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Review Article

Efficacious Oxime for Organophosphorus Poisoning: A Minireview

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Abstract

Oximes are well known as acetylcholinesterase reactivators and are used in organophosphorus poisoning to reactivate inhibited acetylcholinesterase. Therapeutically available oximes, namely, pralidoxime (2-PAM), obidoxime, trimedoxime and Hagedorn oxime (HI-6), have no broad-spectrum activity against structurally different kinds of organophosphorus anticholinesterases. The widely used oxime, 2-PAM, is least effective. The focus of the review is to find an oxime that is broad spectrum and superior to the presently available oximes for the treatment of organophosphorus poisoning. Numerous oxime-based reactivators have been synthesized - in laboratories in Croatia, United States of America, Israel and most recently in Czech Republic. Some experimental oximes synthesized in Czech Republic and named as K-series of oximes have been found promising. Among them, K-27 and K-48 have higher or comparable efficacy to all available oximes though it is not effective against all organophosphorus (OP) nerve agents. They are also efficacious in pretreatment protocol for OP anticholinesterases. K-27 oxime is a promising candidate to replace therapeutically available oximes with respect to insecticide/pesticide organophosphorus poisoning. K27 and K48 may be candidates to replace the only approved pretreatment drug, pyridostigmine, in military combat medicine for OP nerve agent.

Keywords: *K-oximes, K-27 and K-48 oxime, Bispyridinium aldoxime, Acetylcholinesterase reactivators, OPC poisoning.*

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INTRODUCTION

Organophosphorus anticholinesterase compounds (OPCs) have a wide variety of applications, but they also constitute a serious threat with regard to occupational hazard, self-poisoning, unintentional misuse, terrorists attack and warfare. OPCs are among the most frequent agents involved in suicidal and accidental intoxication [1,2] and food poisoning [3]. Acute organic insecticides poisoning is a major health problem all over the world, particularly in developing countries where organophosphates are the most common suicidal poison with high mortality and morbidity [4]. They account for several hundreds of thousands of death worldwide every year and even a greater number of casualties [5]. According to Eddleston et al [2] organophosphorus pesticide self-poisoning is an important chemical problem in rural regions of the developing world and kills an estimated 200,000 people every year [6]. One worldwide mortality study reported mortality rates ranging from 3 – 25 % [7]. In 2005, 15 victims were poisoned after accidently ingesting ethion (an OPC) contaminated food in a social ceremony in Magrawa, India [7]. Food contamination by organophosphates in humans mostly occurs among farmers and agriculture workers [8]. A brief history of OPCs is shown in Table 1.

There are hundreds of different organophosphorus compounds (OPCs) ranging from the deadly toxic nerve agents to moderately toxic compounds used in insecticides and pesticides, but all have the same mechanism of action, that is, irreversible inhibition of acetylcholinesterase at nerve synapse. Oximes (nucleophilic agents) are acetylcholinesterase reactivators which are used as adjunct treatment in OPC poisoning to reactivate inhibited acetylcholinesterase (AChE).
Unfortunately, the therapeutically available oximes are not equally effective for different kinds of OPC poisons. Therefore, there is a pressing need to develop an oxime with universal antidotal efficacy.

Table 1: A brief history of organophosphorus compounds

Year	Event
1854	The process of synthesis of first organophosphorus compound, tetraethyl pyrophosphate (TEPP) was reported.
1936	The first organophosphorus nerve poison, tabun was produced in Germany
1938	Another nerve agent belongs to organophosphorus group was developed and named sarin
1944	The third neurotoxic compound of the same group was developed in Germany, named soman.
1957	VX, another nerve agent of the same group developed in Britain and weaponized by Americans.
1983-84	Iraqi troops used tabun nerve agent against Iranian soldiers during the war.
1988	Sarin was used against Kurdish in Iraq by Iraqi troops.
1991	It is also believed that allied troops have been exposed to sarin during the gulf war.
1994	In Matsumoto, Japan a terrorist attack was reported with sarin which caused seven deaths and many casualties.
1994/1995	Assassination attempt with VX was made in Japan.
1995	A terrorist attack by sarin was reported in Tokyo Subway, Japan.

