

**EXECUTIVE SUMMARY OF THE FINAL REPORT OF THE
WORK DONE ON THE PROJECT**

PROJECT TITLE

“Synthesis and stereochemical studies of 6-hydroxy-4,8,9,10-tetraphenyl-1,3-diazaadamantanes and 6-amino-4,8,9,10-tetraphenyl-1,3-diazaadamantanes”

UGC Ref. No.: F. No. 42-358/2013 (SR) dated 25.05.2013

Major Research Project Final Report Submitted to
University Grants Commission
New Delhi

By

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Report of the work done

Brief objectives of the project

- ❖ To reduce the ketones in order to obtain the corresponding hydroxyl compounds using various reducing agents
- ❖ To synthesis 4,8,9,10-tetraaryl-1,3-diazaadamantane-6-one and oximes of the corresponding ketones.
- ❖ To reduce the oximes in order to obtain the corresponding amino compounds using various reducing agents.
- ❖ Spectral and XRD studies of alcohols and amines will be carried out to understand the spectro chemical nature of compounds.
- ❖ Biological activities of the newly synthesized alcohols and amines will be studied.

Objectives done on the project and additional outcome of the project

- ❖ The reduction of a ketone would normally yield on alcohol and we expected 6-hydroxy-4,8,9,10-tetraaryl-1,3-diazaadamantane from the reduction of 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-one. But, to our surprise, the product on analysis by FT-IR, ¹H, ¹³C NMR and 2D NMR spectral study was found to be 2,4,6,11-tetraaryl-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane.
- ❖ Five new compounds were synthesised, three of the compounds were unambiguously confirmed by a single crystal XRD. Furthermore, crystal packing arrangement, Hirshfeld surfaces and two-dimensional fingerprint analysis of three compounds were carried out.
- ❖ The above five new piperidine and oxaquinuclidine core containing derivatives as an efficient corrosion inhibitor for copper in nitric acid medium: electrochemical,

DFT, molecular dynamic simulation and surface morphological studies were carried out.

- ❖ Fifteen 4,8,9,10-tetraaryl-1,3-diazaadamantane-6-one oximes were synthesized and conformed by 1D, 2D NMR and single crystal XRD.
- ❖ Stereochemical orientation of the four phenyl groups and conformation of the bispidine ring was studied using 2D NMR (COSY, NOESY, HSQC, HMBC).
- ❖ Unexpected iodine catalyzed rearrangement of tetraarylpiperidin-4-ones: Synthesis, structure analysis and biological investigation of 5-aryl-2-methoxy-2,4-diphenyl-1H-pyrrole-3-ones were studied.
- ❖ Quantum chemical, experimental, theoretical spectral (FT-IR and NMR) studies and molecular docking investigation was carried out in 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-ones.
- ❖ Copper corrosion inhibition studies of Diaza-adamantane derivatives were investigated.

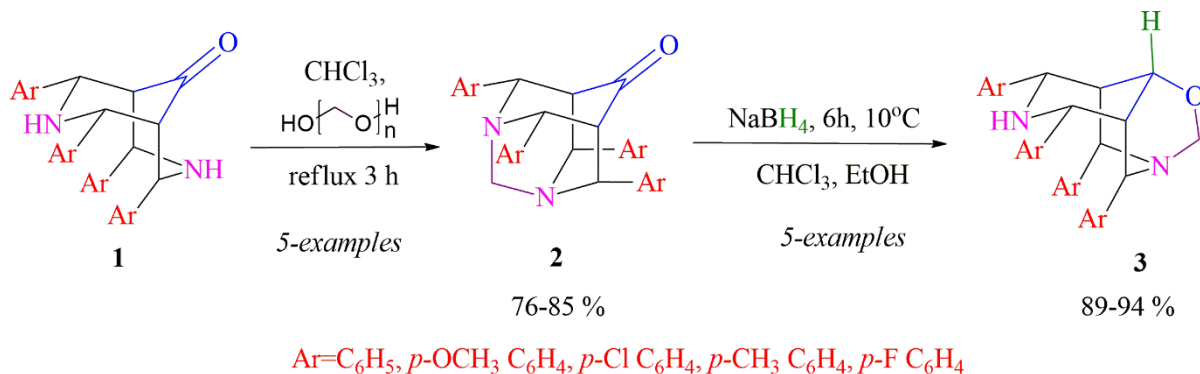
Summary of the findings

Unprecedented synthesis, 1D, and 2D NMR spectral studies of 2,4,6,11-tetraaryl-9-oxa-1,5-diazatricyclo[5.3.1.0^{3,8}] undecane via a novel rearrangement

