SUMMARY OF FINAL PROJECT COMPLETION REPORT

UGC MINOR RESEARCH PROJECT

(February 2010 - January 2012)

Submitted to

UNIVERSITY GRANTS COMMISSION

BAHADUR SHAH ZAFAR MARG

NEW DELHI – 110 025

Project Title: "Design and Synthesis of Acetylcholinesterase Inhibitors"

File No.: 37-591/2009(SR)

Principal Investigator: **Dr. NASIMUL HODA**
Professor
Department of Chemistry
Jamia Millia Islamia
New Delhi 110 025

Department of Chemistry
Jamia Millia Islamia
New Delhi 110025

1. Name of the Faculty/ Department: **Department of Chemistry, F/o Natural Sciences**
2. Project Title: "**Design and Synthesis of Acetylcholinesterase Inhibitors"**
3. PI (name, affiliation and photograph):

Dr. Nasimul Hoda
Department of Chemistry,
Jamia Millia Islamia,
New Delhi 110025

4. Co-PI (if any) (name, affiliation and photograph): **NA**
5. Funding Agency: **University Grant Commission, New Delhi**
6. Amount funded: **Rs. 1,12000/-**
7. Duration of the project: **Two Years**
8. Starting date of the Project (and date of completion of projects for projects under category (II): **01/02/2010**
9. Project objectives (max 100 words):

   The main objectives of the proposed research programme are:

   (1) Design of Acetylcholinesterase inhibitors with the aid of molecular docking and Molecular dynamics tools .

   (2) Synthesis of designed inhibitors having various heterocyclic scaffolds.

   (3) Enzyme inhibition assay of designed inhibitors.

(4) $A\beta_{1-42}$ disaggregation, metal binding studies, CD spectroscopic, ADME property and TOPKAT analysis were also performed.

10. A brief overview/write up of the project (max 250 words; might include few important photographs or video files (can be sent separately) pertaining to the project): **NA**

11. Infrastructure created from the project (write up of max 50 words): **NA**

12. Project outcomes (research papers, articles, books, patents, seminars, workshops, conferences, training, innovations and AV materials etc.; kindly be provided in tabular form):

PI Publications:

1. A. Shandilya, **N. Hoda,** S. Khan, E. Jameel, J. Kumar, B. Jayaram, De novo lead optimization of triazine derivatives identifies potent antimalarials. ***Journal of Molecular Graphics and Modelling.*** 71 (2017) 96–103.
2. A. Singh, M. Maqbool, M. Mobashir, **N. Hoda*,** Dihydroorotate dehydrogenase: A drug target for the development of antimalarials. ***European Journal of Medicinal Chemistry.*** 125 (2017) 640–651.
3. J. Kumar, T. Umar, T. Kausar, M. Mobashir, S.M. Nayeem, **N. Hoda*,** Identification of lead BAY60-7550 analogues as potential inhibitors that utilize the hydrophobic groove in PDE2A: a molecular dynamics simulation study. ***Journal of Molecular Modeling.*** 23 (2017) 7.
4. E. Jameel, H. Naz, P. Khan, M. Tarique, J. Kumar, S. Mumtazuddin, S. Ahamad, A. Islam, F. Ahmad, **N. Hoda*,** M.I. Hassan. Design, synthesis, and biological evaluation of pyrimidine derivatives as potential inhibitors of human calcium/calmodulin-dependent protein kinase IV, ***Chemical Biology & Drug Design.*** (2016).
5. J. Kumar, P. Meena, A. Singh, E. Jameel, M. Maqbool, M. Mobashir, A. Shandilya, M.

Tiwari, **N. Hoda*,** B. Jayaram, Synthesis and screening of triazolopyrimidine scaffold as multi-functional agents for Alzheimer's disease therapies. ***European Journal of Medicinal Chemistry.*** 119 (2016) 260–277.

6. M. Maqbool, A. Manral, E. Jameel, J. Kumar, V. Saini, A. Shandilya, M. Tiwari, **N. Hoda*,** B. Jayaram. Development of cyanopyridine–triazine hybrids as lead multitarget anti-Alzheimer agents. ***Bioorganic & Medicinal Chemistry.*** 24 (2016) 2777–2788.
7. E. Jameel, T. Umar, J. Kumar, **N. Hoda*.** Coumarin: A Privileged Scaffold for the Design and Development of Antineurodegenerative Agents. ***Chemical Biology & Drug Design.*** 87 (2016) 21–38.
8. M. Maqbool, M. Mobashir, **N. Hoda*.** Pivotal role of glycogen synthase kinase-3: A therapeutic target for Alzheimer's disease, ***European Journal of Medicinal Chemistry.*** 107 (2016) 63–81.
9. H. Naz, E. Jameel, **N. Hoda*,** A. Shandilya, P. Khan, A. Islam, et al., Structure guided design of potential inhibitors of human calcium–calmodulin dependent protein kinase IV containing pyrimidine scaffold. ***Bioorganic & Medicinal Chemistry Letters.*** 26 (2016) 782–788.
10. **N. Hoda,** H. Naz, E. Jameel, A. Shandilya, S. Dey, M.I. Hassan, et al., Curcumin specifically binds to the human calcium-calmodulin-dependent protein kinase IV: fluorescence and molecular dynamics simulation studies. ***Journal of Biomolecular Structure & Dynamics.*** 34 (2016) 572–84.
11. T. Umar, **N. Hoda*.** Selective inhibitors of phosphodiesterases: therapeutic promise for neurodegenerative disorders. ***Med. Chem. Commun.*** 6 (2015) 2063–2080.

Summary and Findings:

In our endeavour towards the development of potent multitargeted ligands for the treatment of Alzheimer's disease, a series of triazine-triazolopyrimidine hybrids were designed, synthesized and characterized by various spectral techniques. Molecular docking tools were used to design the molecules and were synthesized *via* feasible convergent synthetic routes. In total, seventeen compounds were synthesized in which the di-substituted triazine-triazolopyrimidine derivatives (**9a-9d**) showed better acetylcholinesterase (AChE) inhibitory activity than the corresponding tri-substituted triazine-triazolopyrimidine derivatives (**10a-10f**). Out of the disubstituted triazine-triazolopyrimidine based compounds, **9a** and **9b** showed encouraging inhibitory activity on AChE with IC_{50} values 0.065 and 0.092 μM, respectively. Interestingly, **9a** and **9b** also demonstrated good inhibition selectivity towards AChE over BuChE by ~28 folds. Furthermore, kinetic analysis and molecular modeling studies showed that **9a** and **9b** target both catalytic active site as well as peripheral anionic site of AChE. In addition, these derivatives effectively modulated Aβ self-aggregation as investigated through CD spectroscopy, ThT fluorescence assay and electron microscopy. Besides, these compounds exhibited potential antioxidants (2.15 and 2.91 trolox equivalent by ORAC assay) and metal chelating properties. *In silico* ADMET profiling highlighted these novel triazine derivatives have appropriate drug like properties and possess very low toxic effects in the primarily pharmacokinetic study. Overall, the multitarget profile exerted by these novel triazine molecules qualified them as potential anti-Alzheimer drug candidates in AD therapy.