

UNIVERSITY GRANTS COMMISSION

BAHADUR SHAH ZAFAR MARG

NEW DELHI – 110 002

Final Report of the work done on the Major Research Project

Title of research project

Azo (-N=N-) and imine (-C=N-) functionalized sulfamethoxazole and their metal complexes:

Spectral, structural, photophysical, redox characterization and biochemical activities

UGC Reference No.F. 42-333/2013(SR) dated 22.3.2013

Period of report: 1st April, 2013 to 31st March, 2017

Name & Address of the Principal Investigator

PROF. CHITTARANJAN SINHA

Department of Chemistry

Jadavpur University

Kolkata – 700 032

West Bengal, India

UNIVERSITY GRANTS COMMISSION

BAHADUR SHAH ZAFAR MARG

NEW DELHI – 110 002

ASSESSMENT CERTIFICATE

It is certified that the proposal entitled, "Azo (-N=N-) and imine (-C=N-) functionalized sulfamethoxazole and their metal complexes: Spectral, structural, photophysical, redox characterization and biochemical activities" UGC Reference No.F. 42-333/2013(SR) dated 22.3.2013 executed by Prof. Chittaranjan Sinha, Department of Chemistry, Jadavpur University, Kolkata - 700 032 has been assessed by the Expert Committee consisting the following members for submission to the University Grants Commission, New Delhi for financial support under the scheme of Major Research Projects for the full Period, 1st April, 2013 to 31st March, 2017.

Details of Expert Committee

1. Prof. Debasis Das,

Professor, Department of Chemistry,

University of Calcutta, Rajabazar Campus,

dasdebasis2001@yahoo.com; 9830345023;

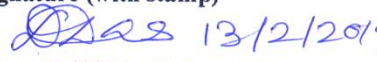
2. Prof. Surajit Chattopadhyay,


Professor, Department of Chemistry,

Kalyani University, Kalyani,

scha8@rediffmail.com, 9830141198.

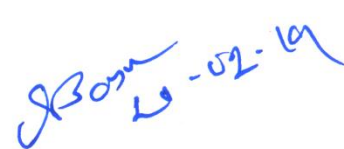
Signature (with stamp)


Dr. DEBASIS DAS
Professor
Dept. of Chemistry
UNIVERSITY OF CALCUTTA
92, A.P.C. Road, Kolkata- 700009


Prof. Surajit Chattopadhyay
Dept. of Chemistry
University of Kalyani

We have assessed and examined the research work done in the above mentioned UGC Sanctioned MRP Scheme and it is found that major research work performed as per proposal sanctioned in addition some other works. Out of fifteen papers ten are published in peer reviewed internationally acclaimed journals. One researcher received Ph. D. Degree and two others have completed their works for submission of Thesis. Both quality and quantity of research is significantly of high quality which is confirmed not only from publication in RSC, Elsevier, Springer and National journals but also from development of new idea for further research. It is an excellent research performed out of this proposal.

The proposal is as per the guidelines.


-02-19

(REGISTRAR/PRINCIPAL)

Registrar
Jadavpur University

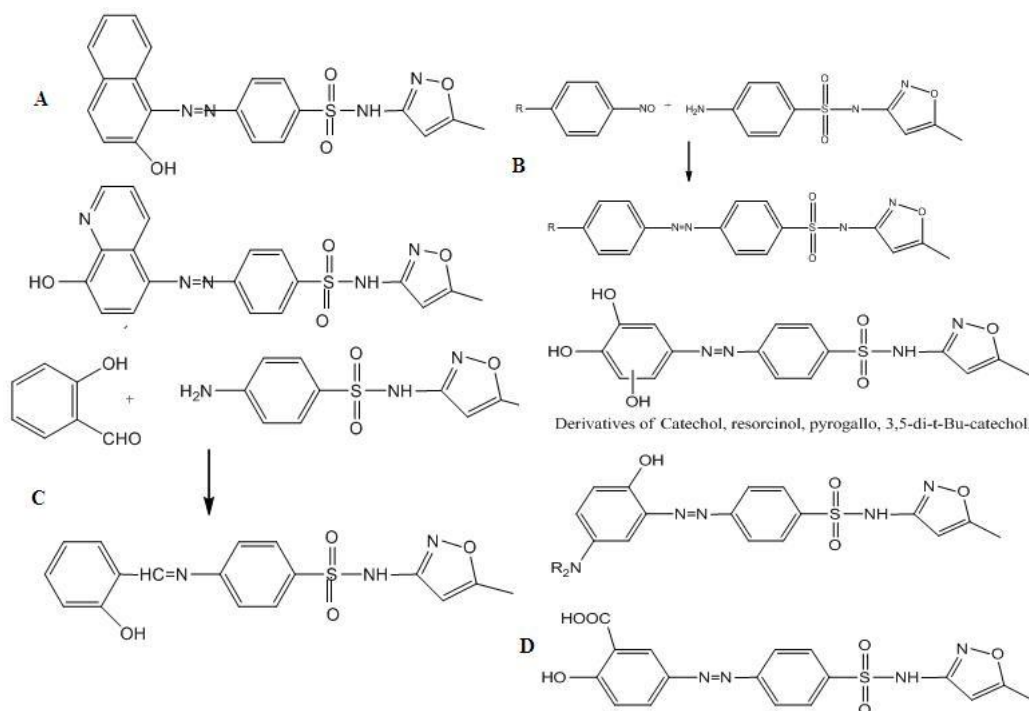
Annexure -VIII
UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002

Final Report of the work done on the Major Research Project.