Reactivation of inhibited AChE by removal of phosphyl moiety from the AChE active site, serine, is considered to be the primary mechanism of action for oximes [9-11]. 2-PAM is the first clinically available oxime, developed in the 1950s [12]. The scientific world was introduced to the use of this oxime by 1956 and was used for the first time

against parathion poisoning in Japan [13]. **2-**PAM is structurally a monopyridinium aldoxime and is formulated as various salts, e.g., chloride, iodide, bromide, lactate, methyl sulphate, methanesulfonate which mostly differ in their stability and solubility [14]. Further research in this field resulted in the synthesis of more efficacious bispyridinium aldoximes, namely, TMB4 (trimedoxime) in 1957, MMC4 (methoxime) in 1959, BI6 and LüH-6 (obidoxime) in 1964, HI-6 in 1967, and HLö-7 in 1968 [15]. It is interesting to note that all the oximes were primarily synthesized for use against organophosphorus (OP) nerve agents such as tabun and sarin, which are liable to be used in warfare, and secondarily, the oximes have been tested and are being used to counter intentional or unintentional OP insecticide/pesticide poisoning. Among the clinically available oximes, obidoxime is considered the best for countering pesticide OP poisoning **[**16] while HI-6 and HLö-7 are good for OP nerve agents poisoning [17]. 2-PAM, is most often used by physicians worldwide but its efficacy in clinical trials is controversial and its low or null efficacy is well documented in literature [4,18,19].

Another important aspect is that oximes are not used alone but rather as an adjunct treatment to atropine sulphate. Clinically, while atropine relieves muscarinic signs and symptoms, oximes are supposed to shorten the duration of the respiratory muscle paralysis by reactivation of cholinesterase [20]. According to Petroianu [21], the therapy of organophosphate poisoning is known by the catchy acronym, AFLOP, which stands for 'Atropine, Fluids, Oxygen, and Pralidoxime'.

During the past few years, some comprehensive reviews on oximes have been reported **[**1**,**14,15,22-25]. Clinical opinion on the value of oximes as adjunct in the therapy of organophosphorus pesticide intoxication of human remains divided. It has been argued that oximes are unnecessary when intoxication is not severe [20]. Some reported that their clinical experience with oximes is disappointing [18,25-26] while Peter et al stated that using meta-analysis, oximes either gave null effect or possible harm [19]. According to Jokanovic [27], oximes are beneficial if used properly and WHO recommendations are followed.

In fact, there are some limitations with oxime therapy. First, a particular oxime may be effective against a specific organophos-phorus acetylcholinesterase inhibitor and ineffective against others. Hence, there would be limited basis for choosing one oxime over another in an unknown exposure. Secondly, AChE inhibited by OPCs undergoes a process of ageing and an aged enzyme cannot be reactivated [14]. The ageing kinetics of different OPCs is different, ranging from a few minutes to many hours. Second, dosing and time of treatment also plays a vital role in successful oxime therapy. Other factors that influence oxime therapy include inhibition potency of OPCs, and its toxicokinetics, ageing kinetics of inhibited AChE, reactivating potency of oxime and its pharmacokinetics, correct dosing and evaluation for the persistent need of oxime therapy, and correct timing, i.e., whether oxime is started too late or discontinued too early, etc.

The aim of the present review is to propose an acetylcholinesterase reactivator with broad spectrum for all kinds of organophosphorus anticholinesterases. Laboratory *in vivo* and *in vitro* data and literature search suggests that there is a pressing need for a universal oxime.

Which Oxime should be therapeutically used in op poisoning?

