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Chemical Biology
LETTERS

Role of Acetylcholinesterase (AChE) reactivators in the treatment of Organophosphorus poisoning: *in vivo*, *in vitro,* and *in silico* studies

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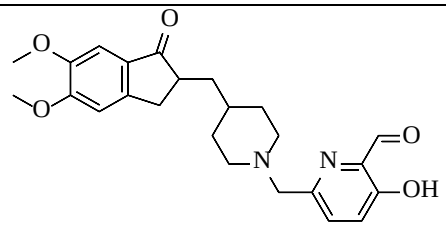
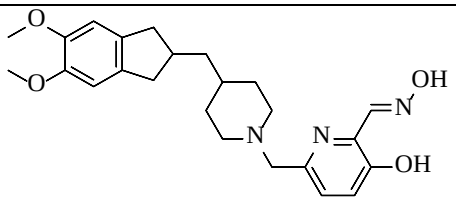
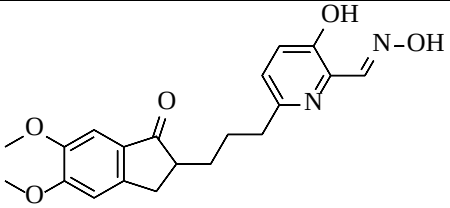
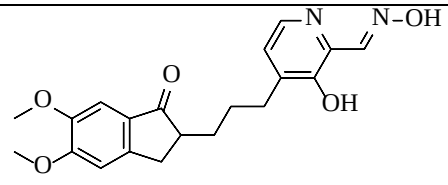
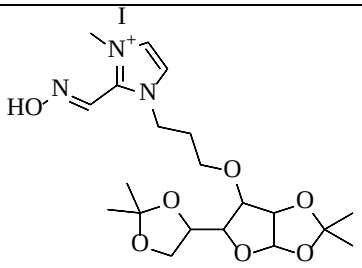
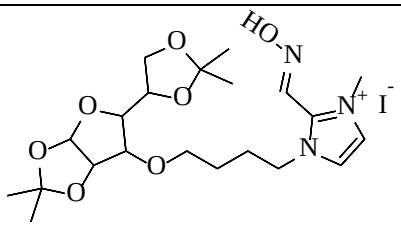
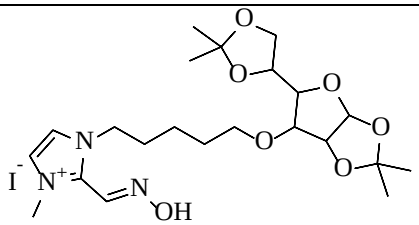
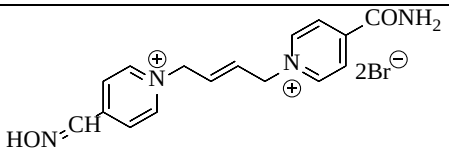
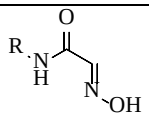
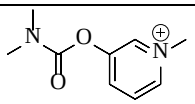
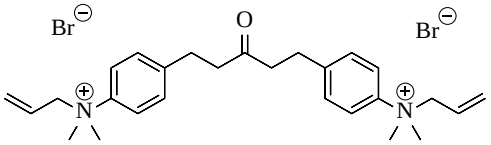
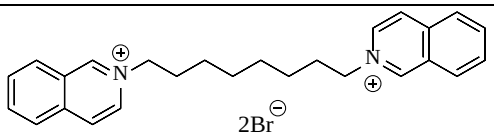
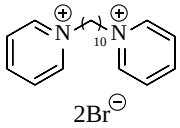
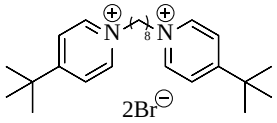
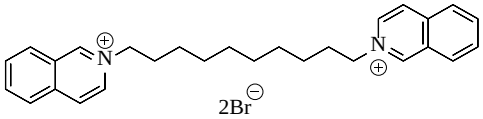
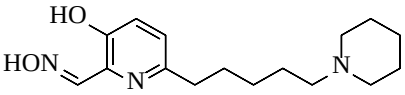
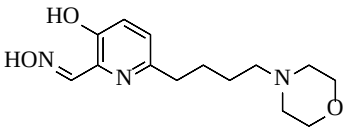
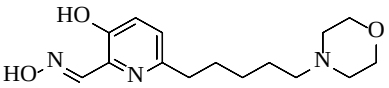
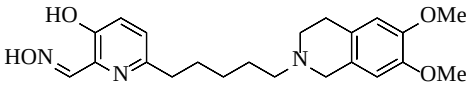
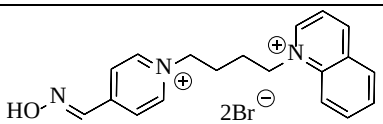
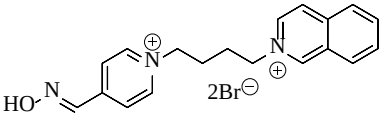
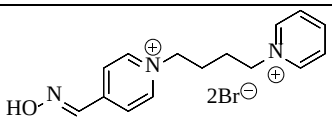
Supplementary file

