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A new group of monoquaternary reactivators of acetylcholinesterase inhibited by nerve agents

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Abstract

Reactivators of acetylcholinesterase (AChE; EC 3.1.1.7) are able to treat intoxication by organophosphorus compounds, especially with pesticides or nerve agents. Owing to the fact that there exists no universal "broad-spectrum" reactivator of organophosphates-inhibited AChE, many laboratories have synthesized new AChE reactivators. Here, we synthesized five new and three previously known quaternary monopyridinium oximes as potential reactivators of AChE inhibited by nerve agents. Potencies to cleave *p*-nitrophenyl acetate (PNPA), which is commonly used as a model substrate of nerve agents, were measured. Their cleaving potencies were compared with 4-PAM (4-hydroxyiminomethyl-1-methylpyridinium iodide), which is derived from the structure of the currently used AChE-reactivator 2-PAM (2-hydroxyiminomethyl-1-methylpyridinium iodide). Three newly synthesized oximes achieved similar nucleophilicity at the similar pK_a according to 4-PAM, which is very promising for using these derivatives as AChE reactivators.

Keywords: *Acetylcholinesterase, Reactivator, PNPA, Reactivation, Nerve agents, Inhibition*

Introduction

Sarin, soman, tabun and VX belong to the most toxic synthetic compounds called nerve agents [1,2]. They irreversibly inhibit the enzyme acetylcholinesterase (AChE; EC 3.1.1.7). The inhibitory effect is based on phosphorylation or phosphonylation of a serine hydroxy group at the esteratic site of the active centre of the enzyme [3,4].

For the treatment of the toxic effects of these agents, parasympatolytics (as functional antidotes) and AChE reactivators (as causal antidotes) are commonly used [4–7]. Several of these reactivators are currently applied as first aid-treatment antidotes—pralidoxime (2-hydroxyiminomethyl-1-methylpyridinium chloride), obidoxime (1,3-bis(4-hydroxyiminomethylpyridinio)-2-oxapropane dibromide) and H-oxime HI-6 (1-(2-hydroxyiminomethylpyridinio)-3-(4-carbamoylpyridinio)-2-oxapropane dichloride) [See Figure 1] [8].

AChE reactivators are chemical substances able to restore the activity of AChE inhibited by toxic organophosphates. All of them are powerful nucleophilic agents, which can cleave the P–O bond formed by the reaction of the serine hydroxyl with the inhibiting reactive organophosphorus compound [4,5,9]. Structurally most of the reactivators can be characterized as mono- or bisquaternary pyridinium salts with one or two aldoxime groups at the pyridinium rings at positions two or four [10,11].

However, existing reactivators of AChE do not have sufficient efficacy to reactivate AChE inhibited by all types of nerve agents [6,12].

The goal of our investigation was to synthesize new group of AChE reactivators, which differs from the currently used AChE reactivators in the type of oxime group; the aldoxime group is replaced by a substituted ketoxime group. Variation of "substituents" attached directly on the oxime function could allow dramatical

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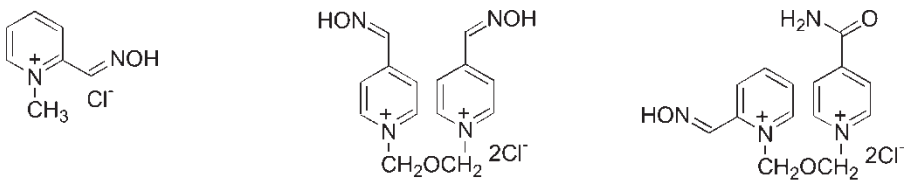


2-PAM **Obidoxime** **HI-6**

Figure 1. Structures of the currently used acetylcholinesterase reactivators.

changes in oxime group reactivity. Structures of the synthesized potential AChE reactivators are shown in Figure 2.

We have evaluated their potency to cleave *p*-nitrophenyl acetate (PNPA), which is commonly used as a model substrate of the nerve agents [13–15]. Their potencies to cleave PNPA were compared with 4-PAM (**1**; 4-hydroxyiminomethyl-1-methylpyridinium iodide), which is derived from the structure of the currently used AChE-reactivator 2-PAM (2-hydroxyiminomethyl-1-methylpyridinium iodide).

Material and methods

Synthesis

Oximes **1, 2** and **3** were prepared by the procedure published by Ginsburg and Wilson [16] and ketoxime **4** according to Poziomek et al. [17] 4-[Amino-(hydroxyimino)methyl]-1-methylpyridinium iodide **5** was synthesized by quaternization of one part of pyridine-4-carboxhydroximamide with two parts of iodomethane in methanol [18].