A novel rearrangement of a methylene group from nitrogen to oxygen was observed during sodium borohydride or lithium aluminium hydride reduction of 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-one. Resulting new compounds, 2,4,6,11-tetraaryl-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane, containing an oxaquinuclidine skeleton, was

characterized along with its stereochemistry by 2D-NMR and single crystal XRD techniques.

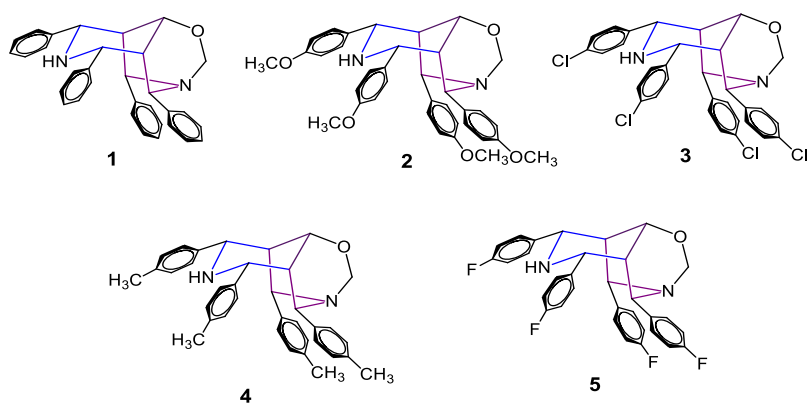
Reaction Scheme



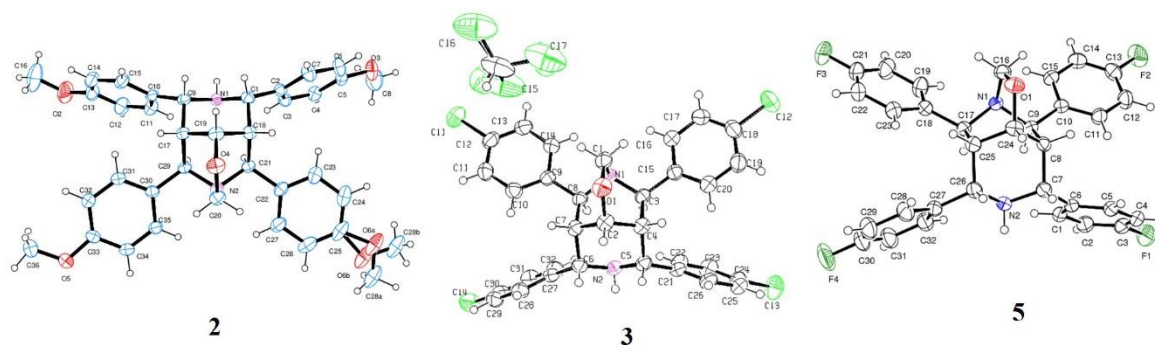
Highlights

- ❖ An unusual rearrangement of a methylene group from nitrogen to oxygen is reported for the synthesis of novel 2,4,6,11-tetraaryl-9-oxa-1,5-diazatricyclo [5.3.1.0^{3.8}] undecane derivatives.
- ❖ The mechanism for this unusual rearrangement is proposed.
- ❖ The synthesized compounds have been characterized by 1D, 2D-NMR techniques and single crystal XRD.

Structure of the newly synthesized compounds



Crystal structure of the compound 2, 3 and 5



Crystal structure and Hirshfeld surface analysis of compound 2, 3 and 5

The crystal structures of 2,4,6,11-tetraaryl (4-methoxyphenyl)-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane (**2**), C₃₆H₃₈N₂O₅, 2,4,6,11-tetraaryl (4-chlorophenyl)-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane (**3**), C₃₂H₂₆Cl₄N₂O and 2,4,6,11-tetraaryl (4-fluorophenyl)-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane (**5**), C₃₂H₂₆F₄N₂O. The compounds crystallize in monoclinic space group P 21/c (**2**), P 21/n (**3** and **5**) with four molecules in the unit cell (Z=4). The crystal packing of the compounds (**2**), (**3**) and (**5**) are largely stabilized by C–H...O, C–H...Cl and C–H...F hydrogen bonding interactions, respectively. Two of the crystal ribbons layers are further stabilized by C–H... π and π ... π interactions. Hirshfeld surfaces and two-dimensional fingerprint analysis shows that H...H van der Waals interactions are majorly present in the crystal packing.

