SYNOPSIS

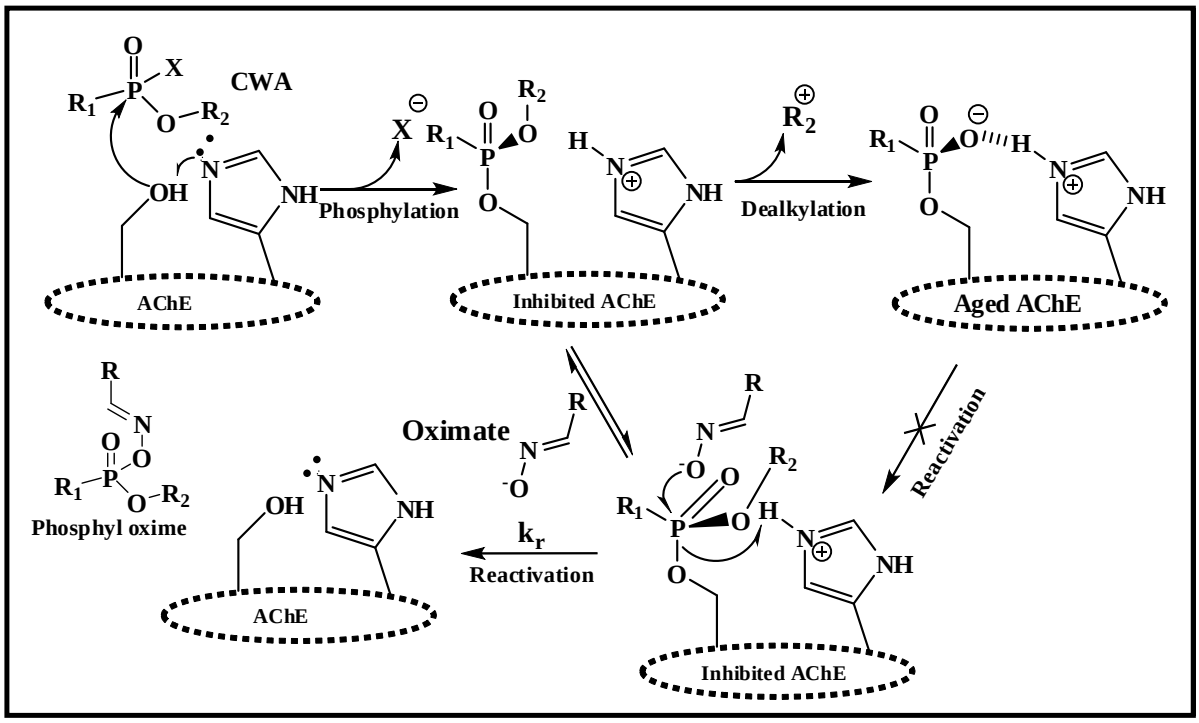
1. TITLE OF THE THESIS

"**DESIGN, SYNTHESIS AND DEVELOPMENT OF AROMATIC, HETERO AROMATIC AND GLYCO-CONJUGATES AS CHOLINESTERASE REACTIVATORS**"

2. INTRODUCTION

Cholinesterase (Acetylcholinesterase; AChE and butyrylcholinesterase; BChE) is a serine hydrolase enzyme which plays an important role in the human neuronal system degrading neurotransmitter acetylcholine into choline and acetic acid within the synaptic cleft[1]. Cholinesterase enzyme is found in several types of conducting tissues: cholinergic and noncholinergic fiber nerves and muscles, central and peripheral tissues, and motor and sensory fibers, the activity of AChE is higher in motor neurons than in sensory neurons, also in the red blood cell membranes.[2] There is an ample of natural or artificial compounds present that are capable of inhibiting AChE activity.[3-4] The reversible AChE inhibitors are used for various purposes such as treatment of alzheimer disease and myasthenia gravis.[5] On the other hand, the irreversible AChE inhibitors such as organophosphate inhibitors (OPI) belong to the most dangerous and toxic compounds. The OPI, including nerve agents (e.g., tabun, soman, sarin, VX), pesticides (e.g., paraoxon, parathion, diazinon), or industrial compounds (e.g., tributylphosphate, tri-O-cresylphosphate), covalently bind to the serine residue at the AChE active site and block its activity[6-7] (Scheme 1). Consequently, the neurotransmitter acetylcholine cannot be degraded and permanently stimulates the cholinergic receptors. The inhibition of AChE triggers an accumulation of acetylcholine in synaptic cleft, resulting in permanent saturation of muscarinic (e.g., lacrimation, miosis, salivation) and nicotinic (e.g., muscle spasms) receptors and ultimately leads to a wide cholinergic crisis and subsequently the organism is endangered by failure of breath centre in central nervous system and subsequent death from suffocation.[7-8] Therefore, reactivation of organophosphorus compound (OPC) inhibited AChE is necessary to get back its catalytic activity towards the hydrolysis of ACh. [9-12] Structure-activity relationship for oxime efficacy are poorly understood because oxime reactivation has a complex dependency on the nucleophilicity and orientation of the oxime as well as on the structure of the OP-AChE