1. Project report No. 1st /2nd /3rd/Final : Final Report
2. UGC Reference No.F. 42-333/2013(SR) dated 22.3.2013
3. Period of report: from 1st April, 2013 to 31st March, 2017
4. Title of research project : Azo (-N=N-) and imine (-C=N-) functionalized sulfamethoxazole and their metal complexes: Spectral, structural, photophysical, redox characterization and biochemical activities
5. (a) Name of the Principal Investigator : CHITTARANJAN SINHA
 (b) Deptt.: Department of Chemistry, Inorganic Chemistry Section, Jadavpur University.
 (c) University/College where work has progressed : Jadavpur University
6. Effective date of starting of the project : 1st April, 2013
7. Grant approved and expenditure incurred during the period of the report:
 - a. Total amount approved Rs.13,72,133.00
 - b. Total expenditure Rs. 13,59,490.00
 - c. Report of the work done: (Please attach a separate sheet)

Please find attached Bound Report

- i. Brief objective of the project
 - (i) Synthesis of azosulfamethoxazoles, their spectroscopic and structural characterization (**Scheme 1**).
 - (ii) Synthesis of imine functionalized sulfamethoxazoles, their spectroscopic and structural characterization.
 - (iii) Metal complexes of azophenolato and iminephenolato sulfamethoxazole will be synthesized and characterized by spectroscopic and X-ray structural studies.
 - (iv) All these compounds will be screened for microbacterial activity and other biochemical activities.
 - (v) Auto-docking will be done using these molecules to find interaction with enzymes (Cyt-P450) and MM will be done using AMBER programme to obtain energy minimized structure.



Scheme 1. Sulfonamide derivatives

- ii. Work done so far and results achieved and publications, if any, resulting from the work (Give details of the papers and names of the journals in which it has been published or accepted for publication)
- (1) S. K. Sarkar, M. S. Jana, T. K. Mondal, C. Sinha "Use of a Ru/Os-CO-diiodide precursor to synthesize heteroleptic 1-alkyl-2-(arylo)imidazole complexes: The structural characterization, electrochemistry and catalytic activity" **Polyhedron** **50** (2013) 246–254.
 - (2) S. Roy, T. K. Mondal, P. Mitra, C. Sinha "Copper(I)/silver(I)-phosphine-N-((2-pyridyl)methylidene)-6-coumarin complexes: Syntheses, structures, redox interconversion, photophysical properties and DFT computation" **Polyhedron** **51** (2013) 27–40.
 - (3) K. Das, A. Datta, S. Roy, J. K. Clegg, E. Garribba, C. Sinha*, H. Kara "Doubly phenoxo-bridged M–Na (M = Cu(II), Ni(II)) complexes of tetradentate Schiff base: Structure, photoluminescence, EPR, electrochemical studies and DFT computation" **Polyhedron** **78** (2014) 62–71.
 - (4) "Structural characterization of new Schiff bases of sulfamethoxazole and sulfathiazole, their antibacterial activity and docking computation with DHPS protein structure" : Sudipa Mondal, Santi M. Mandal, Tapan Kumar Mondal, Chittaranjan Sinha ; **Spectrochim. Acta Part A**, **150** (2015) 268-279.
 - (5) "Fluorescence sensing and intracellular imaging of Al³⁺ ions by using naphthalene based sulfonamide chemosensor: structure, computation and biological studies" by Sudipa Mondal, Anup Kumar Bhanja, Durbadal Ojha, Tapan Kumar Mondal, Debprasad Chattopadhyay and Chittaranjan Sinha*, **RSC Adv.**, **5** (2015) 73626–73638.