Comparison of five new piperidine and oxaquinuclidine core containing derivatives as an efficient corrosion inhibitor for copper in nitric acid medium: electrochemical, DFT, molecular dynamic simulation and surface morphological studies

The inhibition efficiency of copper corrosion in 1 M HNO₃ by five piperidine and oxaquinuclidine core containing compounds namely 2,4,6,11-tetraaryl-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane (**1**), 2,4,6,11-tetraaryl (4-methoxyphenyl)-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane (**2**), 2,4,6,11-tetraaryl (4-chlorophenyl)-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane (**3**), 2,4,6,11-tetraaryl-p-tolyl-9-oxa-1,5-diazatricyclo

[5.3.1.0^{3,8}] undecane (**4**), and 2,4,6,11-tetraaryl (4-fluorophenyl)-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane (**5**) were investigated using gravimetric method, electrochemical studies, FT-IR, scanning electron microscopy (SEM), energy dispersive X-ray analysis (EDX), DFT and molecular dynamic stimulation techniques. The results obtained from the above methods reveal that compound **2** is the best inhibitor among the five studied compounds and the efficiency of the inhibitor increases with increasing the concentration of inhibitors. The adsorption of tested inhibitors on copper surface obeyed Langmuir adsorption isotherm. Potentiodynamic polarization results show that compounds are acting as a mixed type of inhibitors. FT-IR, SEM, and EDX analyses supported the formation of a protective film on the copper surface. Quantum chemical parameters and molecular dynamics stimulation studies further evidenced by the inhibitor adsorption of the copper surface. The Fukui function and Molecular electrostatic potential (MEP) analysis used to identify the electron donating and accepting the ability of atoms/groups.

Synthesis, 1D and 2D NMR spectral assignments and stereochemical studies of some 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-one oximes

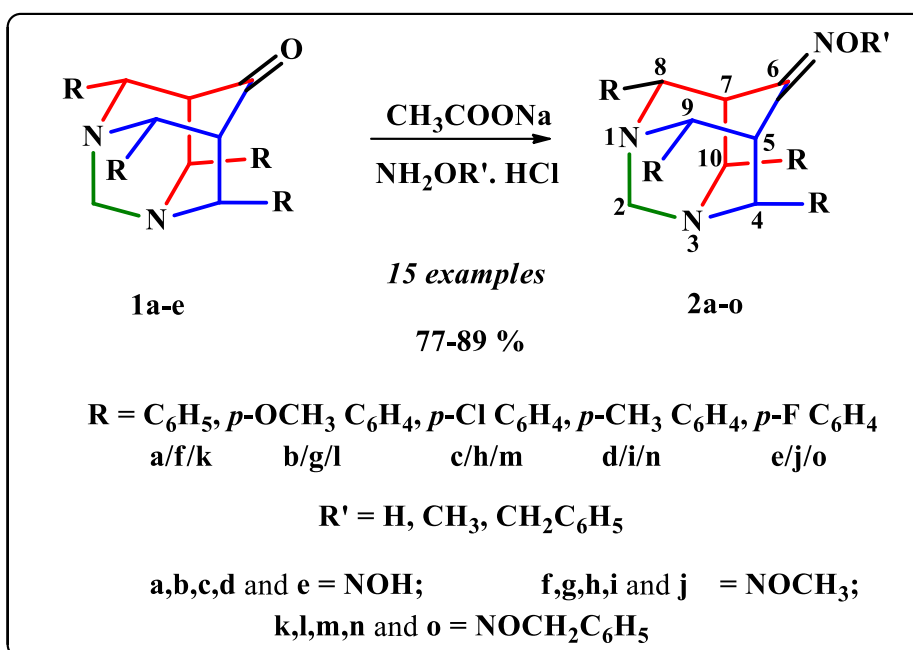
A series of 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-one oximes (**1-5**) have been synthesized. ¹H and ¹³C NMR spectra of these oximes were recorded. Chemical shifts have been assigned and the stereochemistry of the compounds was established using 1D and 2D NMR spectral data. A detailed spectral investigation was carried out for one of the representative compounds (**1**) with COSY, NOESY, HSQC, HMBC, DEPT-135 and ¹⁵N NMR spectral data. The NMR result clearly indicated the twin chair conformation of the two piperidine rings. The NMR results proved the axial orientation of two aryl groups (C4 and C10) in one piperidine ring and equatorial orientation of two aryl groups (C8 and C9) in another piperidine ring. The effect of allylic (A^{1,3}) interaction between the oxime hydroxyl