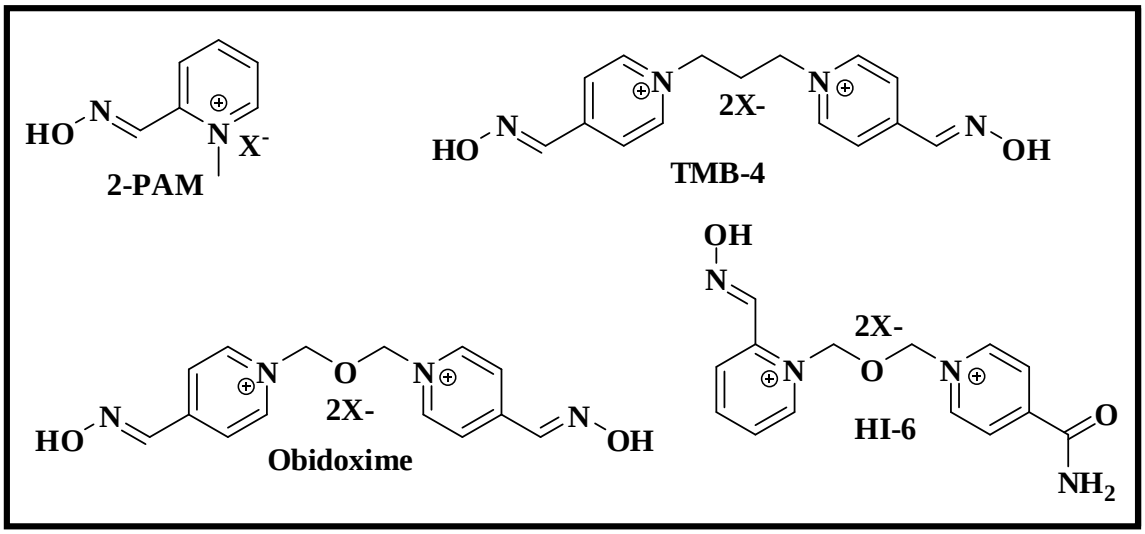
conjugate. Hence efficient reactivators of OP inhibited AChE must be explored. Oximes with greater efficiency for the reactivation of AChE are needed. A large number of mono and bis-pyridinium oximes has been synthesized and evaluated as cholinesterase reactivators in last decade.



Scheme 1. Mechanism of AChE inhibition by organophosphorus nerve agents, aging, and reactivation by oximes

But few of them viz. 2-PAM (N-methyl pyridine-2-aldoxime), Obidoxime (1,3-bis-(4-hydroxyiminomethylpyridino-1-yl)-2- oxapropane dichloride), TMB-4 (1,3-bis-(4-hydroxyiminomethylpyridino-1-yl) propane dibromide), and HI-6 (1-(2-hydroxyiminomethylpyridino-1-yl)-3-(4-carbamoylpyridino-1-yl)-2-oxapropane dichloride) are available as antidote for OP-poisoining[13-16] as presented in (Scheme 2).