There is no definite answer. Oximes are unfortunately not equally effective against all available organophosphorus acetylcholinesterase inhibitors. Hence, it may not be a simple choice for clinicians to choose an oxime for unknown OPC exposure. Secondly, there is a lack of

published clinical trials regarding the beneficial role and efficacy of oximes particularly dose regimen, oxime choice and outcome of the treatments. There is a clear demand for an oxime with universal broad spectrum antidotal potency. The literature shows that obidoxime may be a good choice for pesticide/insecticide OPCs poisoning, better than the most widely used pralidoxime, while HI-6 is good for nerve agent poisoning..

Since no oxime has been proved or is clinically available as a universal broad spectrum agent for structurally different kinds of OP acetylcholinesterase inhibitor; numerous attempts have been made to improve the antidotal properties of the conventional mono and bis pyridinium oximes by modifying their structures. The efforts yielded the synthesis of imidazolium, quinuclidinium, pyridinium-imidazolium, pyridinium-quinuclidinium and quinuclidinium-imidazolium oximes [25] which are still at the experimental stage. The synthesis of oximes like compound by Kamil Kuca and Kamil Musilek in Czech Republic introduced series of so called K-oximes during the last few years. The oximes were basically targeted for tabun and other OP nerve agent [17] but tests were extended for pesticides induced AChE inhibition and found promising potential. More than 200 structurally different K-oximes have been synthesized since 2003 [28] but the most promising among them are K-027 [17, 23, 28-38].

Other potentially promising reported K-oximes are K-48, K-53, K-74, K-75 and K-203, etc. Structurally all the K-oximes are either asymmetrical or symmetrical bispyridinium aldoximes with changes in the position of functional aldoxime as well as in some cases changes in linker chain. Many of them were found to be better than the therapeutically available oximes but still no single oxime could be identified as a broad spectrum universal oxime for structurally different kinds of OPCs. K-27 [39] and K-48 [40] are the two promising oximes in the series of K-oximes. Experimental evidence from animal studies reveals that K-27 is a strong candidate to replace the available oximes. K-27 has been reported to be effective against many OPC compounds except the nerve agents, soman and cyclosarin [41].

Structures of Conventional And Experimental K-Oximes

K-27 (1-(4-hydroxyiminomethylpyridinium)-**3**-(4-carbamoylpyridinium)–propane dibromide) and K-48 (1-(4-hydroxyiminomethylpyridinium)-**4**-(4-carbamoylpyridinium)-butane dibromide) are bisquaternary asymmetric pyridinium aldoximes with only one functional aldoxime group in position four of the pyridine ring. Structural requirements of acetylcholinesterase reactivators, particularly new oximes, have been reviewed by Kuca *et al* [42] and others [43,44]. Structures of conventional oximes and two promising experimental K-oximes are given in Figure 1.

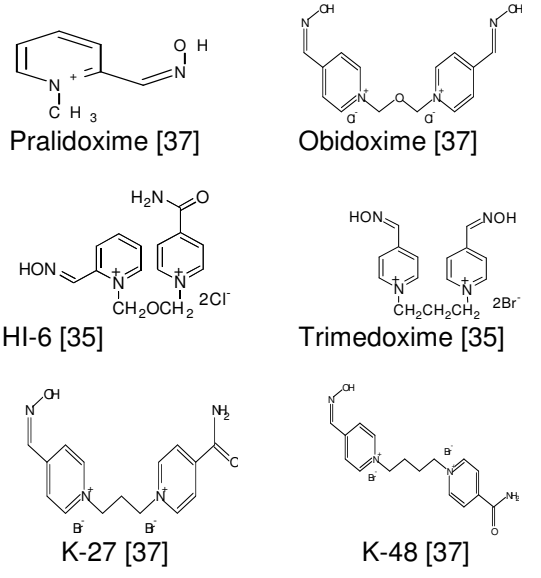

Figure 1: Structures of conventional and two promising K-oximes.