- (6) “In search of Tuberculosis drug design : An *in silico* approach to azoimidazolyl derivatives as antagonist for cytochrome P450” by S. Pradhan, S. Mondal and C. Sinha*, **J. Indian Chem. Soc.**, **93 (2016) 1-18.**
- (7) “*Mycobacterium tuberculosis* Sterol 14 α demethylase inhibitor sulfonamides: Identified by high-throughput screening” by S. Pradhan and C. Sinha*, **J. Indian Chem. Soc.**, **94(2016) 1-12.**
- (8) “The structural characterization, biological activity of sulfamehtoxazolyl-azo-*p*-cresol; its copper(II) complex and their theoretical studies” by N. Sahu, D. Das, S. Mondal, S. Roy, P. Dutta, N. Sepay, S. Gupta, E. López-Torres, and C. Sinha* **New J. Chem.**, **40 (2016) 5019—5031.**
- (9) “Antibacterial activities of sulfamethoxazolyl-azo-phenols and their Cu(II) complexes along with molecular docking properties” by N. Sahu, S. Mondal, N. Sepay, S. Gupta, E. Torres-Lopez, S. Tanaka, T. Akitsu and C. Sinha*, **J Biol Inorg Chem**, **22 (2017) 833-850.**
- (10) “Spectroscopic characterization, antimicrobial activity, DFT computation and docking studies of sulfonamide Schiff bases”, S. Mondal, S. M. Mandal, T. K. Mondal, C. Sinha, **J. Mol. Str.** **1127 (2017) 557-567.**
- (11) “Copper(II)-sulfonamide Schiff base complexes : Structure, biological activity and theoretical interpretation” by S. Mondal, K.. Mondal, Y. Rajesh, M. Mandal and C. Sinha. *, **Polyhedron** **151 (2018) 344-354.**
- (12) “High Throughput screening identification of Sulfonamide derivatives as DHPS and DHFR inhibitors of *Mycobacterium tuberculosis*” by S. Pradhan and C. Sinha* , **J. Indian Chem. Soc. (submitted).**
- (13) “Combating prostate cancer by sulfonamide compounds: Theoretical prediction” by S. Pradhan and C. Sinha*, **J. Indian Chem. Soc.**, **94 (2017) 1113-1122.**
- (14) “Spectroscopic characterization, antimicrobial activity and Molecular Docking Study of novel azo-imine functionalized sulphamethoxazoles” by N. Sahu, S. Mondal, K. Naskar, A. Das Mahapatra, S. Gupta, A. M. Z. Slawin , D. Chattopadhyay and C. Sinha* , **J. Mol. Str.** **1155 (2018) 152-164.**
- (15) “High throughput screening based highly potent sulfonyl-benzamide anti-diabetic drug” by S. Pradhan and C. Sinha*, **Current Drug Therapy**, **13 (2018) 000.**

iii. Has the progress been according to original plan of work and towards achieving the objective. if not, state reasons

Yes. Primary objective is retained in the progress of the work. There are three steps in this research – (i) synthesis and characterization; (ii) biological / biomedical activity and (iii) theoretical evaluation by Docking and DFT computation.

iv. Please indicate the difficulties, if any, experienced in implementing the project

Technically we don't find any problem either from UGC or from University side.

v. If project has not been completed, please indicate the approximate time by which it is likely to be completed. A summary of the work done for the period (Annual basis) may please be sent to the Commission on a separate sheet.

Project has been formally completed on 31st March, 2017 at the end of four years of its Sanction.

vi. If the project has been completed, please enclose a summary of the findings of the study. One bound copy of the final report of work done may also be sent to University Grants Commission.

Please find attached bound copy of the project report.

vii. Any other information which would help in evaluation of work done on the project. At the completion of the project, the first report should indicate the output, such as (a) Manpower trained, (b) Ph. D. awarded, (c) Publication of results, (d) other impact, if any

(a) Man power trained : Mr. Dipankar Das, Mrs. Nilima Sahoo and Mr. Sayantan Pradhan worked in this Scheme at different time.

(b) Ph. D. Awarded : Mr. Dipankar Das, Mrs. Nilima Sahoo and Mr. Sayantan Pradhan are awarded Ph. D. Degree. Mr. Dipankar Das has received Ph. D. (Sc) from Jadavpur University in 2016 and Mrs. Nilima Sahoo and Mr. Sayantan Pradhan awarded Ph. D. (Sc) from Jadavpur University in 2018.

(c) Publication of results : Fourteen original research articles are published in peer reviewed high impact internationally reputed journals and one paper is under processing. Publications appeared in Polyhedron – 4 papers; Spectrochim Acta – 1 paper; J. Mol. Str. - 2; RSC Adv. -1; New J. Chem. – 1; J. Indian Chem. Soc. -4; J. Biol. Inorg. Chem. – 1; Current Drug Therapy – 1.

Chittaranjan Sinha
SIGNATURE OF THE PRINCIPAL INVESTIGATOR
Professor of Chemistry
Department of Chemistry
Jadavpur University
Kolkata - 700 032

SIGNATURE OF THE CO-INVESTIGATOR

Bam
9/02/19
REGISTRAR

(Seal)

Registrar
Jadavpur University

**UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002**

**PROFORMA FOR SUBMISSION OF INFORMATION AT THE TIME OF SENDING
THE FINAL REPORT OF THE WORK DONE ON THE PROJECT**

1. Title of the Project : Azo (-N=N-) and imine (-C=N-) functionalized sulfamethoxazole and their metal complexes: Spectral, structural, photophysical, redox characterization and biochemical activities
2. Name and Address of the Principal Investigator
Dr. Chittaranjan Sinha
Department of Chemistry, Inorganic Chemistry Section, Jadavpur University, Kolkata - 700 032
3. Name and Address of the Institution
Jadavpur University, 188, Raja Subodh Chandra Mallick Rd, Jadavpur University Campus Area,
Jadavpur, Kolkata, West Bengal 700032
4. UGC approval letter No. and Date : F. 42-333/2013(SR) dated 22.3.2013
5. Date of Implementation : 1st April, 2013
6. Tenure of the Project : 4 Years
7. Total Grant Allocated : 13,72,133.00
8. Total Grant Received : 13,06,800.00
9. Final Expenditure : 13,59,490.00
10. Title of the Project : Azo (-N=N-) and imine (-C=N-) functionalized sulfamethoxazole and their metal complexes: Spectral, structural, photophysical, redox characterization and biochemical activities
11. Objectives of the Project :
 - (i) Synthesis of azosulfamethoxazoles, their spectroscopic and structural characterization.
 - (ii) Synthesis of imine functionalized sulfamethoxazoles, their spectroscopic and structural characterization (iii) Metal complexes of azophenolato and iminephenolato sulfamethoxazole will be synthesized and characterized by spectroscopic and X-ray structural studies.
 - (iv) All these compounds will be screened for microbacterial activity and other biochemical activities.
 - (v) Auto-docking will be done using these molecules to find interaction with enzymes (Cyt-P450) and MM will be done using AMBER programme to obtain energy minimized structure.
12. Whether Objectives were Achieved :
Yes. Primary objective is retained in the progress of the work. There are three steps in this research – (i) synthesis and characterization; (ii) biological / biomedical activity

and (iii) theoretical evaluation by Docking and DFT computation. For detail please find bound project report.