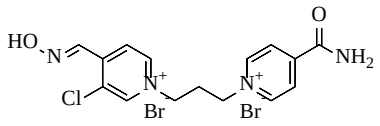
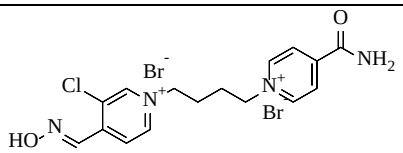
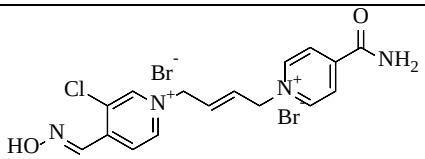
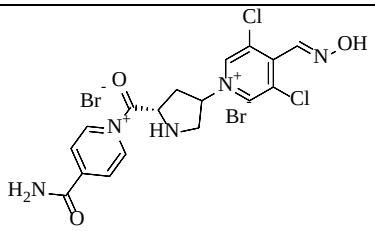
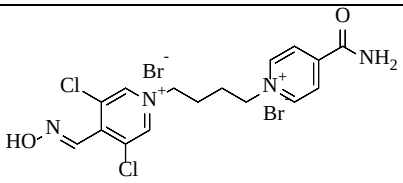
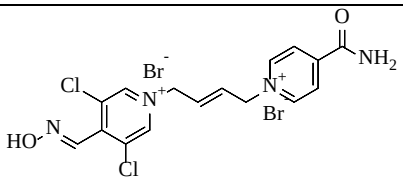
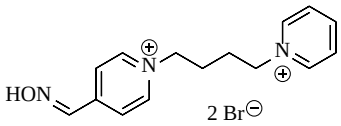
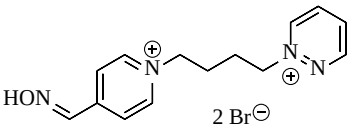
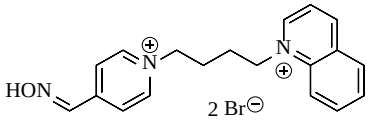
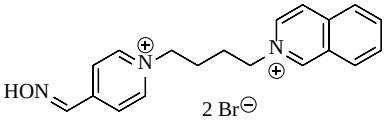
All Tables

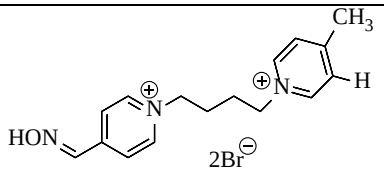
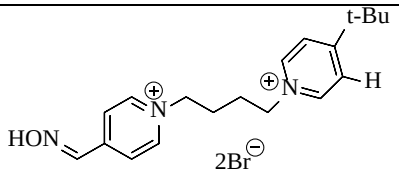
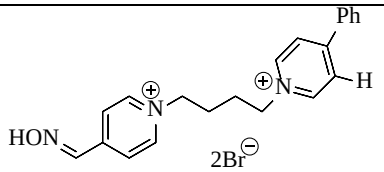
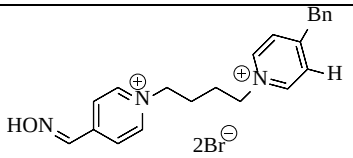
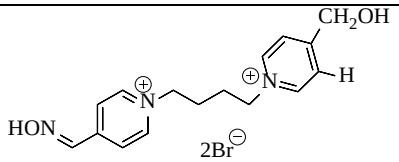
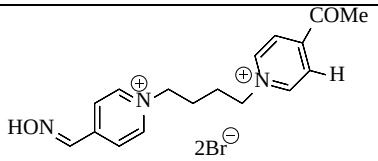
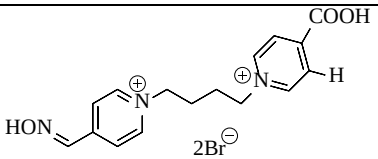
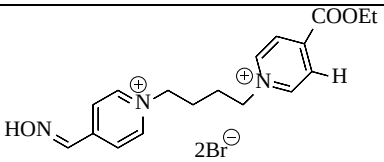
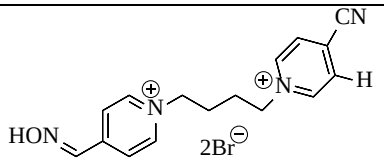
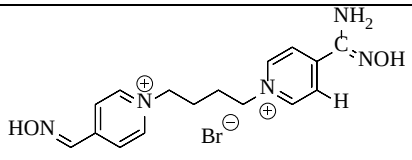
Table 1. Oxime-based pyridinium compounds studied as AChE reactivators