Table 2: Physicochemical and toxicological characteristics of oximes

Oxime	Molecular weight	LogP*	LD_{50}(*in vivo*) mg/kg**	IC_{50} of rats blood (*in vitro*) (µM) *	IC_{50} of human blood (*in vitro*) (µM) *
Pralidoxime	172.61	-2.31	121	412	592
Obidoxime	359.21	-3.12	177	193	702
HI-6	377.30	-3.39	781***	663	310
Trimedoxime	446.14	-2.07	74**** [a]	NA	652
K-27	446.16	-2.66	612	1054	414
K-48	460.16	-2.61	246	643	461

**ref 46; **ref 37; ***ref 50; ****ref 51; [a]Mice LD_{50}*

Physicochemical Properties of Oximes

Table 2 corroborates the basic physico-chemical properties of the under discussed oximes. The in vivo intrinsic toxicity of oximes is quantified by LD_{50}. Both K-27 and K-48 have been shown to possess low toxicity which makes them more beneficial than others. The low toxicity and its benefits has also been reported by Calic et al [17] and Kuca et al [41] .Some other physico-chemical parameters have been discussed by Kuca et al [39, 40]. IC_{50} (50 % of maximum inhibitory concentration) values in columns 5 and 6 of Table 2 reflect the *in vitro* data for acetylcholinesterase inhibitory activity of the oximes. According to rat blood *in vitro* data, K-27 has higher IC_{50}, which means it is less toxic than others and this is in line with *in vivo* data as well. Log P values in the first column of Table 2 reflect the lipophilicity/ hydrophilicity of the compounds. A negative value indicates the hydrophilic nature of the oximes, and hence cannot pass the blood brain barrier. Literature shows that only about 5 – 10 % of oximes reach the brain [45].

The negative value of logP indicates the hydrophilicity of the oximes. The toxicity data, in terms of LD_{50} (last column) indicate that K-27 is the least toxic of the therapeutically available oximes. Trimedoxime is more toxic and this militates against its usage.

***In vivo* data for some oximes**

Table 3 shows the life-preserving capability of widely used oximes for some pesticides OP. 2-PAM and obidoxime are poorer in this regard than the experimental K oximes, K-27 and K-48. The other two therapeutically available oximes are also inferior in efficacy. These data were obtained from experiments using Wistar rats. The rats were intoxicated with different doses intraperitoneally, including supra lethal doses of experimental OPC and subsequent treatment with equitoxic doses of oximes that are half of their LD_{50}. Relative risk of death was estimated by Cox regression using SPSS statistical analysis software. The higher or comparable efficacy of the two K-oximes against various OPCs have been well documented in the literature [29,33-38,48-50]. This makes them promising substances for the therapy of poisoning with a wide variety of OPCs.

***In vitro* data**

Kuca et al [41] tested the reactivation potency of K-27 as a potential reactivator of AChE inhibited by tabun, sarin, cyclosarin, soman, VX, Russian VX, paraoxon, methylchlorpyrifos, and dichlorvos (2,2-dichlorovinyl dimethyl phosphate (DDVP). They found that K-27 reactivated AChE which had been inhibited by almost all the tested inhibitors at a level > 10 %, and this is believed to be sufficient for saving the lives of intoxicated organisms. In the case of cyclosarin- and soman-inhibited AChE, K-27 did not reach sufficient reactivation potency. The ability to protect AChE *in vitro* from inhibition by paraoxon, methyl paraoxon, diisopropylfluorophosphate (DFP), tabun and VX have been reported by many workers [35,51-55].