group and H-5e has been observed. Long-range coupling between H-10e and H-2 which are in 'W' arrangement is noted.

Synthesis, 1D and 2D NMR spectral assignments and stereochemical studies of some 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-one oxime ethers

Series of 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-one oximes and the oxime ethers (**2a-2o**) have been synthesised. ^1H and ^{13}C NMR spectra of these oximes were recorded. Chemical shifts have been assigned and the stereochemistry of the compounds was established using 1D and 2D NMR spectral data. A detailed spectral investigation was carried out for the representative compounds (**2a**, **2j** and **2o**) with COSY, NOESY, HSQC, HMBC and DEPT-135 NMR spectral data. Compound **2h** further confirmed by single crystal XRD. The NMR and XRD results proved that, these compounds exhibit same type of orientation and conformation of the rings in 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-one oximes. The effect of allylic ($A^{1,3}$) interaction and oximation effect only varies in these compounds.

Reaction Scheme



Iodine mediated rearrangement of tetraarylpiperidin-4-ones: Synthesis, structure analysis and biological studies of 5-aryl-2-methoxy-2,4-diphenyl-1H-pyrrole-3-ones

An interesting iodine/methanol mediated rearrangement of tetraarylpiperidin-4-ones to 2-methoxy-2,4,5-triaryl-1H-pyrrole-3-ones is described. The structural features of the products are investigated by spectral data and single crystal X-ray analysis. The antifungal, antibacterial and antioxidant characteristics of the synthesised compounds were studied.

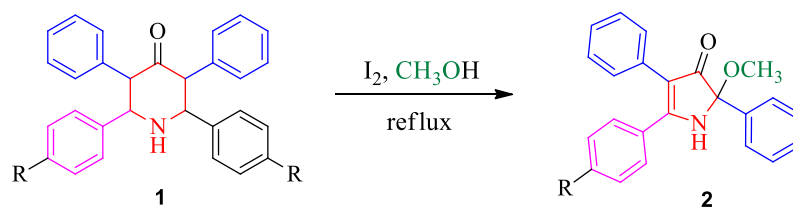
Unexpected reaction

In an attempt to dehydrogenate tetra aryl substituted piperidin-4-one to pyridine-4-ol, the oxidative aromatization of 2,3,5,6-tetraarylpiperidin-4-one (**1**) was aimed employing iodine and methanol. It was anticipated that the presence four aryl groups could drive the piperidone ring to complete aromatization providing conjugation delocalizing the pyridyl ring electrons. The reaction was carried out with iodine in methanol. The product obtained has been shown to be 2,4,5-triaryl-2-methoxy-1H-pyrrol-3-one (**2**) (*vide infra*) instead of the expected 3,5-diphenyl-2,6-diaryl pyridin-4-ol.