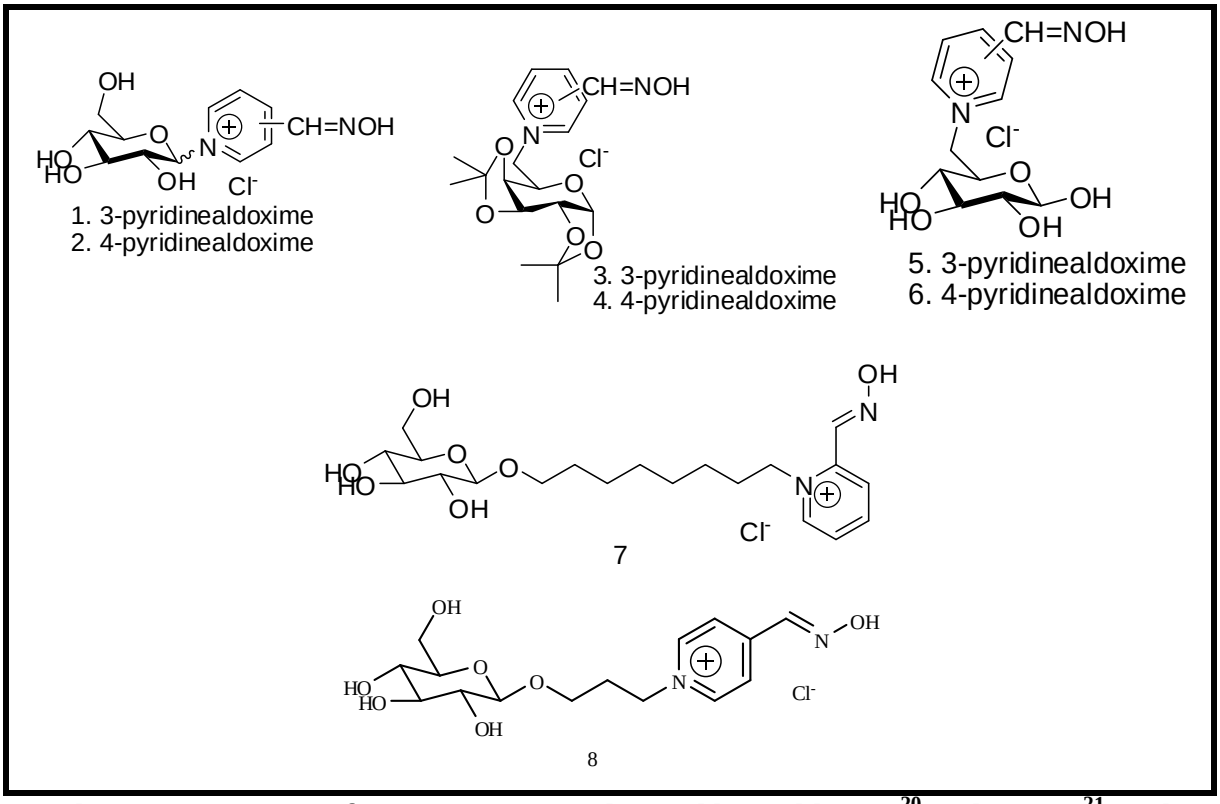
Apart from the inability to regenerate aged AChE, charged oximes are also impermeable to blood brain barrier (BBB) which is composed of endothelial cells that separates CNS from PNS. The presence of tight junction (TJ) between endothelial cells makes BBB nearly impenetrable to viruses, bacteria, proteins, and polar molecules.[17-18] OP chemical warfare agents, being small lipophilic molecules, can easily penetrate the BBB by free diffusion and thereby inhibit AChE in the central nervous system (CNS).



Scheme 2. Structure of clinically used oxime reactivators

However, due to the presence of permanent positive charge on the pyridinum ring, these commonly used reactivators may have difficulty in crossing the BBB.[18-19] Heldman *et al*.[20] suggested that sugar oximes (Scheme 3) may cross the BBB due to recognition of sugar moiety by facilitative glucose transporters. Keeping this viewpoint, the group synthesized some sugar based oxime by replacing the second pyridinum aldoxime nucleus with a sugar moiety. This study was further continued by Garcia *et al.*[21] and synthesized six novel sugar oxime (Scheme 3) along with eight previously reported by Heldmann *et al.*[20]. In extension, the group investigated reactivating efficacy against sarin and VX inhibited human red blood cell AChE and plasma butyrylcholinesterase. The observed data revealed[21] that only few compounds were better than other tested oximes with equal reactivation efficiency as that of 2-PAM. Sugar based neutral glycosylated oximes can pass through the BBB. So this can be the way to cross the barrier and reactivate the CNS inhibited AChE.

