituted thiazole derivatives for antimicrobial properties. Among the
five molecules taken for docking studies 2-(8-quinolinyl)-4-(2, 5-dichloro-thienyl)-1, 3-thiazole showed minimum binding and docking energy and may be considered as good inhibitor of GlcN-6-P synthase. Ganesh et al. (2010) reported the synthesis and antifungal evaluation of triazole derivatives of 7-hydroxy-4-methylcoumarins. 2-ketophenyl-3-substituted aryl-1-thiazolidin-4-one compounds were synthesized and their antifungal activity was demonstrated (Vats et al., 2010). Thareja et al. (2010) synthesized chromeneimidazole derivatives and demonstrated their antifungal activity. Synthesis of quinoxaline derivatives and their antifungal activity was reported by Singh et al. (2010).

References:


16.6 The relevance and expected outcome of the proposed study

In this project, we have proposed to pursue the quest of antifungal agents’ development by strategic design, synthesis and evaluation of different enzyme inhibitor molecules. The research will lead to development of efficient antifungal agents. These
agents may be further pursued as potential drug candidates for the control of fungal human pathogens. Sci molecules India Pvt. Ltd., Pune has principally agreed for further development of potential molecule as antifungal drug for topical application.

16.7 Preliminary work done so far

Total 14 uridine nucleosides with 1,2,3-triazoles substitution at 5’ position of uridine were synthesized. The design for this target was based on replacing the peptide bond of nikkomycin with triazole moiety. 1,2,3-Triazole unit may be considered as a surrogate for a peptide bond as these triazoles have atom placement and electronic properties similar to the peptide bond. The nucleosides have been synthesized by following click reaction chemistry and demonstrated to possess good CS inhibitory activity (Chaudhary et al., 2009). Their antifungal property was demonstrated by different assays like hyphal tip bursting, germ tube inhibition and whole cell growth inhibition of clinical isolates of Candida sp., C. neoformans and Aspergillus sp.

17. Specific objectives

- Synthesis of monomeric and dimeric inhibitors of CS and GlcN-6-P synthase.
- Synthesis of hybrid molecules with dual mode of action against CS and GlcN-6-P synthase.
- Characterization and evaluation of synthesized molecules for their antifungal potential in laboratory studies.
- To study transport and stability of synthesized molecules inside the cell.
- Validation of the study using different clinical isolates of human pathogens and toxicity studies.

18. Work Plan:

18.1 Work plan (methodology/experimental design to accomplish the stated aim)

- Synthesis of monomeric and dimeric inhibitors of CS and GlcN-6-P synthase
  a. Synthesis of CS inhibitors

  As nikkomycin is multifunctional molecule, it offers different sites for derivatization (Fig. 4). Synthesis of nikkomycin derivatives will be done by building different heterocycles at C5’ position. Active inhibitors will be identified
and their dimmers will be synthesized. Along with this, derivatives of obovatol and phellinsin will also be synthesized (Fig 5).

b. Synthesis of GlcN-6-P synthase inhibitors

Known inhibitors FMDP, tetaine and their modifications such as FMDP ester, butyl or dibutyl derivatives will be synthesized.

- Synthesis of hybrid molecules with dual mode of action against CS and GlcN-6-P synthase.
  Lead CS and GlcN-6-P synthase inhibitors will be joined together with hydrolysable and non-hydrolysable linkers for the synthesis of hybrid molecule with dual mode of action. Secondly, molecules binding to glutamine binding domains and sugar binding domains of GlcN-6-P synthase will also be joined.

- Characterization and evaluation of synthesized molecules for their antifungal potential in laboratory studies.
  Physicochemical characterization of all synthesized molecules will be done using different techniques such as $^1$H NMR, $^{13}$C NMR, IR, X-ray, mass spectrometry and elemental analysis.
  Biological evaluation of synthesized compounds will be carried out using different assays

  1. Whole cell growth inhibition: All compounds will be tested against different human pathogenic fungi such as Candida albicans, other Candida sp., Cryptococcus neoformans, Aspergillus fumigatus, A. flavus, A. niger etc.