13. Achievements from the Project :

Ten original research articles are published in peer reviewed high impact internationally reputed journals; one paper is under revision and four papers have been submitted. This research has generated a total of fifteen publications.

Three researchers join in this proposal; one has received Ph.D. degree and two others will shortly submit their Ph. D. Thesis for Ph. D. degree from Jadavpur University.

14. Summary of the Findings (in 500 words) : Find attached short report in Annexure-X

15. Contribution to the Society (Give details) :

Modern microbiological and chemotherapeutical research begins with L. Pasteur (1822–1895) followed by Jenner (1749–1823), Lister (1827–1917), Koch (1843–1910), and, more especially, Ehrlich (1854–1915). Sulfonamides are widely used in the past. The most common side effect is gastrointestinal upset along with many effects like nausea, headache, stomach or abdomen pain, skin rashes, hives, or trouble breathing or swallowing. Metabolites of sulfonamides such as, hydroxylamine (SMX-NOH), nirosamine (SMX-NO) induce lymphocyte toxicity and act as immune suppressor. The $-NH_2$ group in sulfamethoxazole is susceptible to oxidation in cells by cytochrome P450 to SMX-NOH and SMX-NO. Thus blocking $-NH_2$ may subside toxic metabolites. The coupling or condensation of sulfonamide- NH_2 with other organic molecules may block the sensitivity of precursor and a new less sensitive product may be designed. Besides, the functionalisation may input new groups to bind with biologically important metal ions. Thus, new molecule may serve as metal ion carrier to the cells. Metal ion binding reduces the polarity of the organic molecule and increases lyophilicity and hence membrane transportation, absorption to cells is increased. A low concentration of molecules is sufficient to execute the activity. Hence, side effect and cost will be reduced.

In the field of drug discovery the design of molecules and their interaction with target (drug-target such as proteins etc.) and toxicity of the molecule (ligand) and/or metabolites may be assessed theoretically by computer aided drug design There are two major types of drug design: ligand-based drug design and structure-based drug design. Quantitative structure-activity relationships (QSAR) represent an attempt to correlate structural or functional property of compounds with activities. ADMET (Absorption, distribution, metabolism, excretion and toxicity) filtration, Lipinski's rule of five (Ro5) are the part of Molecular Docking studies. The parameters like hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods.

In this research a series of functionalized sulfonamides have been characterized and their transition metal complexes are also structurally established. Antimicrobial activities of these hitherto unknown compounds have been examined and have been interpreted by Molecular Docking and DNA interaction studies. Besides, CADD approach is adopted to propose structure of effective or lead molecule in a particular disease target. This is helping us in the selection of drug motifs.

Azo-Sulfonamides

Sulphamethoxazolyl azo and imine functionalized molecules are characterized by spectroscopic (UV-Vis, IR, Mass, ^1H NMR, ^{13}C NMR) and also structures are confirmed by single crystal X-ray diffraction measurements. **Fig. 1.** shows azo functionalized-SMX derivatives and their complexes. Biological activities such as antimicrobial and molecular docking have been studied. DFT and TDDFT computations of ligands and metal complexes have been carried out to determine the composition and energy of the molecular levels.

Sulfonamide Schiff bases

Sulfonamide Schiff bases containing phenolic group have been prepared in this work. Imine ($-\text{C}=\text{N}-$) derivatives are obtained when Sulfamethoxazole, Sulfathiazole, Sulfapyridine, Sulfadiazine, Sulfamerazine and Sulfaguanidine have been condensed with different aromatic aldehydes to synthesize Sulfonamide Schiff bases. The derivatives are characterized by spectroscopic techniques (IR, Mass, NMR) and the crystal structures of some of them have been established. Chemical, anti-bacterial activity as well as chemo-sensing property of the ligands have been investigated.

Drug design and Docking Studies

Molecular docking is an important tool for drug discovery. It can be used to model the interaction between a small molecule and a protein at the atomic level, which allows to study the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites and assessment of the binding affinity. The aim of molecular docking is to give a prediction of the ligand-receptor complex structure using computation methods. Basic Local Alignment Search Tool, or BLAST, is an algorithm for comparing primary biological sequence information. After completion of identifying target, validating a target, finding three dimensional structure of target and then using their structural information a new compound may be searched from ZINC database. The molecules with the binding energy better than the natural docked molecule are reported for further analysis. QSAR is also done for all the proposed molecules. Molecular dynamics simulations (MDS) have been done to observe the effect of explicit solvent molecules on the drug-protein complex and stability to achieve time-averaged attributes of the bimolecular system, along with diverse thermodynamic parameters. Drug likeness has been examined following Lipinski's rule of five filter. The molecular orbitals are used to calculate the electronic configuration, molecular reactivity and stability of the compounds by Density Functional Theory (DFT). Pharmacophore map generation has also done to observe steric and electronic features of best docked molecules that ensured the optimal interactions with a receptor and to block its biological response. Finally filtration was done for evaluation of druglikeness of the target molecules by ADMET properties.

