Report on participation of the ICMR International Fellow (ICMR-IF) in Training/Research abroad

1. Name and designation of ICMR- IF : Dr. Prashant Revan Murumkar
   Assistant Professor

2. Address : Faculty of Pharmacy
   Kalabhavan Campus
   The Maharaja Sayajirao University of
   Baroda,Vadodara-390 001
   Gujarat

3. Frontline area of research in which
   Training/research was carried out: Discovery of novel drugs for the treatment of
   Alzheimer's disease (AD)

4. Name & address of Professor and host Institute:
   Dr. Darreh-shori T
   Karolinska Institute
   Department of Neurobiology,
   Care Sciences and Society,
   Division of Translational Alzheimer
   Neurobiology
   Stockholm, Sweden

5. Duration of fellowship : Six Months

6. Highlights of work conducted

   i. Technique/expertise acquired:

   Successfully established High-Throughput Screening (HTS) *in-vitro* assay techniques based on 384 well-plate and used to screen a library of synthetic in-house database of novel compounds for their potential for Alzheimer's disease treatment.

   ii. Research results, including any papers, prepared/submitted for publication:

   A large in-house database of synthetic compounds having more than 200 compounds representing different scaffolds along with Tacrine and Donepezil reference standards were screened for their potential for the treatment of AD. A High-Throughput assay based on 384 well-plates was developed and used to determine the *In vitro* enzymatic activity of the cholinesterases, namely BuChE and AChE. The most potent compounds showed Ki values in the lower micromolar range for both AChE and/or BuChE. Only those compounds which

showed more than 75% inhibition of AChE/BuChE activity were selected for Ki determination. Total 12 compounds showed more than 75% inhibition of AChE. The most potent compound (comp. **150**) among the screened database showed AChE Ki value of 3.54 μM and found to be acting as competitive inhibitor. The other compounds (compound **3**, **9** and **49**) showed AChE Ki value of 17.68, 59.80 and 129.70 μM respectively. Compound **3** showed competitive type of inhibition whereas compound **9** and **49** showed non-competitive and mixed type of inhibition respectively (**Figure 1**).

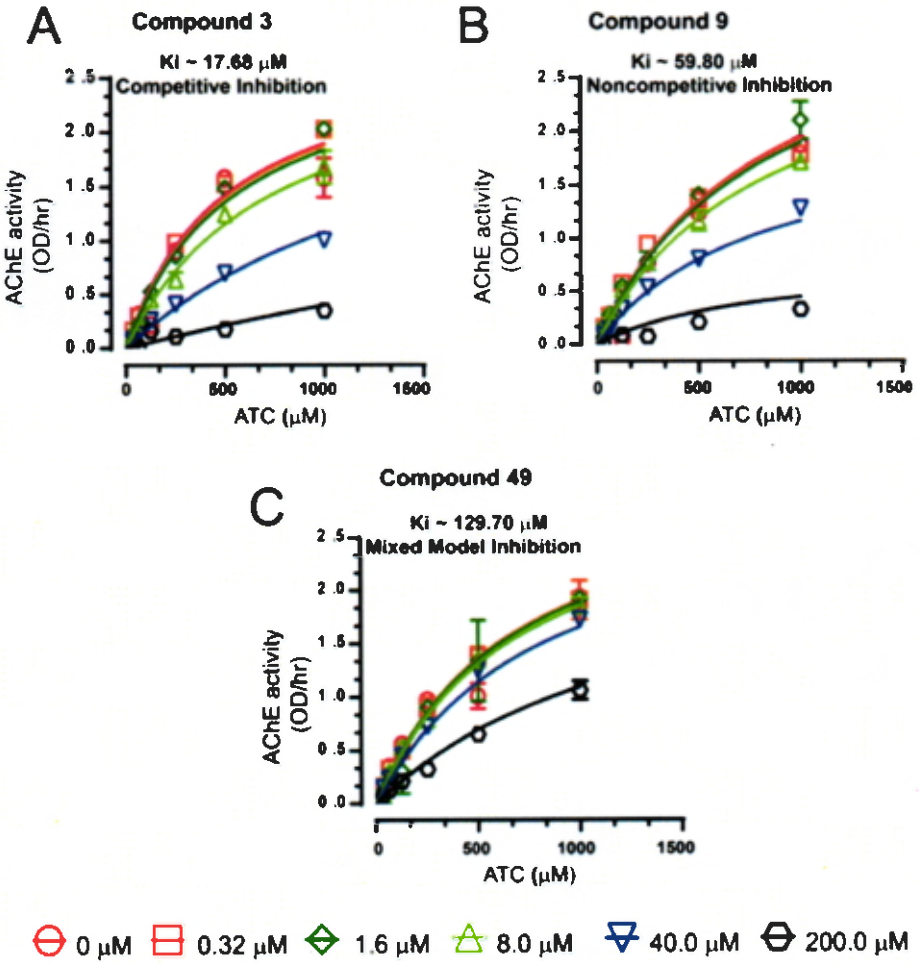

Figure 1: The substrate-velocity curve of AChE inhibition by **A.** Compound**(3)B.**Compound**(9)** and **C.**Compound **(49).**

As far as BuChE inhibitory activity is concerned, total 13 compounds showed more than 75% inhibition of BuChE. The most potent compound (compound **17**) among the screened database showed BuChE Ki value of 1.7 μM and found to be acting as competitive inhibitor (**Figure 2**). Other compounds (compound **2**, **9**, **18** and **24**) showed BuChE Ki values of 3.79, 17.58, 1.70, 2.00 and 129.70 μM respectively. Compound **2** and **18** showed competitive type of inhibition whereas compound **9** and **24** showed mixed-model inhibition. These compounds provided interesting scaffolds which have never been disclosed till

date having ChE inhibitory activity thus acting as templates for the development of novel ChE inhibitors.