  2. Hyphal tip bursting: It is quick test to identify fungal cell wall inhibitors. This will be carried out using Benjiaminella poitrasii.

  3. Enzyme inhibition assay:
    a. CS assay: CS assay will be carried out using CS activity of Benjiaminellia poitrasii cells in presence and absence of the compounds using a non-radioactive assay developed by Lucero et al. (2002). The assay involves binding of synthesized chitin to WGA-coated surface followed by detection of polymer with horseradish peroxidase-WGA conjugate. Activity of horseradish peroxidase is determined by measuring absorbance at 430 nm.
    b. GlcN-6-P synthase assay: GlcN-6-P synthase assay will be carried out using modified Elson-Morgan procedure reported by Ghosh et al. (1960).

  4. Yeast to hypha transition inhibition:
Most of the pathogenic fungi change their morphology reversibly between unicellular yeast form and filamentous hypha for survival and proliferation in the host. In other words, it is a change from a nonpathogenic/saprophytic to pathogenic form. Therefore, the compounds which retard this dimorphic transition can have a potential as an antifungal drug. A nonpathogenic dimorphic fungus *B. poitrasii* will be used as a model to check the effect of the compounds on yeast to hypha transition.

- To study transport and stability of synthesized molecules inside the cell.
  
  Experiments will be carried out to demonstrate the mode of action through uptake and *in vivo* inhibition of the enzymes. Transport, *in vivo* localization, stability and enzyme inhibition will be studied by High Performance Liquid Chromatography (HPLC), Fluorescence microscopy etc.

- Validation of the study using different clinical isolates of human pathogens and toxicity studies.
  
  Different clinical isolates of human pathogenic fungi will be obtained from pathological laboratory and activity validation of lead molecules will be done. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay using different cell lines will be carried out to check the cytotoxicity of all the synthesized compounds. The cytotoxicity assay will be done at National Center for Cell Science, Pune.

18.2 *Connectivity of the participating institutions and investigators* (in case of multi-institutional projects only) – Not applicable

18.3 *Alternate strategies* (if the proposed experimental design or method does not work what is the alternate strategy)

- Instead of hybrid molecules, the designed molecules will be used singly for the development. Preliminary work done so far (Chaudhary *et al.*, 2009) has proved their effectiveness as potential antifungal agents.
19. Timelines: (Please provide quantifiable outputs)

<table>
<thead>
<tr>
<th>Task</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Recruitment of project staff</td>
<td>I-I</td>
</tr>
<tr>
<td>2. Procurement of equipment and chemicals</td>
<td>I---I</td>
</tr>
<tr>
<td>3. Synthesis of monomeric and dimeric compounds</td>
<td>I--------</td>
</tr>
<tr>
<td>4. Synthesis of hybrid molecules</td>
<td>I--------</td>
</tr>
<tr>
<td>5. Antifungal activity testing</td>
<td>I--------</td>
</tr>
<tr>
<td>6. Transport, stability and mechanistic studies</td>
<td>I--------</td>
</tr>
<tr>
<td>7. Validation and cytotoxicity studies</td>
<td>I--------</td>
</tr>
<tr>
<td>8. Preparation of manuscripts, reports</td>
<td>I--------</td>
</tr>
</tbody>
</table>
20. Name and address of 5 experts in the field

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Name</th>
<th>Designation</th>
<th>Address</th>
</tr>
</thead>
</table>
| 1.     | Prof. Rajendra Prasad    | Professor           | School of Life Sciences, Jawaharlal Nehru University, New Delhi – 110067  
rp47jnu@gmail.com  
rp47@mai.jnu.ac.in  
Phone: 011-26704509  
Fax: 011-26741081                                                   |
| 2.     | Dr. B. V. Rao             | Scientist G         | Indian Institute of Chemical Technology, Tarnaka, Uppal Road, Hyderabad – 500007  
vittalrao@iict.res.in  
Phone: 040-27193150  
Fax: 040-27191234                                                   |
| 3.     | Prof. T. Satyanarayana    | Professor           | Department of Microbiology, University of Delhi South Campus, Benito Juarez Road, New Delhi-110021  
tsnarayana@gmail.com  
Phone: 011-24112008  
Fax: 011-24115270                                                   |
| 4.     | Dr. A. A. Natu            | Visiting Faculty    | Indian Institute of Science Education and Research (IISER), 900, NCL Innovation Park, Dr. Homi Bhabha Road, Pashan, Pune-411008  
aa.natu@iiserpune.ac.in  
Phone: 020-25908001  
Fax: 020-25899790                                                   |
| 5.     | Prof. N. S. Punekar       | Professor           | Department of Biosciences and Engineering, Indian Institute of Technology-Bombay, Powai, Mumbai – 400076  
nspp@iitb.ac.in  
Phone: 022-25767775  
FAX: 022-25723480                                                   |
PART IV: BUDGET PARTICULARS
Biochemical Sciences Group, NCL, Pune
Budget (In Rupees)