Hence octanol-water partition coefficient [log *P*], which is based on the concept of partition of substances between oil and water, is a useful parameter for the prediction of drug transport properties and is also important for evaluating the ability of different drugs to penetrate through the BBB.[20-21] The pK_a values should also be taken into consideration while searching for new oxime reactivators essentially due to the fact that deprotonated oxime group is involved in the nucleophilic attack during reactivation and its concentration is pH dependant, therefore for the calculation of effective reactivation parameters, the effective concentration of oxime at particular pH should be determined.[22-23]



Scheme 3. Structure of sugar oximes synthesized by Heldmann[20] and Garcia[21] *et al.*

Calculation of several molecular descriptor viz. (polar surface area, PSA (60-70A$^{\circ 2}$); molecular weight (<450Da); number of H-bond donors, HBD (≤3); number of H-bond acceptors, HBA (<7); number of freely rotatable bounds, FRB (<8)) provides the influence of chemical structure on their biopharmaceutical profile and for penetration ability of compounds through biological membranes. An optimal range for the values of molecular descriptor conditioning a good distributuion in the central nervous system is generally accepted.[24-28] Most of the oximes are much effective against inhibited AChE, so in order to diagnose the structural requirements of oxime it is necessary to study their reactivation kinetics. Kinetic approach leads to the assessment of oxime efficacy and mechanism of oxime action too.

In the present investigation an attempt will be made to develop some efficient charged and uncharged cholinesterase reactivators. Further their physicochemical properties and reactivation kinetics against pesticide and nerve agent poisoned AChE will be studied.

3. A BRIEF REVIEW OF THE WORK ALREADY DONE IN THE FIELD

In past decade large number of oximes have been synthesized and evaluated as cholinesterase reactivators across the world.[29-33] A major contribution to this effort was made by Prof. I. Hagedorn from the University of Freiburg, Germany, who synthetized more than 1000 oximes including some of the most effective reactivators, e.g. obidoxime, HI-6 and HLo¨ 7.[34] The significant contribution of Kuca *et al.*[35] and Acharya *et al.*[33] deserves special mention in this context. Acharya *et al.*[22] synthesized mono and bis-pyridinium oximes connecting with different linkers having hetero atom in chain and evaluated their reactivation potential against structurally different OPI. Apart from that Taylor, Worek, Renard and others groups have also made significant contribution to this field. Recently, Taylor *et al.*[36] synthesized several non-pyridinum based reactivators with an exocyclic quaternary nitrogen atom along with hydroxyl group, and studied their reactivation for VX, cyclosarin and paraoxon inhibited human butylcholinesterase (hBChE). Musilek[37] and group summarized the design, evaluation and structure-activity-relationships studies of AChE reactivators, mainly focused on pesticide poisoning. A systematic account was presented by Renard *et al.*, [38] on recent strategies adopted for the development of cholinesterase reactivators. The group further highlighted, limited efficacy and modifications of oxime reactivators for BBB penetration. Garcia *et al.*, [21] and Heldmann *et al.*,[20] synthesized a large number of glyco-conjugated oximes with varying side chain and studied their lipophilicity and reactivation potency against nerver agent poisonings. Assessment of reactivation kinetics as an essential feature for selection of promising reactivators is thoroughly delineated by Worek[39] and research group. Renard *et al.* also recently synthesized a large number of oxime reactivators with peripheral site ligands.[40-41] Inspite of tremendous efforts, single broad spectrum AChE reactivator that may be used against all kinds of chemical warfare agents, is still lacking[29]. This fact underlines the necessity to develop an effective medical treatment for the whole range of OP and nerve agents. Some preliminary studies on nucleophilic reactivity of oximes and hydroxamic acids have already been published from our laboratory.[42]

4. OBJECTIVES

The main objectives of the proposed research work are as follows:

I. Synthesis of aromatic and hetero aromatic oximes with different connecting linkers as cholinesterase reactivators.

II. Synthesis of sugar based glycosylated oximes as AChE reactivators.

III. Study of Physico-chemical properties as acid dissociation constant and lipophilicity of synthesized reactivators.

IV. I*n-vitro* reactivation kinetics of oxime based cholinesterase reactivators against nerve agents and pesticides.

V. Micellar hydrolysis of organophosphate based stimulants and pesticides etc. by using oximate and hydroxamate based α-nucleophile.