Table 3: Comparison of the relative risk of death after intoxication with different types of insecticidal/pesticidal OPCs and subsequent treatment with experimental and conventional oximes in rodent model (***Note*:** RR of OPCs is considered as 1 where no oximes were applied)

	Paraoxon-ethyl*	***Paraoxon-methyl****	***Diisopropylflouro-phosphate (DFP)*****	***Azinfos-methyl********
Oxime	**Relative risk of death (RR)**			
Pralidoxime chloride	**0.78**	**0.88**	**0.62**	**0.23**
Obidoxime	**0.64**	**0.93**	**0.26**	**0.37**
HI-6	**0.36**	**0.96**	**0.39**	**N/A**
Trimedoxime	**0.40**	**0.76**	**0.46**	**N/A**
K-27	0.20	0.58	0.21	0.26
K 48	0.32	0.60	0.30	0.33

**ref 46; **ref 34; ***ref 35; ****unpublished data*

Pretreatment Protocol

Pretreatment protocol is a war time or military combat protocol. Pyridostigmine, a weak reversible AChE inhibitor of carbamate group of compound, is the only United States Food and Drug Administration (FDA) approved drug. Its mechanism is to block the cholinesterase temporarily in order to deny access of irreversible inhibitors (OPCs) to the active site of the enzyme on subsequent exposure.

Preliminary studies on K-oximes as pretreatment drugs indicate that they are very promising and are better than the only recommended pretreatment drug (pyridostigmine). According to our unpublished *in vivo* data, K-27 and K-48 were more promising than pyridostigmine when pretreatment protocol was applied with five different acute toxic organophosphorus anticholinesterases at supra lethal doses in rats. Berend *et al* [48] obtained similarly promising results with K-48 against OP nerve agent tabun in mice.

CONCLUSION

Development of a universal broad spectrum oxime for OPCs poisoning is highly needed. The newer experimental K-oxime, K-27, may replace the existing conventional oximes in future for OP insecticides/pesticides poisoning because of its superior efficacy. However, it cannot be considered broad spectrum because of its inefficacy against two OP nerve poisons, soman and cyclosarin. Moreover, many other OPCs groups should be tested for efficacy. The oxime may also replace the only approved pretreatment drug, pyridostigmine, for war time protocol.

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REFERENCES

1. *Buckley NA, Eddleston M, Dawson AH. The need for translational research on antidotes for pesticide poisoning. Clin Exp Pharmacol Physiol 2005; 2: 999-1005.*
2. *Eddleston M, Buckley N, Eyer P, Dawson A. Management of acute organophosphorus poisoning. The Lancet 2008; 371(9612): 597-607.*
3. *Kavalci C, Durukan P, Ozer M, Cevik Y, Kavalci G. Organophosphate poisoning due to a wheat bagel. Inter Med 2009; 48: 85-88.*
4. *Cherian MA, Roshini C, Peter JV, Cherian AM. Oximes in organophosphorus poisoning. IJCCM 2005; 9(Pt 3): 155-163.*
5. *Karalliedde L, Senanayake N. Organophosphorus insecticide poisoning. J Int Fed Clin Chem 1999; 11(2): 4-9.*