Compound No.	Name of compound	Structure	Type of compound	Reference
1	6-((4-((5,6-Dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)piperidin-1-yl)methyl)-3-hydroxypicolinaldehyde oxime		Donepezil based oxime reactivators	36
2	6-((4-((5,6-Dimethoxy-2,3-dihydro-1H-inden-2-yl)methyl)piperidin-1-yl)methyl)-3-hydroxypicolinaldehyde oxime		Donepezil based oxime reactivators	36
3	6-(3-(5,6-Dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)propyl)-3-hydroxypicolinaldehyde oxime		Donepezil based oxime reactivators	36
4	4-(3-(5,6-Dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)propyl)-3-hydroxypicolinaldehyde Oxime		Donepezil based oxime reactivators	36

5	(E)-1-(3-((5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)propyl)-2-((hydroxyimino)methyl)-3-methyl-1H-imidazol-3-ium iodide		Quaternary imidazole oximes	55
6	(E)-1-(4-((5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)butyl)-2-((hydroxyimino)methyl)-3-methyl-1H-imidazol-3-ium iodide		Quaternary imidazole oximes	55
7	(E)-1-(5-((5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)pentyl)-2-((hydroxyimino)methyl)-3-methyl-1H-imidazol-3-ium iodide		Quaternary imidazole oximes	55
8	K203 (E)-1-(4-carbamoylpyridinium)-4-(4-hydroxyimino-methylpyridinium)-but-2-ene dibromide)		3rd generation oxime reactivator	53
9	$H_2N(CH_2)_2$	$H_2N(CH_2)_2$	α – nucleophile oxime derivatives	56
10	$Me_2N(CH_2)_2$	$Me_2N(CH_2)_2$		
11	$Me_3N+(CH_2)_2$	$Me_3N+(CH_2)_2$		
12	$Et_2N(CH_2)_2$	$Et_2N(CH_2)_2$		
13	$(CH_2)_4N(CH_2)_2$	$(CH_2)_4N(CH_2)_2$		
14	$Me_2N(CH_2)_3$	$Me_2N(CH_2)_3$		
15	$Im(C_2)$-CH_2	$Im(C_2)$-CH_2		
16	$H_2NCH_2CH(OH)CH_2$	$H_2NCH_2CH(OH)CH_2$		
17	$HOCH_2CH(OH)CH_2$	$HOCH_2CH(OH)CH_2$		
		 with 9 to 17 with different amine scaffold & same oxime core.		
18	Pyridostigmine		Bisquaternary compounds	31
19	BW284c51		Bisquaternary compounds	31

20	K298		Bisquaternary compounds	31
21	K344		Bisquaternary compounds	31
22	K474		Bisquaternary compounds	31
23	K524		Bisquaternary - compounds	31
24	3-Hydroxy-6-[5-(piperidin-1-yl)pentyl]picolinaldehyde oxime		3-hydroxy-2-pyridine aldoxime reactivator	54
25	3-Hydroxy-6-(4-morpholinobutyl)picolinaldehyde oxime		3-hydroxy-2-pyridine aldoxime reactivator	54
26	3-Hydroxy-6-(5-morpholinopentyl)picolinaldehyde oxime		3-hydroxy-2-pyridine aldoxime reactivator	54
27	6-{5-[6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl]pentyl}-3-hydroxypicolinaldehyde oxime		3-hydroxy-2-pyridine aldoxime reactivator	54
28	K131 4-hydroxyiminomethyl-1,10-(but-1,4-diyl)-1-pyridinium-10-quinolinium dibromide		Bisquaternary - aldoximes	57
29	K142 4-hydroxyiminomethyl-1,10-(but-1,4-diyl)-1-pyridinium-10-isoquinolinium dibromide		Bisquaternary - aldoximes	57
30	K153 4-hydroxyiminomethyl-1,10-(but-1,4-diyl)-bispyridinium dibromide		Bisquaternary - aldoximes	57