A. Non-Recurring (e.g. equipments, accessories, etc.)

<table>
<thead>
<tr>
<th>S. No.</th>
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<th>Year 2</th>
<th>Year 3</th>
<th>Total</th>
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<tbody>
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<td>-----</td>
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Sub-Total (A) = 3,00,000

B. Recurring

B.1 Manpower (See guidelines at Annexure-III)

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<thead>
<tr>
<th>S. No.</th>
<th>Position No.</th>
<th>Consolidated Emolument</th>
<th>Year 1</th>
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<tbody>
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<td>2,30,400</td>
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Sub-Total (B.1) = 12,38,400

B.2 Consumables

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<th>Quantity</th>
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<th>Year 2</th>
<th>Year 3</th>
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<tbody>
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<td>Glass ware, chemicals, solvents, media components, fine chemicals for enzyme assay</td>
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Other items

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<th>Year 2</th>
<th>Year 3</th>
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<td>B.3 Travel</td>
<td>30,000</td>
<td>30,000</td>
<td>30,000</td>
<td>90,000</td>
<td></td>
</tr>
<tr>
<td>B.4 Contingency</td>
<td>30,000</td>
<td>30,000</td>
<td>30,000</td>
<td>90,000</td>
<td></td>
</tr>
<tr>
<td>B.5 Overhead</td>
<td>72000</td>
<td>72000</td>
<td>72000</td>
<td>2,16,000</td>
<td></td>
</tr>
<tr>
<td>Sub-total of B (B.1+B.2+B.3+B.4+B.5)</td>
<td>562400</td>
<td>562400</td>
<td>512400</td>
<td>1637200</td>
<td></td>
</tr>
<tr>
<td>Grand Total (A + B)</td>
<td><strong>8,62,400</strong></td>
<td><strong>5,62,400</strong></td>
<td><strong>5,12,400</strong></td>
<td><strong>19,37,200</strong></td>
<td></td>
</tr>
</tbody>
</table>

Justification

Non-consumables: Micro plate reader is a sensitive spectrophotometric and fluorimetric device with UV/visible range and detection of large number of samples with small sample
volume. This instrument will be required for whole cell inhibition assays by NCCLS methods and enzyme activity estimations in 96 well plates. It will also be useful in toxicity testing against cell lines.

**Manpower:** One JRF with life sciences background will work on biological evaluation of the synthesized molecules.

**Consumables:** The amount requested is for purchase of chemicals and reagents (substrates, known antifungal compounds, activators and inhibitors of CS, GlcN-6-P synthase, dehydrated culture media, medium supplements), gases, membrane filters, various types of glassware, plastic-ware including micropipettes, tips, stationary items etc.

**Travel:** The amount requested is for undertaking travel by the project investigators and staff for attending conferences, meetings etc. in India.

**Contingency:** For maintenance of instruments, cytotoxicity studies which will be outsourced to NCCS, Pune and other contingencies.