1-(4-Pyridyl)propane-1,2-dione-1-oxime **7** was obtained from ketone **6** by a reaction modified from the literature [19,20]. The quarternization of compound **7** using iodomethane afforded 4-[1-hydroxyimino-2-oxopropyl]-1-methylpyridinium iodide **8** (Scheme 1).

2-Methylsulfonyl(4-pyridyl)ethan-1-one-oxime **10** was prepared by reaction of ketone **9** with hydroxylamine [21]. 4-[1-Hydroxyimino-2-(methylsulfonyl) ethyl]-1-methyl-pyridinium iodide **11** was obtained by reaction of compound **10** with iodomethane (Scheme 2).

N,*N*-Diethyl-1-(4-pyridylcarbonyl)methanesulfonamide **14** and 2-phenylsulphonyl(4-pyridyl)ethan-1-one **18** were prepared using a modified procedure according to Brienne et al. [22] by reaction of ethylisonicotinate **12** and *N*,*N*-diethylmethansulfonamide **13**,[23] or methylphenylsufone **17** in the presence of potassium hydride, respectively. Reaction of **14** or **18** with hydroxylamine gave *N*,*N*-diethyl-2-hydroxyimino-2-(4-pyridyl)ethansulfonamide **15** and 2-phenylsulfonyl-(4-pyridyl)ethan-1-on-oxime **19**, respectively. The quarternization of compounds **15** and **19** using iodomethane afforded 4-[(1-hydroxyimino-2-(*N*,*N*-(diethylsulfamoyl)ethyl)]-1-methylpyridinium iodide **16** and 4-[(1-hydroxyimino-2-(phenylsulfonyl)ethyl)]-1-methyl pyridinium iodide **20**, respectively (Scheme 3).

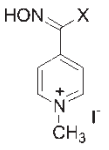
The intermediates **7**,**10**,**14**,**15**,**18**,**19**, and the target molecules **5**,**8**,**11**,**16**,**20** were identified by their melting points (Boetius block), ^{1}H NMR spectra (Varian Gemini 300; 300 MHz) and by their elemental analysis (Perkin Elmer CHN Analyser 2400 Serie II):

5: m.p.189–192°C; EA: For $C_7H_{10}IN_3O$ (279.08) Calc. C, 30.13; H, 3.61; I, 45.47; N, 15.06; Found C, 29.83; H, 3.51; I, 45.66; N, 14.85%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.31 (s, 3H, N^+CH_3), 6.40 (s, 2H, NH_2), 8.25 (d, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 6.75$ Hz, 2H, H-3 and H-5), 8.95 (d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 6.74$ Hz, 2H, H-2 and H-6), 10.90 (s, 1H, NOH).

7: m.p. 205.5–207.5°C; EA: For $C_8H_8N_2O_2$ (164.16) Calc. C, 58.53; H, 4.91; N, 17.06; Found. C, 58.31; H, 4.89; N, 16.88%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.43 (s, 3H, $COCH_3$), 7.22 (d, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 6.15$ Hz, 2H, H-3 and H-5), 8.60(d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 6.15$ Hz, 2H, H-2 and H-6).

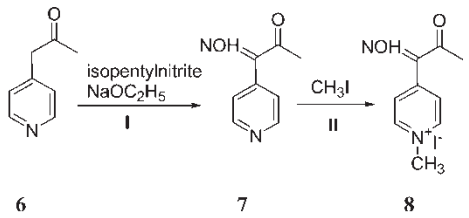
8: m.p. 212–214°C; EA: For $C_9H_{11}IN_2O_2$ (306.10) Calc. C, 35.31; H, 3.62; I, 41.46; N, 9.15; Found. C, 35.28, H, 3.55; I, 46.43; N, 8.97%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.48(s, 3H, $COCH_3$), 4.35(s, 3H, N^+CH_3), 8.03 (d, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 6.45$ Hz, 2H, H-3 and H-5), 9.02(d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 6.75$ Hz, 2H, H-2 and H-6).

10: m.p. 222–225°C; EA: For $C_8H_{10}N_2O_3S$ (214.24) Calc. C, 44.85; H, 4.70; N, 13.08; S,



1	**2**	**3**	**4**	**5**
H	CH_3	C_6H_5	CN	NH_2
8	**11**	**16**	**20**	
$COCH_3$	$CH_2SO_2CH_3$	$CH_2SO_2N(CH_2CH_3)_2$	$CH_2SO_2C_6H_5$	

Figure 2. Structures of the synthesized potential AChE reactivators.