6. *World Health Organization Public health impact of pesticides used in agriculture. 0edn. WHO; Geneva 1990.*
7. *Kenneth DK, Daniel EB, Kisa K. Toxicity, Organophosphate. [cited 2011 Feb 8]. Available from http://emedicine.medscape.com/article/167726 overview*
8. *Littefield MH. Estimates of acute pesticide poisoning in agricultural workers in less developed countries. Toxicol Rev 2005; 24: 271-278.*
9. *Marrs TC. Organophosphate poisoning. Pharmacol Therapeut 1993; 58(1): 51-61.*
10. *Mileson BE, Chambers JE, Chen WL, Dettbarn W, Ehrich M, Eldefrawi AT, Gaylor DW, Hamernik K, Hodgson E, Karczmar AG, Padilla S, Pope CN, Richardson RJ, Saunders DR, Sheets LP, Sultatos LG, Wallace KB. Common mechanism of toxicity: A case study of organophosphorus pesticides. Toxicol Sci 1998; 41: 8-20.*
11. *Pope CN. Organophosphorus pesticides: Do they all have same mechanism of toxicity? J Toxicol Environ Health (Part B) 1999; 2(Pt 2): 161-181.*
12. *Wilson IB, Ginsburg SA. Powerful reactivator of alkyl phosphate inhibited acetylcholinesterase. Biochim Biophys Acta 1955; 18: 168-170.*
13. *Namba T, Hiraki K. PAM (pyridine-2-aldoxime methiodide) therapy for alkyl-phosphate poisoning. J Am Med Assoc 1958; 166: 1834-1839.*
14. *Antonijevic B, Stojijkovic MP. Unequal efficacy of pyridinium oximes in acute organophosphate poisoning. Clin Med Res 2007; 5(Pt 1): 71-82.*
15. *Stojiljkovic MP, Jokanovic M. Pyridinium oximes: Rationale for their selection as casual antidotes against organophosphate poisonings and current solutions for auto injectors. Arh Hig Rada Toksikol 2006; 57: 435-443.*
16. *Worek F, Eyer P, Aurbek N, Szinicz L, Thiermann H. Recent advances in evaluation of oxime efficacy in nerve agent poisoning by in vitro analysis. Toxicology and Applied Pharmacology 2007; 219: 226-234.*
17. *Kassa J, Kuča K, Cabal J, Paar M. Comparison of the efficacy of new asymmetric bispyridinium oximes (K-27, K-48) with currently available oximes against tabun by in vivo methods. J Toxicol Environ Health A 2006; 69: 1875-1882.*
18. *Peter JV, Cherian AM. Organic insecticides. Anaesth Intensive Care. 2000; 28: 11-21.*
19. *Peter JV, Moran JL, Graham P: Oxime therapy and outcomes in human organophosphate poisoning: an evaluation using meta-analytic techniques. Crit Care Med 2006; 34: 502-510.*
20. *Johnson MK, Jacobsen D, Meredith TJ, Eyer P, Heath AJ, Ligtenstein DA, Marrs TC, Szinicz L, Vale JA, Haines JA. Evaluation of antidotes for poisoning by organophosphorus pesticides. Emer Med 2000; 12: 22-37.*
21. *Petroianu GA. Poisoning with organophosphorus compound (OPC): Mythology vs. Reality. The Middle East J Emer Med 2006; 6(Pt 1): 3-8.*
22. *Eddleston M, Szinicz L, Eyer P, Buckley N. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. QJM 2002; 95: 275-283.*
23. *Kassa J, Kuca K, Bartosova L, Kunesova G. The development of new structural analogues of oximes for the antidotal treatment of poisoning by nerve agents and the comparison of their reactivating and therapeutic efficacy with currently available oximes. Curr Org Chem 2007; 11: 267-283.*
24. *Worek F, Thiermann H. Strategies for the development of effective broad spectrum oximes. In defence against the effects of Chemical Hazards: Toxicology, diagnosis and medical countermeasures 2007; p 301-306.*
25. *Primozic I, Odzak R, Tomic S, Simeon-Rudolf V, Reiner E. Pyridinium, imidazolium and quinuclidinium oximes: synthesis, interaction with native and phosphylated cholinesterase and antidotes against organophosphorus compounds. J Med Chem Def 2004; 2: 1-30.*
26. *Kuča K, Bielavský J, Cabal J, Bielavska M. Synthesis of a potential reactivator of acetylcholinesterase – 1-(4-hydroxyiminomethylpyridinium)-3-(carbamoylpyridinium) -propane dibromide. Tetrahedron Lett 2003; 44: 3123-3125.*
27. *Jokanovic M. Medical treatment of acute poisoning with organophosphorus and carbamate pesticides. Toxicol Lett 2009; 190: 107-115.*
28. *Kassa J, Kuca K, Karasova J, Musilek K. The development of new oximes and the evaluation of their reactivating, therapeutic and neuroprotective efficacy against tabun. Mini Rev Med Chem 2008; 8(11): 1134-1143.*
29. *Calic M, Vrdoljak AL, Radic B, Jelic D, Jun D, Kuča K, Kovarik Z. In vitro and in vivo evaluation of pyridinium oximes: mode of interaction with acetylcholinesterase, effect on tabun- and soman-poisoned mice and their cytotoxicity. Toxicology 2006; 219: 85-96.*
30. *Musilek K, Holas O, Kuca K, Jun D, Dohnal V, Dolezal M. Synthesis of assymetrical bispyridinium compounds bearing cyano moiety and evaluation of their reactivation activityagainst tabun and paraoxon-inhibited acetylcholinesterase. Bioorg Med Chem Lett 2006; 16: 5673-5676.*
31. *Musilek K, Kuca K, Jun D, Dohnal V, Dolezal M. Synthesis of the novel series of bispyridinium compounds bearing (E)-but-2-ene linker and evaluation of their reactivation activity against chlorpyrifos-inhibited acetylcholinesterase. Bioorg & Med Chem Lett 2006; 16: 622-627.*
32. *Petroianu GA, Arafat K, Kuča K, Kassa J. Five oximes (K-27, K-33, K-48, BI-6 and methoxime) in comparison with pralidoxime: in vitro reactivation of red blood cell*