**Organic Chemistry Group, NCL, Pune**

**Budget (In Rupees)**

A. Non-Recurring (e.g. equipments, accessories, etc.)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Item</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Sub-Total (A): Rs. 0

B. Recurring

B.1 Manpower (See guidelines at Annexure-III)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Position No.</th>
<th>Consolidated Emolument</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 JRF</td>
<td>1 x16,000/- pm + 20 % HRA</td>
<td>2,30,400</td>
<td>2,30,400</td>
<td>2,30,400</td>
<td>6,91,200</td>
</tr>
</tbody>
</table>

Sub-Total (B.1) = Rs. 432000

B.2 Consumables

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Item</th>
<th>Quantity</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Consumables (fine chemicals, local chemicals, labwares)</td>
<td>--</td>
<td>1,00,000</td>
<td>1,50,000</td>
<td>1,50,000</td>
<td>4,00,000</td>
</tr>
</tbody>
</table>

Sub-Total (B.2) = Rs. 850000
<table>
<thead>
<tr>
<th>Other items</th>
<th>Consolidated Emolument</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.3 Travel</td>
<td></td>
<td>20000</td>
<td>20000</td>
<td>20000</td>
<td>60000</td>
</tr>
<tr>
<td>B.4 Contingency</td>
<td></td>
<td>20000</td>
<td>20000</td>
<td>20000</td>
<td>60000</td>
</tr>
<tr>
<td>B.5 Overhead (If applicable)</td>
<td></td>
<td>60000</td>
<td>60000</td>
<td>60000</td>
<td>180000</td>
</tr>
<tr>
<td>Sub-total of B (B.1+B.2+B.3+B.4+B.5)</td>
<td></td>
<td>4,30,400</td>
<td>4,80,400</td>
<td>4,80,400</td>
<td>13,91,200</td>
</tr>
<tr>
<td>Grand Total (A + B)</td>
<td></td>
<td>4,30,400</td>
<td>4,80,400</td>
<td>4,80,400</td>
<td>13,91,200</td>
</tr>
</tbody>
</table>

Justification:

**Budget for Manpower:** One JRF with masters degree in organic chemistry will work on design and synthesis of different inhibitor molecules.

**Budget for Consumables:** The amount requested is for purchase of chemicals and reagents, various types of glassware, plasticware, stationary items etc.

**Budget for Travel:** The estimated travel amount will be required to attend and present our findings in conferences, DBT monitoring meetings

**Budget for Contingency:** The contingency amount will be utilized for procuring urgent cash purchases of chemicals, glasswares, stationery items. Part of the money will be required for obtaining spectral data from outside NCL.
## PART V: EXISTING FACILITIES

Available equipment and accessories to be utilized for the project:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Infrastructural Facility</th>
<th>Yes/No/ Not required Full or sharing basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Workshop Facility</td>
<td>Yes</td>
</tr>
<tr>
<td>2.</td>
<td>Water &amp; Electricity</td>
<td>Yes</td>
</tr>
<tr>
<td>3.</td>
<td>Laboratory Space/ Furniture</td>
<td>Yes</td>
</tr>
<tr>
<td>4.</td>
<td>Power Generator</td>
<td>Yes</td>
</tr>
<tr>
<td>5.</td>
<td>AC Room or AC</td>
<td>Yes</td>
</tr>
<tr>
<td>6.</td>
<td>Telecommunication including e-mail &amp; fax</td>
<td>Yes</td>
</tr>
<tr>
<td>7.</td>
<td>Transportation</td>
<td>Yes</td>
</tr>
<tr>
<td>8.</td>
<td>Administrative/ Secretarial support</td>
<td>Yes</td>
</tr>
<tr>
<td>9.</td>
<td>Information facilities like Internet/ Library</td>
<td>Yes</td>
</tr>
<tr>
<td>10.</td>
<td>Computational facilities</td>
<td>Yes</td>
</tr>
<tr>
<td>11.</td>
<td>Shaker room</td>
<td>Yes</td>
</tr>
<tr>
<td>12.</td>
<td>Insect rearing and Bioassay facility</td>
<td>Yes</td>
</tr>
<tr>
<td>13.</td>
<td>Pot experiments</td>
<td>Yes</td>
</tr>
<tr>
<td>14.</td>
<td>Cold room</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Equipments available in Investigators laboratory:**