31	4-Carbamoyl-1-(3-{3-chloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}propyl)pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
32	4-Carbamoyl-1-(4-{3-chloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}butyl)pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
33	4-Carbamoyl-1-[(2E)-4-{3-chloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}but-2-en-1-yl]pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
34	4-Carbamoyl-1-(4-{3,5-dichloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}propyl)pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
35	4-Carbamoyl-1-(4-{3,5-dichloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}butyl)pyridinium Dibromide		Chlorinated bispyridinium mono oxime	66
36	4-Carbamoyl-1-[(2E)-4-{3,5-dichloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}but-2-en-1-yl]pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
37	4-Hydroxyiminomethyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
38	4-Hydroxyiminomethyl-1,10 -(but-1,4-diyl)-1-pyridinium-10-pyridazinium dibromide		Novel oxime AChE reactivator	66
39	4-Hydroxyiminomethyl-1,10 -(but-1,4-diyl)-1-pyridinium-10-quinolinium dibromide		Novel oxime AChE reactivator	66
40	4-Hydroxyiminomethyl-1,10 -(but-1,4-diyl)-1-pyridinium-10-isoquinolinium dibromide		Novel oxime AChE reactivator	66

41	4-Hydroxyiminomethyl-40 -methyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
42	4-Hydroxyiminomethyl-40 -(1,1-dimethylethyl)-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
43	4-Hydroxyiminomethyl-40 -phenyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
44	4-Hydroxyiminomethyl-40 -phenylmethyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
45	4-Hydroxyiminomethyl-40 -hydroxymethyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
46	4-Hydroxyiminomethyl-40 -methylcarbonyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
47	4-Carboxy-40 -hydroxyiminomethyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
48	4-Ethylcarboxy-40 -hydroxyiminomethyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
49	4-Carbonitril-40 -hydroxyiminomethyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
50	4-(1-Amino-1-hydroxyiminomethyl)-40 -hydroxyiminomethyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66

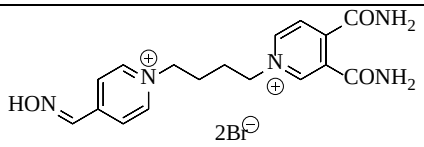
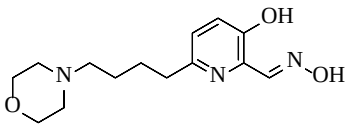
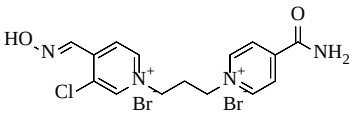
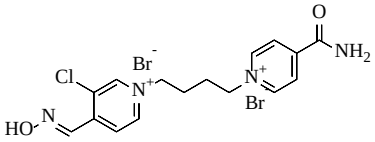
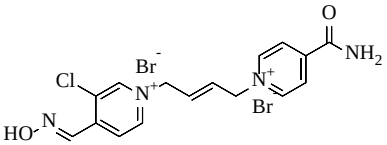
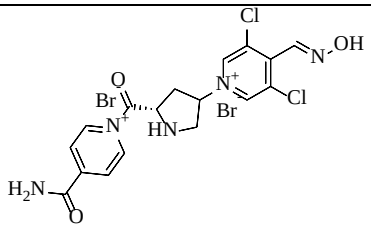
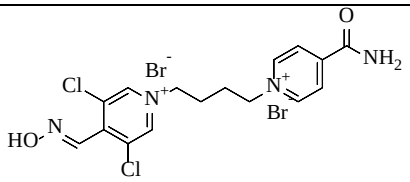
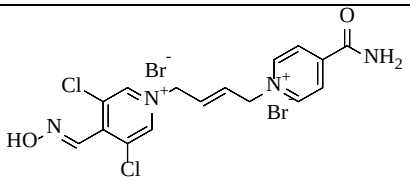
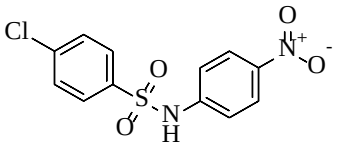
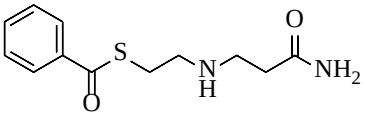
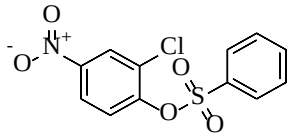
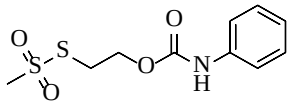
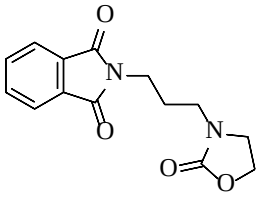
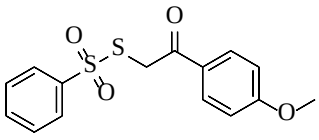
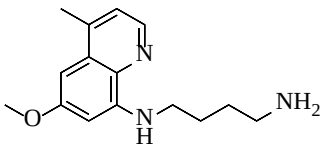
51	3,4-Dicarbamoyl-40 -hydroxyiminomethyl-1,10 -(but-1,4-diyl)-bispyridinium dibromide		Novel oxime AChE reactivator	66
52	(E)-4-(4-(5-Hydroxy-6-((hydroxyimino)methyl)-pyridin-2-yl)butyl) morpholin-4-ium 2,2,2-trifluoroacetate (JR595).		neutral 3-hydroxy-2-pyridine aldoximes	66
53	4-Carbamoyl-1-(3-{3-chloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}propyl)pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
54	4-Carbamoyl-1-(4-{3-chloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}butyl)pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
55	4-Carbamoyl-1-[(2E)-4-{3-chloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}but-2-en-1-yl]pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
56	4-Carbamoyl-1-(4-{3,5-dichloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}propyl)pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
57	4-Carbamoyl-1-(4-{3,5-dichloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}butyl)pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58
58	4-Carbamoyl-1-[(2E)-4-{3,5-dichloro-4-[(hydroxyimino)methyl]-pyridinium-1-yl}but-2-en-1-yl]pyridinium Dibromide		Chlorinated bispyridinium mono oxime	58