6 7 8

Conditions: Reaction **I**: ethanol, 0°C, 12 h; Yield 55%.
Reaction **II**: acetone, reflux, 2.5 h; Yield 80%.

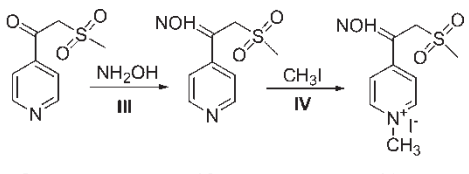
Scheme 1. Preparation of 4-[1-hydroxyimino-2-oxopropyl]-1-methyl-pyridinium iodide **8**

14.92; Found C, 44.80; H, 4.83; N, 13.16; S, 14.83%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.02 (s, 3H, $CH_2SO_2CH_3$), 4.79 (s, 2H, $CH_2SO_2CH_3$), 7.71 (d, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 6.05$ Hz, 2H, H-3 and H-5), 8.59 (d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 6.05$ Hz, 2H, H-2 and H-6).

11: m.p. 190–193°C; EA: For $C_9H_{13}IN_2SO_3$ (356.18) Calc. C, 30.35; H, 3.68; I, 35.63; N, 7.86; S, 9.00; Found. C, 30.57; H, 3.87; I, 35.82; N, 7.63; S, 8.80%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.07(s, 3H, $CH_2SO_2CH_3$), 4.31 (s, 3H, N^+CH_3), 4.96 (s, 2H, $CH_2SO_2CH_3$), 8.37 (d, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 6.33$ Hz, 2H, H-3 and H-5), 8.89 (d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 6.33$ Hz, 2H, H-2 and H-6).

14: m.p. 83°C; EA: For $C_{11}H_{16}N_2SO_3$ (256.32) Calc. C, 51.54; H, 6.29; N, 10.93; S, 12.51; Found C, 51.62; H, 6.49; N, 10.86; S, 12.47%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, $\mathcal{J} = 7.04$ Hz, 6H, $SO_2N(CH_2CH_3)_2$), 3.23 (q, $\mathcal{J} = 7.33$ Hz, 4H, $SO_2N(CH_2CH_3)_2$), 4.54 (s, 2H, CH_2SO_2), 7.83 (d, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 6.16$ Hz, 2H, H-3 and H-5), 8.86 (d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 6.16$ Hz, 2H, H-2 and H-6).

15: m.p. 183–186°C; EA: For $C_{11}H_{17}N_3SO_3$ (271.34) Calc. C, 48.69; H, 6.32; N, 15.49; S, 11.82; Found C, 48.47; H, 6.39; N, 15.19; S, 11.58%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07(t, $\mathcal{J} = 7.04$ Hz, 6H, $SO_2N(CH_2CH_3)_2$), 3.21 (q, $\mathcal{J} = 7.03$ Hz, 4H, $SO_2N(CH_2CH_3)_2$), 4.67 (s, 2H, CH_2SO_2), 7.69 (d, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 5.57$ Hz, 2H, H-3 and H-5), 8.59 (d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 5.57$ Hz, 2H, H-2 and H-6), 12.55 (s, 1H, NOH).



9 10 11

Conditions: Reaction **III**: methanol, reflux, 10 h; Yield 80%.
Reaction **IV**: methanol, reflux, 24 h; Yield 56%.

Scheme 2. Preparation of the 4-[1-hydroxyimino-2-(methylsulfonyl)ethyl]-1-methyl-pyridinium iodide **11**.

16: m.p. 152–155°C; EA: For $C_{11}H_{17}IN_3SO_3$ (413.27) Calc. C, 34.87; H, 4.88; I, 30.71; N, 10.17; S, 7.76; Found C, 34.75; H, 4.81; I, 30.54; N, 9.92; S, 7.70%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08(t, $\mathcal{J} = 7.04$ Hz, 6H, $SO_2N(CH_2CH_3)_2$), 3.16 (q, $\mathcal{J} = 7.04$ Hz, 4H, $SO_2N(CH_2CH_3)_2$), 4.32 (s, 3H, N^+CH_3), 4.82 (s, 2H, CH_2SO_2), 8.34 (d, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 7.04$ Hz, 2H, H-3 and H-5), 8.97 (d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 6.75$ Hz, 2H, H-2 and H-6), 13.51 (s, 1H, NOH).