Rotary evaporator, High vacuum pump, Analytical balance, MSK cell homogeniser, Spectrophotometer, high speed centrifuge, Laminar air flow, Gradient Mixer, Lyophilizer, incubator shakers, Autoclaves, inverted microscope, bright field and fluorescence microscope, electrophoretic equipments, RT-PCR.
PART VI: DECLARATION/CERTIFICATION

It is certified that

a) the research work proposed in the scheme/project does not in any way duplicate the work already done or being carried out elsewhere on the subject.

b) the same project proposal has not been submitted to any other agency for financial support.

c) the emoluments for the manpower proposed are those admissible to persons of corresponding status employed in the institute/university or as per the Ministry of Science & Technology guidelines (Annexure-III)

d) necessary provision for the scheme/project will be made in the Institute/University/State budget in anticipation of the sanction of the scheme/project.

e) if the project involves the utilisation of genetically engineered organisms, we agree to submit an application through our Institutional Biosafety Committee. We also declare that while conducting experiments, the Biosafety Guidelines of the Department of Biotechnology would be followed in toto.

f) if the project involves field trials/experiments/exchange of specimens, etc. we will ensure that ethical clearances would be taken from concerned ethical Committees/Competent authorities and the same would be conveyed to the Department of Biotechnology before implementing the project.

g) it is agreed that any research outcome or intellectual property right(s) on the invention(s) arising out of the project shall be taken in accordance with the instructions issued with the approval of the Ministry of Finance, Department of Expenditure, as contained in Annexure-V.

h) we agree to accept the terms and conditions as enclosed in Annexure-IV. The same is signed and enclosed.

i) the institute/university agrees that the equipment, other basic facilities and such other administrative facilities as per terms and conditions of the grant will be extended to investigator(s) throughout the duration of the project.
j) the Institute assumes to undertake the financial and other management responsibilities of the project.
PART VII: BIOGRAPHICAL SKETCH OF INVESTIGATORS

Principal Investigator

Name: Dr. Mukund V. Deshpande.

Designation: Scientist G

Department/Institute/University: Biochemical Sciences

Date of Birth: 12-9-1952. Sex (M/F): M SC/ST: NA

Education (Post-Graduation onwards & Professional Career)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Institution Place</th>
<th>Degree Awarded</th>
<th>Year</th>
<th>Field of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>University of Pune</td>
<td>M.Sc.</td>
<td>1975</td>
<td>Microbiology</td>
</tr>
<tr>
<td>2</td>
<td>University of Pune</td>
<td>Ph D</td>
<td>1982</td>
<td>Biochemistry*</td>
</tr>
<tr>
<td>3</td>
<td>University of Pune</td>
<td>D Sc</td>
<td>1994</td>
<td>Microbiology**</td>
</tr>
</tbody>
</table>

*Title: Studies on Cellulases and Hemicellulases; **Title: Fungal Differentiation and Biochemical Correlates.

A. Position and Honors

Position and Employment (Starting with the most recent employment)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Institution Place</th>
<th>Position</th>
<th>From (Date)</th>
<th>To (date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>National Chemical Laboratory, Pune</td>
<td>Sci.G</td>
<td>1-3-2009</td>
<td>Till date</td>
</tr>
<tr>
<td>2</td>
<td>National Chemical Laboratory, Pune</td>
<td>Sci.F</td>
<td>1-3-2004</td>
<td>28-2-2009</td>
</tr>
<tr>
<td>3</td>
<td>National Chemical Laboratory, Pune</td>
<td>Sci.E-II</td>
<td>1-3-1998</td>
<td>28-2-2004</td>
</tr>
</tbody>
</table>

Honors/Awards

Doctor of Science degree has been awarded by the University of Pune, 1994.

Elected as Fellow of Maharashtra (State) Academy of Sciences in November 1994.

Awarded Department of Biotechnology Overseas (Short-term) Associateship (1995).

Awarded Commonwealth Science Council Fellowship (1998)

Citations:

The research papers published in Anal. Biochem. (138:481-, 1984) is one of the highly cited (98 citations) papers published from NCL (SMIS, October 8, 2001).