Table 2. Non-oximes studied for AChE reactivators activity

Compound No.	Name of the compound	Structure	Reference
59	4-chloro-N-(4-nitrophenyl)benzenesulfonamide		50
60	S-(2-((3-amino-3-oxopropyl)amino)ethyl)benzothioate		50
61	2-chloro-4-nitrophenyl benzenesulfonate		50
62	S-(2-((phenylcarbamoyl)oxy)ethyl)methanesulfonothioate		50
63	2-(3-(2-oxooxazolidin-3-yl)propyl)isoindoline-1,3-dione		50
64	S-(2-(4-methoxyphenyl)-2-oxoethyl) benzenesulfonothioate		50
65	N1-(6-methoxy-4-methylquinolin-8-yl)butane-1,4-diamine		50

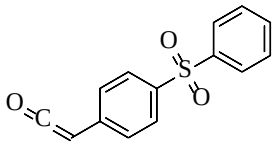
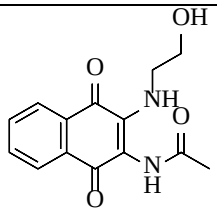
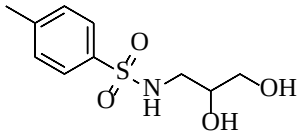
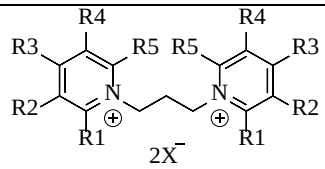
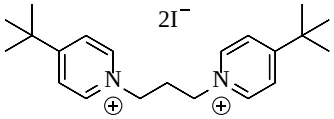
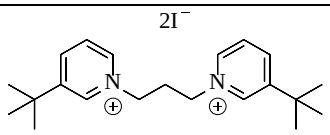
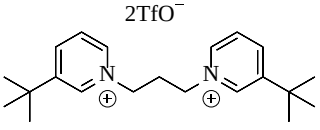
66	2-(4-(phenylsulfonyl)phenyl)ethen-1-one		50
67	N-(3-((2-hydroxyethyl)amino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetamide		50
68	N-(2,3-dihydroxypropyl)-4-methylbenzenesulfonamide		50

Table 3. Bispyridinium non-oxime based AChE inhibitors

Compound No.	Name of the compound	Structure	Reference
69	Bispyridinium compound with substituted groups (R1 – R5)		62
70	MB327 (1,1'-(propane-1,3-diyl)bis(4-tert-butylpuridinium)di(iodide)		62,96
71	PTM0001		63
72	PTM0002		63