18: m.p. 153–156°C; EA: For $C_{13}H_{11}NSO_3$ (261.30) Calc. C, 59.76; H, 4.24; N, 5.36; S, 12.27; Found. C, 59.63; H, 4.24; N, 5.15; S, 12.22%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.38 (s, 2H, $CH_2SO_2C_6H_5$), 7.62 (m, 2H, H-3′ and H-5′), 7.72 (m, 1H, H-4′), 7.79 (d, 2H, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 6.15$ Hz, 2H, H-3 and H-5), 7.89 (m, 2H, H-2′ and H-6′), 8.78 (d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 6.15$ Hz, 2H, H-2 and H-6).

19: m.p. 226–228.5°C; EA: For $C_{13}H_{12}N_2SO_3$ (276.31) Calc. C, 56.51; H, 4.38; N, 10.14; S, 11.60; Found. C, 56.25; H, 4.31; N, 9.96; S, 11.71%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.96 (s, 2H, $CH_2SO_2C_6H_5$), 7.65 (m, 7H, H-3, H-5, H-2′,H-6′, H-3′, H-5′and H-4′), 8.53 (d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 5.57$ Hz, 2H, H-2 and H-6), 12.30(s, 1H, NOH).

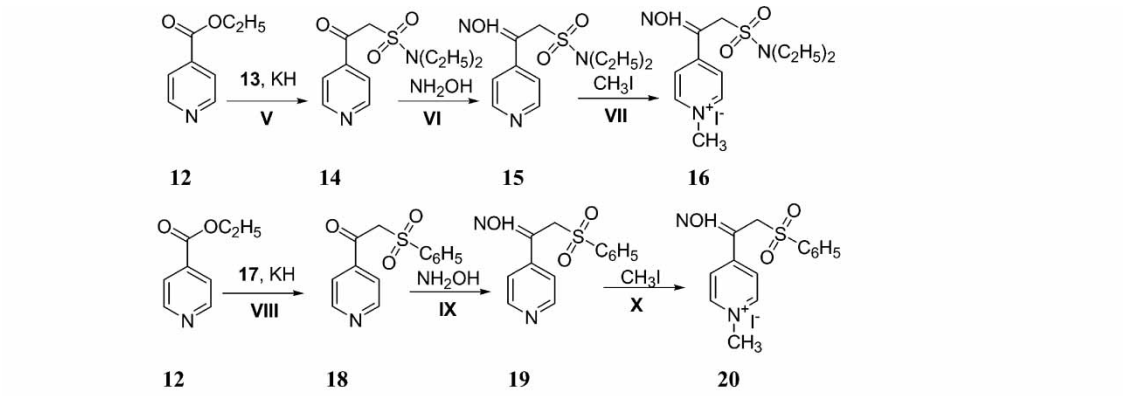
20: m.p. 202–206°C; EA: For $C_{14}H_{15}IN_2SO_3$ (418.25) Calc. C, 40.20; H, 3.61; I, 30.34; N, 6.70; S, 7.67; Found. C, 40.17, H, 3.51; I, 30.49; N, 6.42; S, 7.75; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.32 (s, 3H, N^+CH_3), 5.12 (s, 2H, $CH_2SO_2C_6H_5$), 7.62 (m, 2H, H-3′ and H-5′); 7.78 (m, 3H, H-2′, H-6′ and H-4′), 8.34 (d, 2H, $\mathcal{J}(3,2) = \mathcal{J}(5,6) = 6.74$ Hz, 2H, H-3 and H-5), 8.96 (d, $\mathcal{J}(2,3) = \mathcal{J}(6,5) = 6.74$ Hz, 2H, H-2 and H-6), 13.21 (s, 1H, NOH).

Kinetic measurement

Cleavage of PNPA was observed spectrophotometrically using the standard test [24–26]. Concentration of 4-nitrophenoxide anion was monitored at 400 nm. The rate constants k_{obs} [s^{-1}] were obtained by nonlinear regression analysis of the absorbance *vs* time data. All kinetic measurements were carried out under pseudo-first-order conditions ($c_{PNPA} \ll c_{oxime}$) at 25°C, pH = 7.5 in the cell was maintained by the biological buffer HEPES. The concentration of the oximate anion [OX^-] was calculated using equation (1);

$$[OX^-] = c_{ox} \cdot K_a / ([H^+] + K_a) \qquad (1)$$

where c_{ox} is the analytical concentration of the oxime and K_a is the dissociation constant of the oxime. k_2 [s^{-1}lmol^{-1}] values were obtained from the k_{obs} *vs* [OX^-] plots by linear regression. The slope of these plots represent P the formal second-order rate constants



Conditions: Reaction **V**: diglyme, 85ºC, 1.5 h; Yield 44%. Reaction **VI**: methanol, reflux, 16 h; Yield 77%. Reaction **VII**: acetone, reflux, 8 h; Yield 78%. Reaction **VIII**: diglyme, 85ºC, 1 h; Yield 36%. Reaction **IX**: methanol, reflux, 11 h; Yield 77%. Reaction **X**: acetonitrile and methanol, reflux, 24 h; Yield 73%.