**Professional Experience and Training relevant to the Project**

1. Fungal morphogenesis: Dimorphism in *Benjaminiella poitrasii* and *Yarrowia lipolytica*; Conidiation in *Conidiobolus coronatus*
2. Carbohydrate based enzymes: Cellulases, chitinases and amylolytic enzymes. Other enzymes: Proteinases, nucleases, glucose isomerase and polyphenol oxidase.

Chitin metabolism as a target for biocontrol agents/ antifungal drugs Biosensors.

**B. Publications** (Numbers only) 104
*(Research papers, 64; Reviews, 12; Chapters, 28) Popular articles, 20 (English, Hindi and Marathi); Report, 3; Books, 4; Patents, 4; Technical brochures, 2*

**Selected peer-reviewed publications (Ten best publications in chronological order)**

3. P.Chavan, S. Mane, G.Kulkarni, S. Shaikh, V.Ghormade,D. Nerkar ,Y. Shouche, **M.V.Deshpande**. Natural yeast flora of different varieties of grapes used for wine making in India.(2009) Food Microbiolgy,26, 801-808. (IF 2.8).
Biological Evaluation of Bile Acid Dimers Linked with 1,2,3-Triazole and Bis-β-lactam. Org. Biomol. Chem. 6:3823-3830 (IF 3.55).


List maximum of five recent publications relevant to the proposed area of work.


C. Research Support

Ongoing Research Projects

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Title of Project</th>
<th>Funding Agency</th>
<th>Amount in Rs.</th>
<th>Date of sanction and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Development of sustainable pest management strategies based on entomopathogenic fungi &amp; cuticle degrading enzyme complex against mealybug, <em>Macconellicoccus hirsutus</em> (Green) on grapes in India</td>
<td>DBT, New Delhi</td>
<td>20,33000/-</td>
<td>2009-2012</td>
</tr>
<tr>
<td>2</td>
<td>“Development of Environmentally benign nanomaterial-based enzyme formulations for biocontrol of plant pathogens and pests.”</td>
<td>CSIR, New Delhi</td>
<td>16,51000</td>
<td>2009-2012</td>
</tr>
<tr>
<td>3</td>
<td>Transferring mycoinsecticide technology to the private sector.</td>
<td>SDC and DBT</td>
<td>33,74000/-</td>
<td>2009-2011</td>
</tr>
<tr>
<td>4</td>
<td>Studies on the pink berry disorder during ripening of the non pigmented Thompson Seedless (<em>Vitis Vinifera L</em>) grapes in Maharashtra</td>
<td>CSIR, New Delhi</td>
<td>6,00000/-</td>
<td>2008-2011</td>
</tr>
<tr>
<td>5</td>
<td>Molecular characterization of NADP-dependent glutamate dehydrogenase from zygomycetes fungus <em>Benjamiinia potrassii</em> Role in fungicide development.</td>
<td>DST</td>
<td>18,22000/-</td>
<td>2007-2010</td>
</tr>
</tbody>
</table>

Completed Research Projects (State only major projects of last 3 years)

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Title of Project</th>
<th>Funding Agency</th>
<th>Amount in Rs.</th>
<th>Date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Development of novel fungicides</td>
<td>CSIR</td>
<td>50,72,000/-</td>
<td>2004-2008</td>
</tr>
<tr>
<td>2</td>
<td>Biochemical and molecular profiling of wine spoilage yeasts and filamentous fungi. (Feb 2007-July 2009 DBT, New Delhi)</td>
<td>DBT</td>
<td>17,00000/-</td>
<td>2007-2009</td>
</tr>
<tr>
<td>3</td>
<td>Polyamines, dimorphism in <em>Yarrowia lipolytica</em> and the petroleum oil</td>
<td>DST</td>
<td>9,13,500/-</td>
<td>2004-2008</td>
</tr>
</tbody>
</table>
degradation in marine environment