acetylcholinesterase inhibited by paraoxon. J Appl Toxicol 2006; 26: 64-71.

33. *Petroianu GA, Nurulain SM, Nagelkerke N, Al-Sultan MA, Kuča K, Kassa J. Five oximes (K-27, K-33, K-48, BI-6 and methoxime) in comparison with pralidoxime: survival in rats exposed to the organophosphate paraoxon. J Appl Toxicol 2006; 26: 262-268.*
34. *Petroianu GA, Nurulain SM, Nagelkerke N, Shafiullah M, Kassa J, Kuča K. Five oximes (K-27, K-48, obidoxime, HI-6 and trimedoxime) in comparison with pralidoxime: survival in rats exposed to methyl-paraoxon. J Appl Toxicol 2007; 27: 453-457.*
35. *Petroianu GA, Hasan MY, Nurulain SM, Nagelkerke N, Kassa J, Kuča K. New K-oximes (K-27 and K-48) in comparison with obidoxime (LuH-6), pralidoxime, HI-6 and trimedoxime (TMB-4): survival in rats exposed to the organophosphate paraoxon. Toxicol Mech Method 2007; 17: 401-408.*
36. *Lorke DE, Hasan MY, Nurulain SM, Kuca K, Schmitt A, Petroianu GA. Efficacy of two new asymmetric bispyridinium oximes (K-27 and K-48) in rats exposed to diisopropylfluorophosphate (DFP): comparison with the established oximes pralidoxime, obidoxime, trimedoxime, methoxime and HI-6. Clin Toxicol 2008; 23: 1-7.*
37. *Lorke DE, Hasan MY, Nurulain SM, Kuca K, Kassa J, Petroianu GA. Eight new bispyridinium oximes in comparison with the conventional oximes pralidoxime and obidoxime: In vivo efficacy to protect from diisopropylfluorophosphate (DFP) toxicity. J Appl Toxicol 2008; 28(Pt 7): 920-928.*
38. *Nurulain SM, Lorke DE, Hasan MY, Shafiullah M, Kuca K, Musilek K. Efficacy of eight experimental bispyridinium oximes against paraoxon induced mortality: Comparison with the conventional oximes pralidoxime and obidoxime. Neurotox Res 2009; 16(Pt 3): 60-67.*
39. *Kuča K, Bielavský J, Cabal J, Bielavska M. Synthesis of a potential reactivator of acetylcholinesterase – 1-(4-hydroxyiminomethylpyridinium)-3-(carbamoylpyridinium) -propane dibromide. Tetrahedron Lett 2003; 44: 3123-3125.*
40. *Kuča K, Bielavský J, Cabal J, Kassa J. Synthesis of a new reactivator of tabun-inhibited acetylcholinesterase. Bioorg Med Chem Lett 2003; 13: 3545-3547.*
41. *Kuča K, Musilek K, Jun D, Pohanka M, Ghosh KK, Hrabinova M. Oxime K027: novel low-toxic candidate for the universal reactivator of nerve agent and pesticide inhibited acetylcholinesterase. J Enz Inhib Med Chem 2010; 25(4): 509-512.*
42. *Kuča K, Jun D Musilek K. Structural requirements of acetylcholinesterase reactivators. Mini Rev Med Chem 2006; 6(3): 269-277.*
43. *Musilek K, Dolezal M, Gunn-Moore F, Kuca K. Design, evaluation and structure-activity relationship studies of the AChE reactivators against organophosphorus pesticides. Med Res Rev 2009; Dec 21. DOI:10.1002/med.20192*