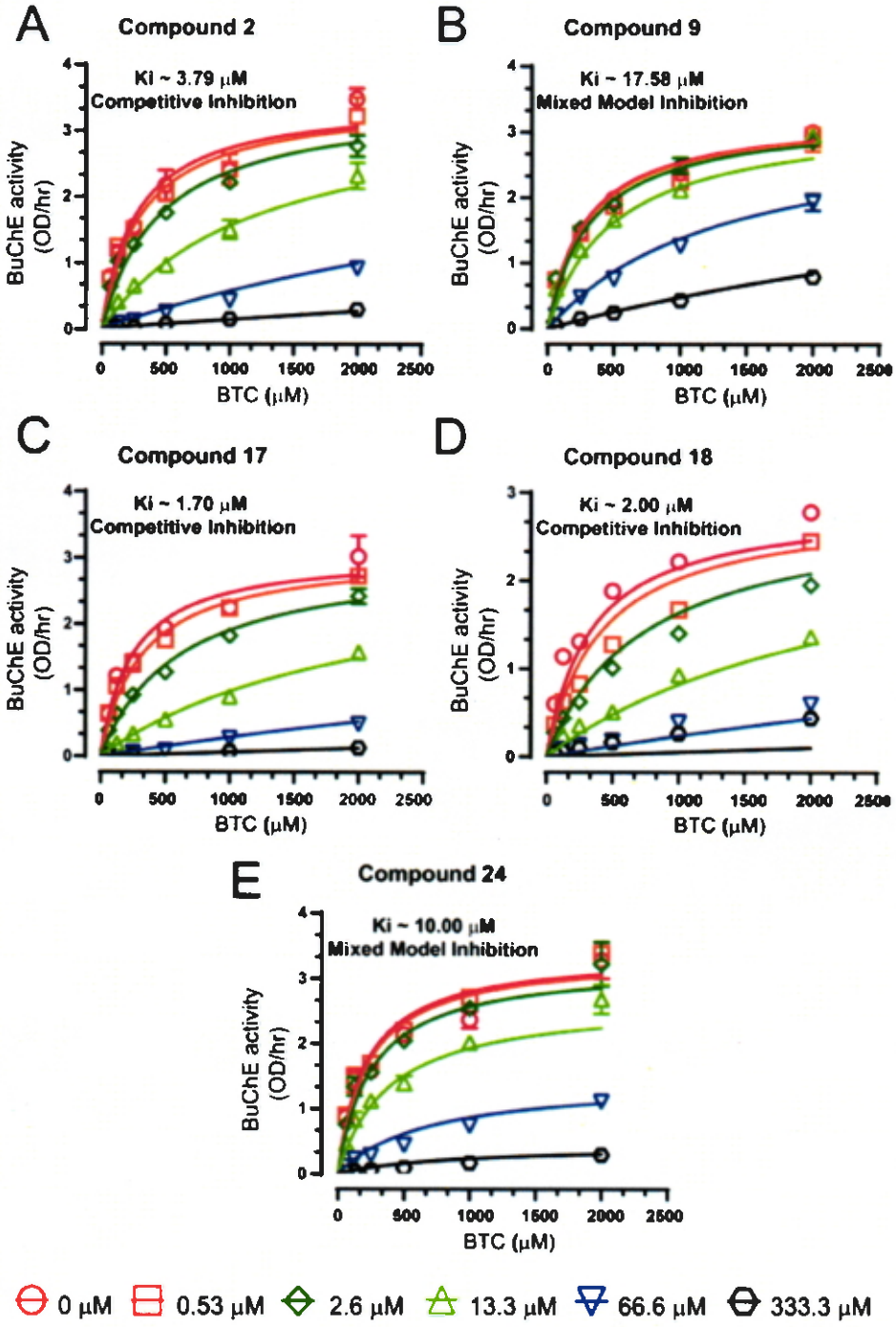

Figure 2: The substrate-velocity curve of BuChE inhibition by **A**. Compound**(2)** **B**.Compound**(9)** **C.** Compound**(17)D**.Compound**(18)** and **E.** Compound**(24)**

The more details about results and experimental process are given in **Annexure 1**.

Presentations/Talks:

Talk delivered on a topic entitled, "Assessment of In-House Synthetic Compound Libraries Based on *In-vitro* Inhibition of Cholinesterases" during Division Meeting held at Hotel von Kraemer, Uppsala organized by Division of

Translational Alzheimer Neurobiology, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Sweden on 15th June 2017.

Publications:
Preparation of the manuscripts out of the data generated during the period of six months has already been started and will be published jointly with host institute in the near future in high impact journals.

iii. Proposed utilization of the experience in India: Efforts would be made to establish the *in-vitro* assay facilities to prove the potential of the large data set of the compounds for the treatment of AD using various *in viro* cultural/animal models. Advanced facilities for carrying out research work related to AD would be created in our laboratory.

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Signature of ICMR-IF