Scheme 3. Preparation of 4-[(1-hydroxyimino-2-*N*,*N*-(diethylaminosulfamoyl)ethyl)]-1-methyl-pyridinium iodide **16** and 4-[(1-hydroxyimino-2-(phenylsulfonyl)ethyl)]-1-methyl pyridinium iodide **20**.

k_2 for the cleavage, revealing thus the nucleophilicity of the oximate anions [OX^-].

Results and discussion

Owing to the fact, that none of the currently used AChE reactivators reactivates AChE inhibited by all types of nerve agents [18], searching for a new AChE reactivator, which could reactivate AChE inhibited by a broad spectrum of nerve agents, is needed [7]. That was reason why we have synthesized some new AChE reactivators and tested their potency to cleave PNPA, which is commonly used as a model substrate of the nerve agents [8].

The constants k_2 and pK_a values for the tested oximes are shown in Table I. Bröensted plot was designed from the dependence of k_2 (logarithmic scale) on pK_a.

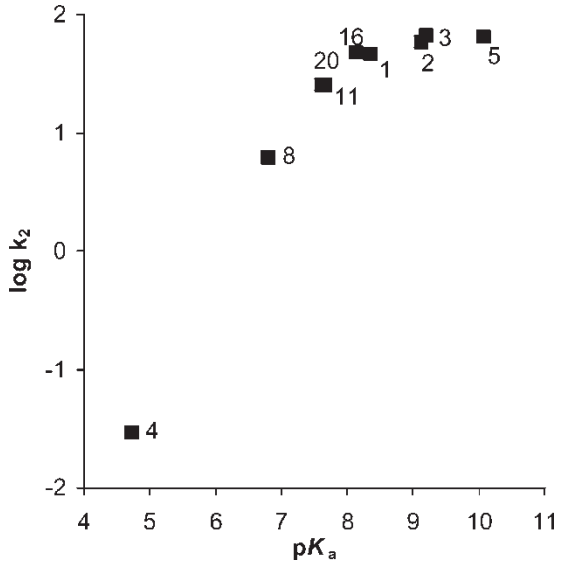


Figure 3. Bröensted plot of oxime-induced cleavage of PNPA.

As can be seen from the plot (Figure 3), the shape of the dependence is characterized as a typical curve for oxime-induced cleavage of PNPA [15,25]. The dependence curve consists of two parts. The first part covers the range of p*K*a from 4 to 8 and the slope is 0.7 whereas the second part covers less acidic oximes (p*K*a range from 8–10) and the slope is almost parallel with the *x* axis.

Compounds **11**, **16** and **20** (p*K*a about 8) appear to be the most prospective cleavage agents. As it can be seen from the Figure 3 and Table I, they have a relatively acidic oxime group which guaranties a high concentration of nucleophilic oximate. Moreover, these oximates show the highest accessible nucleophilicity towards PNPA in the oxime series, studied.

In conclusion, we have synthesized a new group of monoquaternary reactivators of AChE inhibited by nerve agents. Three newly synthesized oximes **11**, **16** and **20** achieved similar nucleophilicity at the similar pK_a according to 4-PAM (**1**; 4-homologue of currently used AChE reactivator 2-PAM), which is very promising for using these derivatives as AChE reactivators. Their reactivation potencies will be tested using standard reactivation *in vitro* [2,7,28] and *in vivo* tests [29].

Table I. Reaction constants k_2 [$s^{-1}1mol^{-1}$] and pK_a values of the synthesized oximes.

Oxime	$p K_a$	k_2
1	8.34	47.3 ± 0.4
2	9.18	68.1 ± 0.5
3	9.11	59.5 ± 0.5
4	4.71	$3.17 \cdot 10^{-2} \pm 0.01 \cdot 10^{-2}$
5	10.05	66.1 ± 0.5
8	6.79	6.4 ± 0.1
11	7.59	25.6 ± 0.4
16	8.11	49.2 ± 0.8
20	7.65	26.3 ± 0.5

Acknowledgements

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