SUMMARY OF FINAL PROJECT COMPLETION REPORT

UGC MAJOR RESEARCH PROJECT

(July 2012 – December 2015)

Submitted to

UNIVERSITY GRANTS COMMISSION

BAHADUR SHAH ZAFAR MARG

NEW DELHI – 110 002

Project Title: Synthesis, Characterization and Biological Evaluation on the Metal Complexes of Novel *N*-substituted Phthalimide Ligands

File No.: 41-238/2012(SR) dated 13 July 2012

Principal Investigator: **Dr. RAHISUDDIN**
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1. Name of the Faculty/ Department: **Department of Chemistry, F/o Natural Sciences**

2. Project Title: "**Synthesis, characterization and biological evaluations on the metal complexes of novel *N*-substituted phthalimide ligands"**

3. PI (name, affiliation and photograph):

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4. Co-PI (if any) (name, affiliation and photograph): **NA**

5. Funding Agency: **University Grant Commission, New Delhi**

6. Amount funded: **Rs. 9,85,800/-**

7. Duration of the project: **Three Years**

8. Starting date of the Project (and date of completion of projects for projects under category (II): **July 2012**

9. Project objectives (max 100 words):

   The main objectives of the proposed research programme are:

   (1) Synthesis and characterization of novel N-Pyrimidinyl substituted phthalimide ligands.

   (2) Synthesis and characterization of novel N-Pyridinyl substituted phthalimide ligands.

   (3) Synthesis and characterization of Ni(II), Cu(II), Ru(III), Pt(II) metal complexes of the ligands.

(4) Calf Thymus DNA interaction of metal complexes by kinetic studies.

(5) Cell line activities of the *N*-substituted phthalimide ligands and their metal complexes.

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):

Published Papers:

1. Pattan Sirajuddin Nayab, Madhusudana Pulaganti, Suresh Kumar Chitta and **Rahisuddin**, A new isoindoline based Schiff base derivative as Cu(II) chemosensor: Synthesis, photophysical, DNA binding and molecular docking studies,
   ***Journal of Fluorescence,* (2015) 25, 1763–1773.**
2. Pattan Sirajuddin Nayab, Madhusudana Pulaganti, Suresh Kumar Chitta, Mohammad Abid and **Rahisuddin**, Evaluation of DNA binding, radicals scavenging and antimicrobial studies of newly synthesized *N*-substituted naphthalimides: Spectroscopic and molecular docking investigations,
   ***Journal of Fluorescence,* (2015) 25, 1905–1920.**
3. Pattan Sirajuddin Nayab, Rizwan Arif, Mohd. Arshad, **Rahisuddin**, Synthesis, characterization, antibacterial, DNA binding and molecular docking studies of novel N-substituted phthalimides,
   ***Heterocyclic Letters*, (2015) 5, 223-239.**
4. Pattan Sirajuddin Nayab, M. Pulaganti, S.K. Chitta, Mohd. Oves, **Rahisuddin**, Synthesis, spectroscopic studies of novel *N*-substituted phthalimides and evaluation of their antibacterial, antioxidant, DNA binding and molecular docking studies,
   ***Bangladesh Journal of Pharmacology*, (2015) 10, 703-713.**
5. Rizwan Arif, Pattan Sirajuddin Nayab, **Rahisuddin**, Synthesis, characterization, DNA binding, morphological studies, antibacterial and antioxidant activity of new bis-phthalimides,
   ***Russian Journal of General Chem*istry, (2016) 86, 1374-1380.**
6. Pattan Sirajuddin Nayab, Madhusudana Pulaganti, Suresh Kumar Chitta, **Rahisuddin**, Multi-spectroscopic and molecular docking studies on the interaction of new phthalimides with *calf-thymus* DNA: *In vitro* free radical scavenging activities,
   ***Spectroscopy Letters,* (2016) 49, 108-117.**

7. Akrema and **Rahisuddin**, Biomediated unmodified silver nanoparticles as a green probe for Cu^{2+} ion detection,
***Sensor Letters,* (2015) 13, 953-960.**

8. **Rahisuddin** and Akrema, Extracellular synthesis of silver dimer nanoparticles using *Callistemon viminalis* (bottlebrush) extract and evaluation of their antibacterial activity,
***Spectroscopy Letters,* (2016) 49, 268-275.**

9. Pattan Sirajuddin Nayab, Mohammad Irfan, Mohammad Abid, Madhusudana Pulaganti, Chinthakunta Nagaraju, Suresh Kumar Chitta, **Rahisuddin,** Experimental and molecular docking investigation on DNA interaction of N-substituted phthalimides: Antibacterial, antioxidant and hemolytic activities,
***Luminescence,* (2016) DOI 10.1002/bio.3178.**

10. Pattan Sirajuddin Nayab, Akrema, Istikhar A. Ansari, Mohammad Shahid, **Rahisuddin,** New Phthalimide-Appended Schiff Bases: Studies of DNA Binding, Molecular Docking and Antioxidant Activities,
***Luminescence,* (2016) DOI 10.1002/bio.3259.**

Poster/ Paper presented in Conferences:

1. Synthesis, Characterization and Biological Evaluation of Bis-phthalimide Derivatives in International Conference on Chemistry: Frontiers and Challenges, Department of Chemistry, Aligarh Muslim University, Aligarh, UP held on 2-3 March 2013.
2. Design, Synthesis, Characterization and Biological Evaluation of Bis-Phthalimide Derivatives in National Symposium on Chemistry under SAP (DRS-I), Department of Chemistry, Aligarh Muslim University, Aligarh, UP on 22 March, 2014.
3. Synthesis, Characterization and Biological Activity of Ni(II) and Cu(II) Complexes with Macrocyclic Ligand in National Seminar on "Metal Toxicity and Oxidative Stress" that the Department of Biosciences, Jamia Millia Islamia, held on 23-24 September, 2014.
4. Synthesis and Spectroscopic Characterization of Co(II), Ni(II) and Cu(II) Complexes with Schiff Base Ligand in National Conference entitled "Interdisciplinary Approaches in Chemical Sciences" (IACS-2015) Jamia Millia Islamia, New Delhi held on 16 December, 2015.
5. Synthesis and Structural Investigation and DNA Binding Studies of Phthalimide Base Transition Metal Complexes: *In Vitro* Free Radicals Scavenging Activities in International Conference on Recent Advances in Chemical Sciences, Department of Chemistry, Aligarh Muslim University, Aligarh held on 29-30 March, 2016.