Highlights

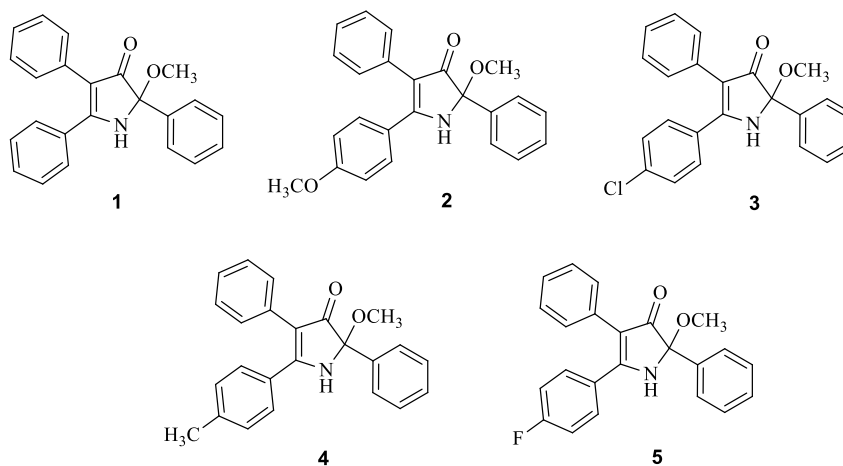
- ❖ The conversion of tetraarylpiperidin-4-ones to 5-aryl-2-methoxy-2,4-diphenyl-1H-pyrrole-3-ones in presence of iodine-methanol is reported.
- ❖ The mechanism for the ring contraction rearrangement is proposed.
- ❖ New compounds obtained after rearrangement have been characterized by 1D, 2D-NMR techniques and single crystal XRD.
- ❖ Synthesized new compounds exhibit good antimicrobial, antifungal and antioxidant properties.
- ❖ Crystal packing, Hirshfeld surface and two-dimensional fingerprint analysis have been carried out.

Reaction Scheme

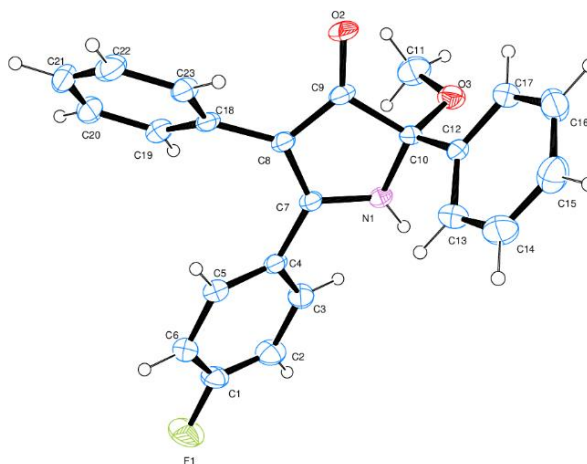


a) R = H; b) R = OCH₃; c) R = Cl; d) R = CH₃; e) R = F

Structure of the new compounds



Single crystal XRD structure of the compound 5



Quantum chemical, experimental, theoretical spectral (FT-IR and NMR) studies and molecular docking investigation of 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-ones

The compounds 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-ones were synthesized and characterized by FT-IR, ¹H and ¹³C NMR spectra, and the spectral data have been

theoretically analyzed by the DFT method. The electronic properties including a highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO) and related parameters were calculated with B3LYP/6-311 G (d, p) basis set. The observed HOMO and LUMO mappings describe the different charge transfer possibilities within the molecule. Besides, the reactive properties of the molecules have been addressed based on the frontier molecular orbital analysis. The Molecular Electrostatic Potential (MEP) and Fukui function analysis reveal the sites for electrophilic attack and nucleophilic reactions in the molecule. The intramolecular contacts have been interpreted using Natural Bond Orbital analysis and the thermodynamic properties also presented. The molecular docking study has been executed to study the binding interactions of the synthesized compounds with H1N1 swine virus-M2 proton channel and COX-2 protein.

Highlights

- ❖ The Quantum Chemical calculations were performed using DFT/B3LYP/6-311 G (d, p) level of theory.
- ❖ Molecular Electrostatic Potential (MEP) and Natural Bond Orbital (NBO) have been evaluated.
- ❖ HOMO, LUMO energies and Fukui functions were calculated.
- ❖ The Molecular docking study confirmed that the compounds are good binding properties against H1N1 swine virus and COX-2 protein.

Diaza-adamantane derivatives as corrosion inhibitor for copper in nitric acid medium