With this view we have designed and characterized significant number of azosulfonamides, sulfonamide Schiff bases and their metal complexes. The drug potency has been examined by antimicrobial studies, and by molecular docking analysis. Some of the compounds show very low toxicity and better drug activity compared to parent antibiotics. By and large, these molecules have huge drug efficiency in the use of Tuberculosis control, microbial population control, and also in some cases cancer control.

In intellectual perspective we have published ten articles in internationally reputed high impact journals and man power development is also economically contributed to the society. Some more papers will be published shortly.

Annexure - IX

16. Whether any Ph. D. enrolled/produced out of the project

Three students Mr. Dipankar Das, Mrs. Nilima Sahoo and Mr. Sayantan Pradhan are awarded Ph. D. Degree. Mr. Dipankar Das has received Ph. D. (Sc) from Jadavpur University in 2016 and Mrs. Nilima Sahoo and Mr. Sayantan Pradhan awarded Ph. D. (Sc) from Jadavpur University in 2018.

17. Number of Publications out of the Project :

Fourteen original research articles are published in peer reviewed high impact internationally reputed journals and one paper is under processing. Publications appeared in Polyhedron – 4 papers; Spectrochim Acta – 1 paper; J. Mol. Str. - 2; RSC Adv. -1; New J. Chem. – 1; J. Indian Chem. Soc. -4; J. Biol. Inorg. Chem. – 1; Current Drug Therapy – 1.

Chittaranjan Sinha
SIGNATURE OF THE PRINCIPAL INVESTIGATOR
Professor of Chemistry
Department of Chemistry
Jadavpur University
Kolkata - 700 032

SIGNATURE OF THE CO-INVESTIGATOR

Aban
20.02.19

REGISTRAR

(Seal)

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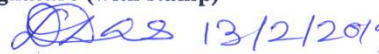
ASSESSMENT CERTIFICATE

It is certified that the proposal entitled, "Azo (-N=N-) and imine (-C=N-) functionalized sulfamethoxazole and their metal complexes: Spectral, structural, photophysical, redox characterization and biochemical activities" UGC Reference No.F. 42-333/2013(SR) dated 22.3.2013 executed by Prof. Chittaranjan Sinha, Department of Chemistry, Jadavpur University, Kolkata - 700 032 has been assessed by the Expert Committee consisting the following members for submission to the University Grants Commission, New Delhi for financial support under the scheme of Major Research Projects for the full Period, 1st April, 2013 to 31st March, 2017.


Details of Expert Committee

1. Prof. Debasis Das,
 Professor, Department of Chemistry,
 University of Calcutta, Rajabazar Campus,
 dasdebasis2001@yahoo.com; 9830345023;

Signature (with stamp)

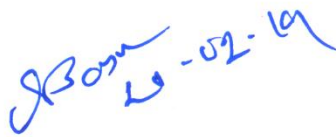

Dr. DEBASIS DAS
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 Dept. of Chemistry
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2. Prof. Surajit Chattopadhyay,
 Professor, Department of Chemistry,
 Kalyani University, Kalyani,
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Prof. Surajit Chattopadhyay
 Dept. of Chemistry
 University of Kalyani

We have assessed and examined the research work done in the above mentioned UGC Sanctioned MRP Scheme and it is found that major research work performed as per proposal sanctioned in addition some other works. Out of fifteen papers ten are published in peer reviewed internationally acclaimed journals. One researcher received Ph. D. Degree and two others have completed their works for submission of Thesis. Both quality and quantity of research is significantly of high quality which is confirmed not only from publication in RSC, Elsevier, Springer and National journals but also from development of new idea for further research. It is an excellent research performed out of this proposal.

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Project Report

Title : Azo (-N=N-) and imine (-C=N-) functionalized sulfamethoxazole and their metal complexes: Spectral, structural, photophysical, redox characterization and biochemical activities

Funding : UGC Reference No.F. 42-333/2013(SR) dated 22.3.2013

Period of report: from 1st April, 2013 to 31st March, 2017

Sulfonamides are used clinically since 1930s in human medicine. Sulfonamides prevent bacterial growth by acting as a competitive inhibitor to *p*-aminobenzoic acid (PABA) of the key enzyme in folate synthesis, the dihydropteroate synthase (DHPS). Prolong consumption of sulfonamides causes several immunological reactions and toxicity that causes fever, skin rashes, breathing trouble, abdomen pain, nausea, headache, vomiting, diarrhea, loss of appetite, kidney damage etc. in case of prolonged administration. To improve drug activity and reduce toxicity the researchers have already engaged in the design, synthesis and to explore the drug-protein interaction of functionalized sulfonamides and their complexes. In this research a series of functionalized sulfonamides have been characterized and their transition metal complexes are also structurally established. Antimicrobial activities of these hitherto unknown compounds have been examined and have been interpreted by Molecular Docking and DNA interaction studies.