Invited Talk:

- DNA Binding Studies of N-Substituted Phthalimide Derivatives: A Green Synthetic Approach in National Conference on Green Chemical Technologies for the Progress of the Nation. SISTech., Bhopal, 19th September, 2015.

Summary and Findings:

In this project, we have synthesized twenty four (**24**) *N*-substituted phthalimide derivatives by the condensation reaction of phthalic anhydride/tetrachlorophthalic anhydride/phthalimide with respective substituted amines. The reaction was monitored by thin layer chromatography in suitable solvent systems. The synthesized *N*-substituted phthalimide derivatives were characterized with the help of CHNS analyzer, melting point apparatus, UV-visible, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry. To examine the DNA binding strength of the compounds absorption spectroscopy, viscosity measurements, cyclic voltammetry and fluoremetric measurements methods were performed and for the elucidation of binding affinity and intercalation modes, molecular docking studies have been carried out. The antibacterial activity of all *N*-substituted phthalimide derivatives was investigated against a panel of bacterial strains *Escherichia coli* (MTCC-739), *Streptococcus mutans* (MTCC-737), *Klebsiella pneumoniae* (MTCC-109), *Salmonella typhimurium* (MTCC-98) and *Staphylococcus aureus* and toxicity was assessed by hemolytic assay performed on human RBCs. The antioxidant potential of the N-substituted phthalimide derivatives was evaluated by DPPH free radical and hydrogen peroxide scavenging assays.

All the synthesized *N*-substituted phthalimide derivatives are stable in air and soluble in DMSO, DMF and ethanol. From the DNA binding studies, it has been concluded that all the *N*-substituted phthalimide derivatives showed non-intercalative mode of binding or grove binding except compounds **12** and **13** which showed intercalative mode of binding. The intrinsic binding constant of the *N*-substituted phthalimide derivatives was calculated with the help of absorption measurements which also revealed the intercalative binding mode of the phthalimide derivatives. In general, small molecules prefer minor groove-binding site, whereas large molecules interact

with the minor groove as the narrow shape of the former. The minimum binding energy was calculated for most potent phthalimide derivatives (**2, 4, 8, 9, 10, 22** and **23)**. More negative relative binding energy of compounds indicated its strong binding ability to the DNA and the results indicate that the Cu(II) complex **23** of *N*-substituted phthalimide ligand (-374 kcal/mol) has made stronger interactions with the B-DNA than all other phthalimide compounds. While comparing antibacterial activity results among all the phthalimide derivatives, it has been found that compounds **2, 12** and **13** showed very promising activity against *E. coli* and *S. mutans* and compound **7** against both *K. pneumoniae* and *S. typhimurium* bacteria strains. Phthalimide derivative **4** strongly inhibit the growth of *E. coli* while it exhibited moderate activity against *S. mutans*. However, phthalimide derivatives **8** and **9** were found to be potent inhibition against *E. coli* and *S. aureus*. The investigation of structure activity relationship (SAR) showed that the strongest potential for the phthalimide derivative **2, 12** and **13** against *E. coli* and *S. mutans* were observed due to presence of lipophilic -OCH_3 group on phenyl ring while introduction of an additional -OH moiety into the *para* position of phenyl ring, bearing –OC_2H_5 group in *meta* position as in compound **4**, led to further increase in its antibacterial activities.

The compound **22** was found to be promising antibacterial agent against *K. pneumoniae* and *E. coli.* Moreover, on complexation with Cu(II) ion, antibacterial potential was increased many fold. Cu(II) complex was found to be very effective against *K. pneumoniae* and *E. coli* strains with MBC 0.062 mg/mL which is consistent with standard drug ciprofloxacin.

On the basis of antibacterial activity findings, most potent phthalimide derivative **8, 9, 10** and **23** were selected for hemolytic assay. At a concentration **125 µg/mL** molecules **8, 9** and **10** exhibited less than 20% hemolysis and concentration was also comparable with their IC_{50} values against *E. coli*. However, compound **10** showed less than 25% hemolysis at its IC_{50} against *S.*

aureus and approximate 62% hemolysis at **125 µg/mL** validate its toxic nature against human RBCs. In the hemolytic assay, Cu(II) complex of phthalimide ligand **23** showed less than 2% hemolysis of human RBCs at MIC indicating its non-toxic nature.

The investigation of antioxidant activity of all the compounds revealed that the compounds **12, 13, 19, 22** and **23** exhibited a greater activity due to the presence of –OH group and -NH group. Phthalimide derivatives with electron donating group displayed good activity whereas other compounds showed moderate activity due to the presence of mild electron donating group such as methyl, chloro and bromo attached to the benzene ring and the compounds **22** and **23** showed the greater rate of H_2O_2 scavenging activity. These results are accordance with the results obtained by DPPH free radical method.

The study leads to identification of small molecule antibacterial compounds that can be developed further after structural optimization and structure activity relationship.