<table>
<thead>
<tr>
<th>No.</th>
<th>Project Description</th>
<th>Funding Agency</th>
<th>Amount</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Development of a mycoinsecticide against <em>Helicoverpa armigera</em> in pluses: from the laboratory to the market</td>
<td>SDC and DBT</td>
<td>38,00,000/-</td>
<td>2004-2007</td>
</tr>
<tr>
<td>5</td>
<td>Scale-up, field demonstration and techno-economics of enzyme complex from <em>Myrothecium verrucaria</em> as a biocontrol agent</td>
<td>DBT</td>
<td>18,10,000/-</td>
<td>2003-2007</td>
</tr>
<tr>
<td>6</td>
<td>Exploration &amp; exploitation of microbial wealth of India for novel compounds and biotransformation processes (c) Chitosan production by fermentation using the fungus <em>Benjaminicella poitrasi</em> &amp; applications in chitosan-based drug carriers and human health care items</td>
<td>CSIR</td>
<td>4,90,850/-</td>
<td>2003-2007</td>
</tr>
</tbody>
</table>

**Co-Investigator**

**Name:** Dr. Sunita R. Deshpande.

Designation: Scientist: E-II

Department/Institute/University: Organic Chemistry Division

Date of Birth: 12-2-1952   Sex (M/F): F   SC/ST: NA

**Education (Post-Graduation onwards & Professional Career)**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Institution Place</th>
<th>Degree Awarded</th>
<th>Year</th>
<th>Field of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>University of Pune</td>
<td>M. Sc.</td>
<td>1974</td>
<td>Organic Chemistry</td>
</tr>
<tr>
<td>2</td>
<td>University of Pune</td>
<td>Ph. D.</td>
<td>1992</td>
<td>Chemistry*</td>
</tr>
</tbody>
</table>

*Title: Synthetic Studies in Bioactive Nitrogen, Oxygen and Sulfur heterocycles.

**Position and Honors**

Position and Employment (Starting with the most recent employment)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Institution Place</th>
<th>Position</th>
<th>From (Date)</th>
<th>To (date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>National Chemical Laboratory, Pune</td>
<td>Sci. E-II</td>
<td>1-2-2003</td>
<td></td>
</tr>
</tbody>
</table>

**Total Publications:**


6. Mitra R.B., Muljiasni Z., Deshpande S.R. Synthesis of 1,2,4-triazole fused heterocycles *Heterocycles*, 27, 1988, 2297


**Name: Dr. Santosh G. Tupe**

Designation: CSIR Research Associate (working in MVD’s group)

Department/Institute/University: Division of Biochemical Sciences


Education (Post-Graduation onwards & Professional Career)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Institution</th>
<th>Degree Awarded</th>
<th>Year</th>
<th>Field of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>University of Pune</td>
<td>M. Sc.</td>
<td>1999</td>
<td>Environmental Science</td>
</tr>
<tr>
<td>2</td>
<td>University of Pune</td>
<td>Ph. D. *</td>
<td>2008</td>
<td>Microbiology</td>
</tr>
</tbody>
</table>

*Title: ‘Microbial interactions with mercury compounds and their biotechnological applications’.

**Honors/Awards**

Post graduate research fellowship - 1998-1999, Awarded by University of Pune.
CSIR – Research Associateship – From April 2010 – till date
Publications:

8 (Research papers, 6; communicated papers 2)

1. Tupe R. S., Tupe S. G., Agte V. V. Dietary nicotinic acid supplementation improves zinc uptake and offers hepatoprotection against oxidative damage. British Journal of Nutrition, in press. (IF – 3.446)


Research papers communicated:


8. Maurya I. K., Pathak S., Sharma M., Sanwal H., Chaudhary P. M., Tupe S. G., Deshpande M. V., Chauhan V. S. and Prasad R. Novel synthetic antimicrobial peptides display fungicidal effect against various fungi and in Candida albicans the effect is via disruption of cell wall and accumulation of reactive oxygen species. Journal of Antimicrobial Chemotherapy Under review

Publication relevant to the proposed area of work

1. Maurya I. K., Pathak S., Sharma M., Sanwal H., Chaudhary P. M., Tupe S. G., Deshpande M. V., Chauhan V. S. and Prasad R. Novel synthetic antimicrobial peptides display fungicidal effect against various fungi and in Candida albicans the
effect is via disruption of cell wall and accumulation of reactive oxygen species. *Journal of Antimicrobial Chemotherapy* Under review