5. NOTEWORTHY CONTRIBUTION IN THE FIELD OF PROPOSED WORK

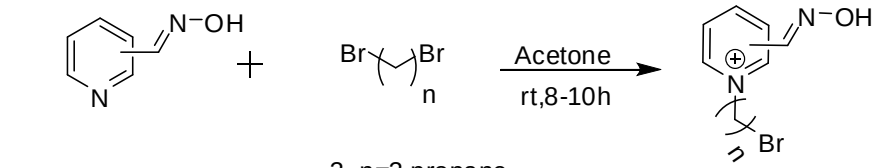
Various highly toxic organophosphorus compounds (OP) were developed in the past and used as chemical warfare agents (nerve agents) during military conflicts and terrorist attacks. Besides chemical warfare agents, OP based pesticides and insecticides viz. ethyl paraoxon, methyl paraoxon, diazinon, chloropyrifos etc. also pose a serious threat to common civilians due to their extensive agricultural applications.[3,43] According to the WHO report, more than two million suicidal poisonings and one million serious accidental cases with pesticides occur worldwide every year, mostly in developing countries.[44-46] Numerous oxime based reactivators were synthesized by different research groups after the development of 2-PAM, TMB-4 and Obidoxime. Physicochemical properties and reactivation kinetic studies of synthesized reactivators are of paramount importance to get insight into the structural requirement to obtain a novel antidote for all kind of OP poisoning. In last few years considerable efforts have been made by our research group to study the physico-chemical and reactivation kinetics parameter of novel oxime reactivators for OP inhibited AChE and their role in detoxification process.[47-50]

6. PROPOSED METHODOLOGY

The entire work will be carried out in the following steps:

I. Synthesis of aromatic and hetero aromatic oximes with different connecting linker as cholinesterase reactivators.

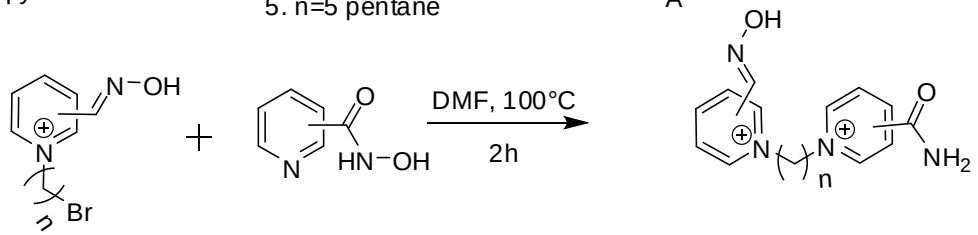
A series of novel bis-pyridinum mono-oxime with different kinds of connecting linkers will be synthesized and evaluated as cholinesterase reactivators for different organophosphate based chemical warfare agents. A generalized route for the synthesis of proposed reactivators shown here:



1= 2-pyridinium aldoxime
2= 4-pyridinium aldoxime

3. n=3 propane,
4. n=4 butane
5. n=5 pentane

A



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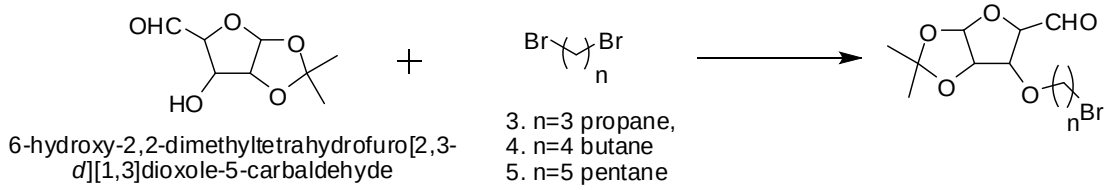
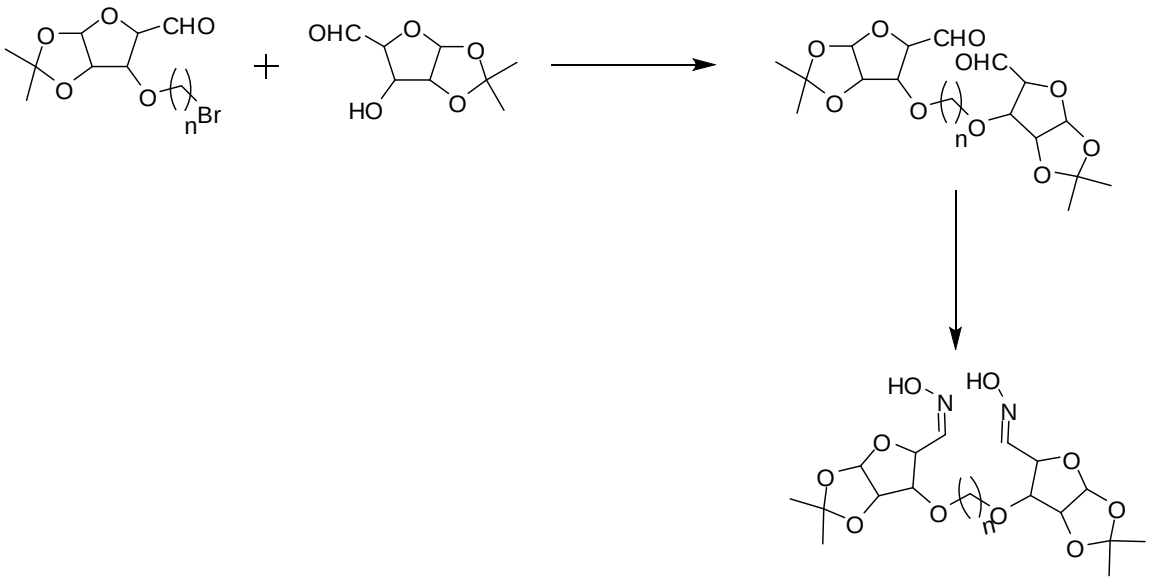
II. Synthesis of sugar based glycosylated oximes as AChE reactivators.

Sugar based novel and efficient AChE reactivators will be synthesized and evaluated as AChE reactivators. These will be further tested for their ability to cross BBB. Here is the propose methodology for the synthesis of glycosylated oximes connecting with different bridging.



6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole-5-carbaldehyde

3. n=3 propane,
4. n=4 butane
5. n=5 pentane

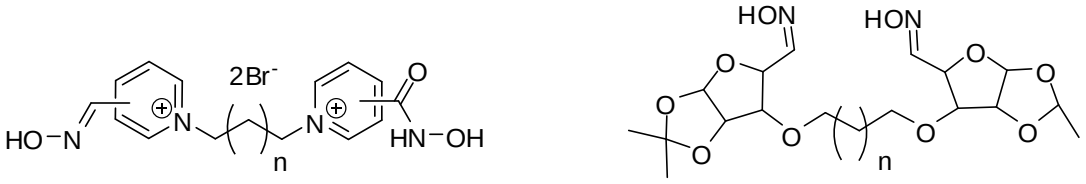


III. Study of physicochemical properties as acid dissociation constant and lipophilicity of oxime based cholinesterase reactivators.

The acid dissociation constant (pK_a) of all the synthesized reactivatiors (Fig. 1) will be determined spectrophotometrically and will be compared with commercially available reactivators. Partition coefficient (log *P*) will be also examined for all the synthesized oximes to evaluate the BBB penetrating capacity by uv-vis spectrophotometer.

IV. I*n-vitro* reactivation kinetics of oxime based cholinesterase reactivators against nerve agents and pesticides.

For evaluation of real efficacy of newly synthesized oximes (Fig.1) as a reactivator of poisoned AChE, i*n-vitro* reactivation kinetics will be performed by applying modified Ellman's method using uv-vis spectrophotometer.



(a) **(b)**

Fig.1 Structure of quaternary and glycocylated oxime reactivators

V. Micellar hydrolysis of organophosphate based simulants and pesticides etc. by using oximate and hydroxamate α-nucleophile.

Micellar catalyzed hydrolysis of organophosphate based pesticides and stimulants viz. phosphate, thiophosphate and sulphonate esters will be performed by using oximate and hydroxamates α-nucleophile. Their nucleophilic potencies will also be compared.

7. EXPECTED OUTCOME OF THE PROPOSED WORK

The development of newly synthesized oxime based compounds and their role in reactivating AChE will be an important area of defence and academic research. The expected outcome of the present investigation will be the synthesis of some novel, aromatic and sugar based oxime reactivators which can be easily penetrate BBB and counteract OP intoxication. In addition the reactivation kinetic studies of reactivators against OP poisoning will supply an outline to develop structurally different and efficient AChE reactivators. The results of this investigation will be of great significance and enrich our understanding regarding reactivators of AChE along with their promising role in detoxification purposes.