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Sulphamethoxazolyl azo and imine functionalized molecules are characterized by spectroscopic (UV-Vis, IR, Mass, ¹H NMR, ¹³C NMR) and also structures are confirmed by single crystal X-ray diffraction measurements.

Fig. 1. shows azo functionalized-SMX derivatives and their complexes. Biological activities such as antimicrobial and molecular docking have been studied. DFT and TDDFT computations of ligands and metal complexes have been carried out to determine the composition and energy of the molecular levels.

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better than the natural docked molecule are reported for further analysis. QSAR is also done for all the proposed molecules. Molecular dynamics simulations (MDS) have been done to observe the effect of explicit solvent molecules on the drug-protein complex and stability to achieve time-averaged attributes of the bimolecular system, along with diverse thermodynamic parameters. Drug likeness has been examined following Lipinski's rule of five filter. The molecular orbitals are used to calculate the electronic configuration, molecular reactivity and stability of the compounds by Density Functional Theory (DFT). Pharmacophore map generation has also done to observe steric and electronic features of best docked molecules that ensured the optimal interactions with a receptor and to block its biological response. Finally filtration was done for evaluation of druglikeness of the target molecules by ADMET properties. A series of designed drugs for Tuberculosis, diabetic and prostate cancer treatment are added in **Fig. 3**.