44. *Maxwell DM, Koplovitz I, Worek F, Sweeney RE.: A structure-activity analysis of the variation in oxime efficacy against nerve agents. Toxicology Applied Pharmacology 2008; 231: 157-164.*
45. *Lorke DE, Hasan MY, Nurulain SM, Sheen R, Kuča K, Petroianu GA. Entry of two new asymmetric bispyridinium oximes (K-27 and K-48) into the rat brain: comparison with obidoxime. J Appl Toxicol 2007; 27: 482-490.*
46. *Lorke DE, Petroianu GA. Minireview: does in-vitro testing of oximes help predict their in-vivo action after paraoxon exposure? J Appl Toxicol 2009; (6): 459-469.*
47. *Dawson RM. Review of oximes available for treatment of nerve agent poisoning. J Appl Toxicol 1994; 14(5): 317-31.*
48. *Berend S, Radić B, Kuca K, Lucić Vrdoljak A. The antidotal efficacy of the bispyridinium oximes K027 and TMB-4 against tabun poisoning in mice. Chem Biol Interact 2010; 187(1-3): 291-294.*
49. *Lorke DE, Hasan MY, Nurulain SM, Kuca K, Schmitt A, Petroianu GA. Efficacy of two new asymmetric bispyridinium oximes (K-27 and K-48) in rats exposed to diisopropylfluorophosphate: comparison with pralidoxime, obidoxime, trimedoxime, methoxime, and HI-6. Toxicol Mech Methods 2009; 19(4): 327-333.*
50. *Kassa J. The influence of oxime and anticholinergic drug selection on the potency of antidotal treatment to counteract acute toxic effects of tabun in mice. Neurotox Res, 2006; 9(1): 59-62.*
51. *Lorke DE, Hasan MY, Arafat K, Kuča K, Musilek K, Schmitt A, Petroianu GA. In vitro oxime reactivation of red blood cell acetylcholinesterase inhibited by diisopropylfluorophosphate (DFP). J Appl Toxicol, 2008; 28(4): 422-429.*
52. *Petroianu GA, Kalasz HJ. Comparison of the ability of oximes to reactivate human RBC cholinesterases inhibited by ethyl- and methyl-paraoxon. Curr Org Chem, 2008; 11: 1624-1634.*
53. *Kuca K, Bartosova L, Kassa J, Cabal J, Bajgar J, Kunesova G, Jun D. Comparison of the potency of newly developed and currently available oximes to reactivate nerve agent-inhibited acetylcholinesterase in vitro and in vivo. Chem Biol Interact, 2005; 157/158: 367-368.*
54. *Kuca K, Marek J, Karasova J, Pohanka M, Korabecny J, Kalasz H. Novel Acetylcholinesterase Reactivator - Oxime*

K048 - Reactivation Activity In vitro. Med Chem, 2010; 6(1): 1-5.

55. *Kuca K, Kassa J. A comparison of the ability of a new bispyridinium oxime-1-(4-hydroxyimino-methylpyridinium)-4-(4-carbamoylpyridinium) butane dibromide and currently used oximes to reactivate nerve agent inhibited ratbrain acetylcholinesterase by in vitro methods. J Enz Inhib Med Chem, 2003; 18(6): 529-535.*