1. Only the Research Coordinator (i.e. the researcher responsible for the project) should request the login. Applications from students (e.g. graduate, Master or PhD students) are not accepted.

   Let me introduce myself that I am Dr. Prashant Singh and Assistant Professor of Chemistry at Atma Ram Sanatan Dharma College, University of Delhi, Dhaula Kuan, New Delhi-110021 since 2006 and four students are pursuing Ph.D. with me.

2. The project must contains the following parts (maximum 4 pages):
   - Researcher information:
     - Dr. Prashant Singh
     - Assistant Professor
     - Department of Chemistry
     - Atma Ram Sanatan Dharma College, University of Delhi
       Dhaula Kuan, New Delhi-110021
     - psingh@arsd.du.ac.in
   - Title of the Project

     Find potential inhibitors for "nsP2 and nsP3 protease of CHIKV"
   - Keywords: Inhibitors, Docking, MD simulations
   - Introduction

     Origin of the Problem

     Chikungunya fever (CHIKF) is caused by Chikungunya virus (CHIKV) but till date no effective medicine is available in market. The aim is to find various possible interactions between small molecules and non-structural proteins, viz. nsP3 as one of the most important viral elements in CHIKV. The investigator proposed few multicomponent reactions (MCRs) and wish to study the interactions of product i.e. heterocyclic compounds with nsP2 and nsP3 protease of CHIKV.

     Literature

     Fever is an abnormally high body temperature usually accompanied by shivering, headache and in severe instances delirium. An abnormally high body temperature, i.e., slightly greater than 37 ^{0}C is known as condition of fever. There are so many types of fever which are transmitted by mosquitoes. The main four types are dengue, malaria, chikungunya, and zika fever. Dengue is a mosquito borne viral disease occurring in tropical and subtropical areas and the

mosquito responsible for dengue is Aedesaegypti. Symptoms may include fever, bone pain, skin rash. Malaria is disease caused by a plasmodium parasite transmitted by the bite of infected Anopheles mosquito. Symptoms may include fever, vomiting, muscle pain. Zika fever is a disease caused by zika virus that is spread through aedes species mosquito bites. Symptoms may include fever, rash, joint pain, red eyes. Chikungunya is a viral infection transmitted by Aedesaegypti mosquito symptoms may include fever, joint pain, fatigue, rash, muscle pain, headache. It is spread by two types of mosquitoes Aedesalbopictus and Aedesaegypti. Chikungunya fever is a major public health issue in India affecting billions. After 2010, the infection was in a decline until in 2016, when a massive outbreak affected the country. CHIKV is a single stranded RNA virus from the family of Togaviridae and genus alpha virus. CHIKV contain three structural proteins: glycosylated E1 and E2, embedded in the viral envelope, and a nonglycosylated nucleocapsid protein. The non-structural polyprotein is divided into four different proteins (nsP1, nsP2, nsP3, and nsP4) which are necessary for the transcription and translation of viral mRNA inside the cytoplasm of host cells.

Current therapies for CHIKV-infected patients with arthritis/arthralgia mainly involve management of pain and inflammation using non-steroid anti-inflammatory drugs (NSAIDs), along with fluid intake to prevent dehydration. NSAIDs remain the primary approach for disease management as the use of aspirin may pose a risk of bleeding and potentially developing Reye's syndrome (causes swelling in liver and brain), and the administration of corticosteroids is likely to cause immunosuppression and complicate the disease. In patients who exhibit limited response to NSAIDs or those with chronic CHIKVD, disease-modifying anti-rheumatic drugs (the term "**antirheumatic drugs**" refers to agents used in the therapy of inflammatory arthritis) (DMARDs) such as methotrexate, hydroxychloroquine and sulfasalazine have been reported to reduce pain and joint swelling. As there are no licensed antivirals or vaccines available for CHIKV, there is a vital need for the development of novel and potent drugs and vaccines Chikungunya is caused by the Chikungunya virus (CHIKV), the most troublesome human Arboviral illness. It is responsible for Chikungunya fever (CHIKF) in the patients and causes severe joint pains and rashes on the body. CHIKV is a member of the *Alphavirus* genus in the family

Togaviridae. Literature reported that CHIKV is a self-limiting viral infection. In recent years, many researchers have focused on small chemical compounds to find their potential against Chikungunya virus. The breaking of polyproteins outcomes in five structural proteins (C, E3, E2, 6K, E1) as well four nonstructural proteins (nsP1, nsP2, nsP3, nsP4) with distinct functions. The nsP3 protease of CHIKV has the ability to replicate. Crystal structures of CHIKV macro domains are active as adenosine di-phosphoribose 1"-phosphate phosphatases. Macro domains of CHIKV are ADP-ribose binding modules and it is based on structural and functional analysis. A single aspartic acid conserved through macro domains is responsible for the specific binding of the adenine base. Sequence-unspecific binding to long and negatively charged polymers is observed. It is attributed to positively charged patches outside of the active site pocket. Several works have been reported on different flavonoids such as Artemisinin, Paclitaxel, Quinine, Reserpine, Baicalin, Naringenin and Quercetagetin to be potential molecules against different virus.[20-25] Till date, no medicine is currently available for curing CHIKV infection. Computational tools can be used as a cheap and practical approach to screen of potential compounds and find an effective molecule against the CHIKV. Molecular docking is a branch of bioinformatics and it has increased the drug design approach.

- Objectives
  - Design one pot multi-component reaction.
  - Screening of the thiazolidines against nsP2 and nsP3 protease of CHIKV based on their binding will be studied using computational tools like iGEMDOCK, Auto Dock.
  - DFT studies of the potential compounds will be performed.
- Methodology
  - Design one pot multi-component reaction based on thai/oxoazilidinedione.
  - DFT of the mechanism
  - Designing of the library based on the product obtained
  - Screening of the thiazolidines against nsP2 and nsP3 protease of CHIKV based on their binding will be studied using computational tools like iGEMDOCK, Auto Dock.

- DFT studies of the potential compounds will be performed.
- MD simulation

- Perspectives

  The aim is to find potential inhibitors for nsP2 as well nsP3 protease of CHIKV

- Signature