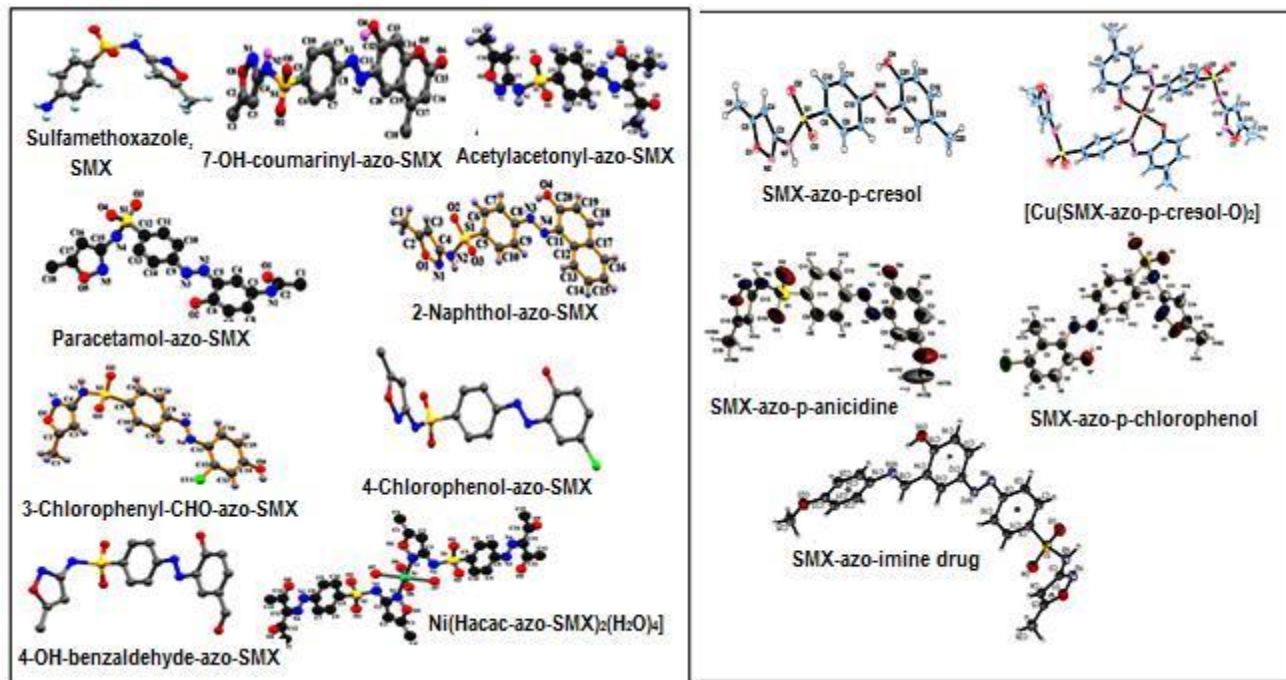


Fig. 1. Azo-Sulfonamides

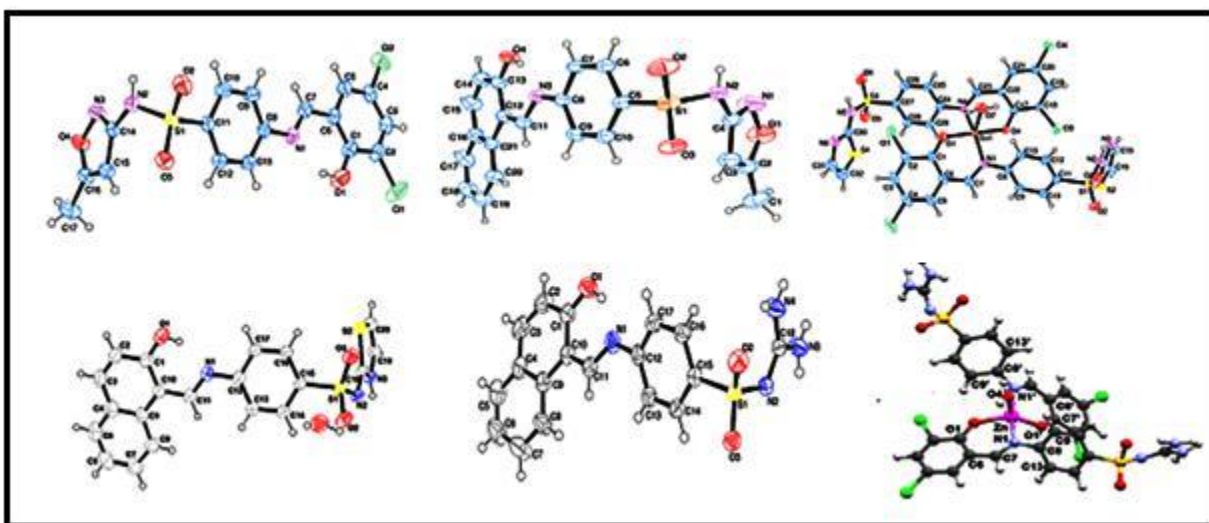


Fig. 2. Sulfonamide Schiff bases

In search of Tuberculosis drug design following target molecules are identified with high docking score and low toxicity on comparing with market available drugs.

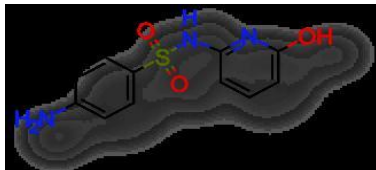

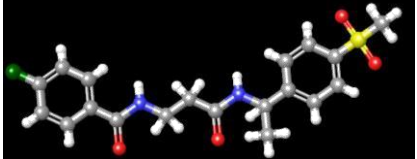

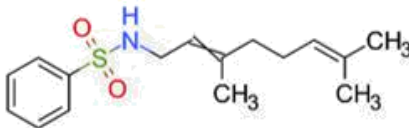

Tubercoulotic Drugs		
<p>(E)-6-((3-((1H-imidazol-2-yl)diazenyl)naphthalen-2-yl)amino)-2H-chromen-2-one Docking score (DS) = -11.6 a.u.</p>	<p>Ethambutanol, DS = -5.2 a.u.</p> <p>Bedaquiline, DS = -8.6 a. u.</p> <p>Used Tubercoulotic Drugs</p>	 <p>4-Amino-N-(6-hydroxypyridin-2-yl)benzenesulfonamide CDI= -43.88 a.u.; -34.18 a.u.</p>  <p>4-Amino-N-(9H-carbazol-2-yl)benzenesulfonamide CDI= -38.86 a.u.; -44.06 a.u.</p>
anti-diabetic drugs		
 <p>4-chloro-N-[3-[[[(1S)-1-(4-methylsulfonylphenyl)ethyl]amino]-3-oxopropyl]benzamide (MSPB) (D.S, -33.98 a.u.)</p>	<p>Dipeptidyl peptidase-4 (DPP4), a serine exopeptidase is encoded by the DPP4 gene. Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) levels increase in presence of DPP-4 inhibitors, which also inhibits release of glucagon. Accordingly, insulin secretion increases and gastric emptying as well as blood glucose levels decrease. Hence, it can be used to treat diabetes mellitus type 2.</p>	 <p>Sitagliptin (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (D.S, -10.58 a.u.)</p>
Combating prostate cancer by sulfonamide compounds		
 <p>N-(3,7-Dimethylocta-2,6-dienyl)benzenesulfonamide</p>	<p>Prostate cancer is the second leading cause of cancer death and the androgen receptor (AR) plays a crucial role. N-Butylbenzene-sulfonamide (NBBS), isolated from <i>P.africanum</i> and <i>Pseudomonas</i> sp. is responsible for AR inhibition and hence useful drug for the treatment of prostate cancer (PCa).</p>	 <p>5-[3-(3-trifluoro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]pyridine-3-sulfonamide</p>

Fig. 3. Drug design and Molecular Docking studies

EXECUTIVE SUMMARY

Title : Azo (-N=N-) and imine (-C=N-) functionalized sulfamethoxazole and their metal complexes: Spectral, structural, photophysical, redox characterization and biochemical activities

Funding : UGC Reference No.F. 42-333/2013(SR) dated 22.3.2013

Period of report: 1st April, 2013 to 31st March, 2017

Sulfonamides are useful antibiotic and prevent bacterial growth by acting as a competitive inhibitor to *p*-aminobenzoic acid (PABA) of the key enzyme in folate synthesis, the dihydropteroate synthase (DHPS). However, prolong use of sulfonamides causes fever, skin rashes, breathing trouble, abdomen pain, nausea, headache, vomiting, diarrhea, loss of appetite, kidney damage etc. Research is going on to improve drug activity and reduce toxicity by designing new derivatives to explore the drug-protein interaction of functionalized sulfonamides and their complexes. In this research work a series of functionalized sulfonamides have been characterized and their transition metal complexes are also structurally established. Antimicrobial activities of these hitherto unknown compounds have been examined and have been interpreted by Molecular Docking and DNA interaction studies.