The effect of newly synthesized 6-hydroxy-5,7-diphenyl-1,3-diazaadamantane (HDDA) and 5,7-diphenyl-1,3-diazaadamantan-6-one (DDA) against the corrosion of copper in 1 M HNO₃ solution was investigated using potentiodynamic polarization, electrochemical impedance spectroscopy (EIS) and weight loss measurements. These

measurements show that the inhibition efficiency (IE %) obtained by these compounds increased by increasing their concentrations, and maximum IE % to 90.84 % for HDDA and 89.87 % for DDA were found at 300 ppm. Data obtained from EIS studies were analyzed by an equivalent circuit model. EIS plots indicated that the inhibitor performance depends on the adsorption of the molecules on the metal surface. Polarization measurements showed that both HDDA and DDA are mixed-type but predominantly cathodic in 1 M HNO₃ solution. The adsorption of inhibitors on the copper surface from the nitric acid follows the Langmuir adsorption isotherm with a negative value of free energy, and these values indicated that adsorption of both HDDA and DDA molecules adsorbs physically on the copper surface. The surface morphology was examined by scanning electron microscope and atomic force microscope. Further, theoretical calculations were carried out and relationships between computed parameters and experimental IE % were discussed. All the results confirmed that e HDDA showed better efficiency in 1 M HNO₃ compared to DDA.

Papers Published

- [1] G.Vengatesh, **M. Sundaravadivelu**, S.Muthusubramanian, Iodine mediated rearrangement of tetraarylpiperidin-4-ones: Synthesis, structure analysis and biological studies of 5-aryl-2-methoxy-2,4-diphenyl-1*H*-pyrrole-3-ones. *J mol str.* (2019). <https://doi.org/10.1016/j.molstruc.2019.126980>
- [2] G. Vengatesh, **M. Sundaravadivelu**, Unprecedented synthesis, 1D, and 2D NMR spectral studies of 2,4,6,11-tetraaryl-9-oxa-1,5-diazatricyclo[5.3.1.0^{3,8}]undecane via a novel rearrangement, *Magn. Reson. Chem.* 57 (2019) 522-529. <https://doi.org/10.1002/mrc.4893>
- [3] G. Vengatesh, **M. Sundaravadivelu**, Robert Swinton Darious, “Crystal structure and Hirshfeld surface analysis of 2,4,6,11-tetrakis (4-fluoro-phenyl)-9-oxa-1,5-diazatricyclo [5.3.1.0^{3,8}] undecane” *Acta Cryst.* E74 (2018) 1867–1871. <https://doi.org/10.1107/S2056989018016122>
- [4] G. Vengatesh, **M. Sundaravadivelu**, Synthesis, 1D and 2D NMR spectral assignments, and stereochemical studies of some 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-one oximes, *Structural Chemistry.* (2019). <https://doi.org/10.1007/s11224-019-01326-9>.
- [5] G.Vengatesh, **M. Sundaravadivelu**, Quantum chemical, experimental, theoretical spectral (FT-IR and NMR) studies and molecular docking investigation of 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-ones, *Res Chem Intermediat.* 45 (2019) 4395-4415. <https://doi.org/10.1007/s11164-019-03838-9>.
- [6] G.Karthik, **M.Sundaravadivelu**, P.Rajkumar and M.Manikandan, Diazaadamantane derivatives as corrosion inhibitor for copper in nitric acid medium, *Res Chem Intermediat.* 41 (2015) 7593–7615.

UNIVERSITY GRANTS COMMISSION

BAHADUR SHAH ZAFAR MARG

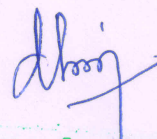
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EVALUATION CERTIFICATE

It is certified that the report entitled “Synthesis and stereochemical studies of 6-hydroxy-4,8,9,10-tetraphenyl-1,3-diazaadamantanes and 6-amino-4,8,9,10-tetraphenyl-1,3-diazaadamantanes” by Prof. M. Sundaravadivelu, Department of Chemistry, The Gandhigram Rural Institute (Deemed to be University) has been evaluated to the University Grants Commission, New Delhi for final support under the scheme of Major Research Project (F. No. 42-358/2013 (SR)).

Details of Expert Committee

The objective mentioned in the proposal were completed. The results are published in international journals with good impact factors. Overall, the outcome of the project is very good. The report is as per the guidelines.



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NEW DELHI – 110 002

EVALUATION CERTIFICATE

It is certified that the report entitled “Synthesis and stereochemical studies of 6-hydroxy-4,8,9,10-tetraphenyl-1,3-diazaadamantanes and 6-amino-4,8,9,10-tetraphenyl-1,3-diazaadamantanes” by Prof. M. Sundaravadivelu, Department of Chemistry, The Gandhigram Rural Institute (Deemed to be University) has been evaluated to the University Grants Commission, New Delhi for final support under the scheme of Major Research Project (F. No. 42-358/2013 (SR)).

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