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9. LIST OF PAPER PUBLISHED/COMMUNICATED IN INTERNATIONAL JOURNAL/NATIONAL CONFERENCE

I. Kinetic studies of cholinesterase reactivators with organophosphate inhibited AChE. **(*Only Abstract*)**
Rahul Sharma, Kallol K. Ghosh.
Toxicol. Lett. 221 **(2013),** S152–S153

II. Interactions between xylene-linked carbamoyl bis-pyridinium mono oximes and organophosphates inhibited-AChE: A kinetic study.
Rahul Sharma, Bhanushree Gupta, J. R. Acharya, M.P. Kaushik, Kallol K. Ghosh.
Toxicology 316 (**2014**) 1-8.

III. *In- Vitro* Reactivation Kinetics of Paraoxon and DFP Inhibited Electric eel AChE using Mono- and Bis-Pyridinium Oximes.
Bhanushree Gupta, **Rahul Sharma**, Namrata Singh , Kamil Kuca, J. R. Acharya, Kallol K. Ghosh.
Arch. Toxicol. 88 (**2014**), 381-390.

IV. Reactivity studies of carbon, phosphorus and sulfur-based acyl sites with tertiary oximes in gemini surfactants.
Bhanushree Gupta, **Rahul Sharma,** Namrata Singh, Yevgen Karpichev, Manmohan L. Satnami and Kallol K. Ghosh.
J. Phys. Org. Chem. 26 **(2013**), 632-642.

V. Mid Year Meeting of Chemical Research Society of India **(*Attended*)**
Central Drug Research Institute (CDRI), Lucknow, on 21-22nd July **2012.**

VI. "Physicochemical properties and nucleophilicity of tertiary oximes against hydrolysis of carboxylates and phosphate esters"
Rahul Sharma, Kallol K. Ghosh
49th Annual Convention of Chemists, NITTTR, Bhopal,
during 12-15th Dec. **2012. (*Received Young Scientist Award*)**

VII. "Physicochemical Aspects of Oxime Based Reactivators of Acetylcholinesterase"
Bhanushree Gupta, **Rahul Sharma**, Kallol K. Ghosh.
15th CRSI national Symposium (NSC-15), held at BHU, Varanasi, during 1-3rd February **2013.**

VIII. "Kinetic studies of cholinesterase reactivators with organophosphate inhibited AChE"
Rahul Sharma, Kallol K. Ghosh.

49th EUROTOX Congress, held in Interlaken, Switzerland during September 1-4, **2013**.

IX. "*In vitro* Reactivation Kinetic Analysis of Xylene Linked Carbamoyl Bispyridinum Mono-Oximes for Organophosphate Poisoning"
Rahul Sharma, Bhanushree Gupta, Kallol K. Ghosh.
50th Annual Convention of Chemists, Punjab University, Chandigarh, 04-07th Dec. **2013. (*Received Young Scientist Award*)**

X. "Kinetic studies of the reaction of Nitrogen and Sulphur based hydroxamic acid for the hydrolysis of phosphate esters in micellar media"
Rahul Sharma, Arvind K. Sahu, Akhilesh Tiwari, R. P. Tripathi, Kallol K. Ghosh.
National conference on Recent Trends in Chemical Sciences (NCRTCS), School of Studies in Chemistry, Pt. Ravishankar Shukla University, Raipur, during 23-25th Jan. **2014.**

XI. "The influence of combination of oximes on the reactivating and therapeutic efficacy of antidotal treatment of organophosphate poisoning"
Rahul Sharma, Arvind K. Sahu, Bhanushree Gupta, Kallol K. Ghosh.
16th CRSI national Symposium (NSC-16), held at IIT, Mumbai, during 6-9th Feb. **2014.**

XII. "Defence strategy to counter attack chemical weapons attack"
Rahul Sharma
12th Chhattisgarh Young Scientist Congress (CYSC) held at Pt. Ravishankar Shukla University, Raipur, during 17th -19th Feb, **2014. (*Received Young Scientist Award in Military & Defence Science Section*)**

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