Azo-Sulfonamides

Sulphamethoxazolyl azo and imine functionalized molecules are characterized by spectroscopic (UV-Vis, IR, Mass, ¹H NMR, ¹³C NMR) and also structures are confirmed by single crystal X-ray diffraction measurements. Biological activities such as antimicrobial and molecular docking have been studied. DFT and TDDFT computations of ligands and metal complexes have been carried out to determine the composition and energy of the molecular levels.

Sulfonamide Schiff bases

Sulfonamide Schiff bases containing phenolic group have been prepared in this work. Imine (-C=N-) derivatives are obtained from Sulfamethoxazole, Sulfathiazole, Sulfapyridine, Sulfadiazine, Sulfamerazine and Sulfaguanidine upon condensation with different aromatic aldehydes. The derivatives are characterized by spectroscopic techniques (IR, Mass, NMR) and the crystal structures of some of them have been established. Chemical, anti-bacterial activities as well as chemo-sensing property of the ligands have been investigated.

Drug design and Docking Studies

Molecular docking is useful tool for drug discovery. Basic Local Alignment Search Tool, or BLAST, is used for primary biological sequence information. After completion of identifying target, validating a target, finding three dimensional structure of target and then using their structural information a new compound may be searched from ZINC database. The molecules with the binding energy better than the natural docked molecule are reported for further analysis. QSAR is also done for all the proposed molecules. Molecular dynamics simulations (MDS) have been done to observe the effect of explicit solvent molecules on the drug-protein complex and stability to achieve time-averaged attributes of the bimolecular system, along with diverse thermodynamic parameters. Drug likeness has been examined following Lipinski's rule of five filter. The molecular orbitals are used to calculate the electronic configuration, molecular reactivity and stability of the compounds by Density Functional Theory (DFT). Pharmacophore map generation has also done to observe steric and electronic features of best docked molecules that ensured the optimal interactions with a receptor and to block its biological response. Finally filtration was done for evaluation of druglikeness of the target molecules by ADMET properties. A series of designed drugs for Tuberculosis, diabetic and prostate cancer treatment are added from this research.

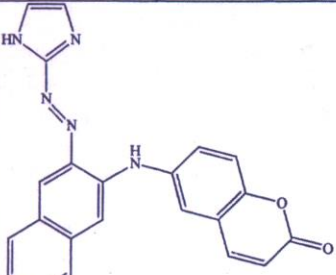
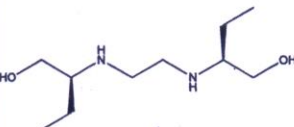
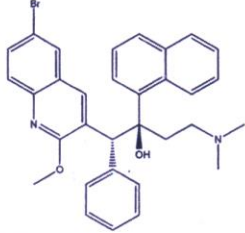
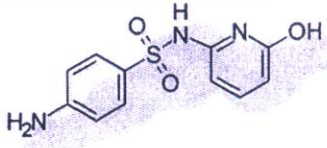
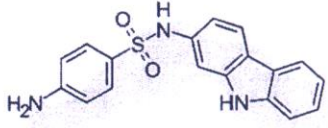
Achievements

So far we have published ten original articles in peer reviewed internationally reputed journals and five are submitted for publications. Three students have pursued their Ph. D. work and one of them received Ph. D. Degree and two are preparing their Thesis for submission.

Drug design and Docking Studies

Molecular docking is an important tool for drug discovery. It can be used to model the interaction between a small molecule and a protein at the atomic level, which allows to study the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites and assessment of the binding affinity. The aim of molecular docking is to give a prediction of the ligand-receptor complex structure using computation methods. Basic Local Alignment Search Tool, or BLAST, is an algorithm for comparing primary biological sequence information. After completion of identifying target, validating a target, finding three dimensional structure of target and then using their structural information a new compound may be searched from ZINC database. The molecules with the binding energy better than the natural docked molecule are reported for further analysis. QSAR is also done for all the proposed molecules. Molecular dynamics simulations (MDS) have been done to observe the effect of explicit solvent molecules on the drug-protein complex and stability to achieve time-averaged attributes of the bimolecular system, along with diverse thermodynamic parameters. Drug likeness has been examined following Lipinski's rule of five filter. The molecular orbitals are used to calculate the electronic configuration, molecular reactivity and stability of the compounds by Density Functional Theory (DFT). Pharmacophore map generation has also done to observe steric and electronic features of best docked molecules that ensured the optimal interactions with a receptor and to block its biological response. Finally filtration was done for evaluation of druglikeness of the target molecules by ADMET properties.

In search of Tuberculosis drug design following target molecules are identified with high docking score and low toxicity on comparing with market available drugs.

Tubercoulotic Drugs		
 <p>(E)-6-((3-((1H-imidazol-2-yl)diazenyl)naphthalen-2-yl)amino)-2H-chromen-2-one Docking score (DS) = -11.6 a.u.</p>	 <p>Ethambutol, DS = -5.2</p>  <p>a.u. Bedaquiline, DS = -8.6 a. u.</p> <p>Used Tubercoulotic Drugs</p>	 <p>4-Amino-N-(6-hydroxypyridin-2-yl)benzenesulfonamide CDI= -43.88 a.u.; -34.18 a.u.</p>  <p>4-Amino-N-(9H-carbazol-2-yl)benzenesulfonamide CDI= -38.86 a.u.; -44.06 a.u.</p>