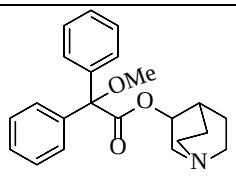
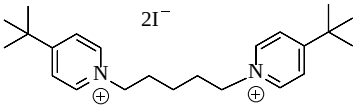
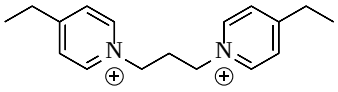
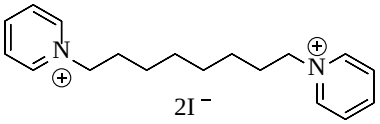
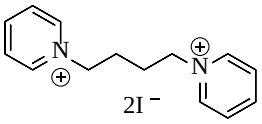
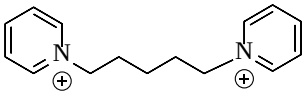
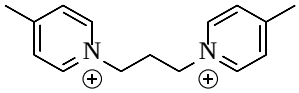
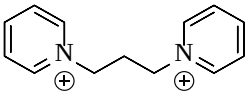
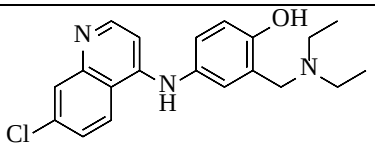
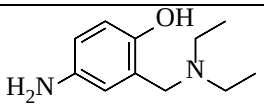
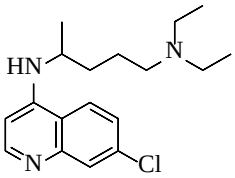
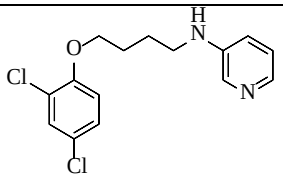
73	MB266		61
74	MB782		61
75	MB454		61
76	MB505		59
77	MB444		64
78	MB442		59
79	MB414		61
80	MB408		64

Table 4. ADQ and Chloroquine based AChE reactivators

Compound no	Name of the compound	Structure	Reference
81	ADQ (Amodiaquine)		69
82	ADOC (4-amino-2-(diethylaminomethyl)phenol)		69
83	CQ (Chloroquine)		69
84	Noval quinoline hybrids		69

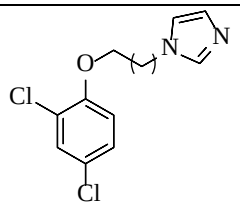
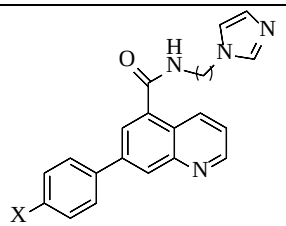
85	Noval quinoline hybrids where n=2-6		69
86	Noval quinoline hybrids where n=2-5, X=Br		69

Table 5. *In Vivo/ In Vitro* reactivation studies data

Compound	**OP-inhibited AChE or BuChE**	**K_D (µM) Dissociation constant**	**k_r (min^{-1}) reactivation rate constant**	**kr_2 ($mM^{-1}min^{-1}$) reactivation rate constant**	**R^2 coefficient of determination**	**R% Reactivation of inhibited AChE**	**k_{obs} (min^{-1}) (oxime concentration µM)**	**References**
1	•VX-hAChE •Sarin-hAChE	•51.4±19.1 •175±47	•0.12±0.02 •0.34±0.05	•2.3 •2	-	-	•0.10 ± 0.006 (100) •0.11±0.01 (100)	36
2	•VX-hAChE •Paraoxon-hAChE •Tabun-hAChE •VX-hBChE	•>200a •160±45 - •96±5	•>0.35a •0.24±0.05 - •0.29±0.01	•1.8±0.05 •1.5 - •3.0	-	-	•0.19±0.01 (100) •0.093±0.005 (100) •0.001±0.001 (100) •0.16±0.005 (100)	36
3	•VX-hAChE •Paraoxon-hAChE •Tabun-hAChE	•>50a •170±70 -	•>0.14a •0.3±0.1 -	2.7±0.1 - -	-	-	•0.14±0.01 (50) •0.070±0.003 (50) •0.004±0.002 (50)	36
4	•VX-hAChE •Paraoxon-hAChE •Tabun-hAChE	•>150a - -	•>0.06a - -	•0.039±0.001 - -	-	-	•0.038±0.002 (100) •0.040±0.001 (100) •0.001±0.002 (50)	36

	•VX-hBChE	-	-	-			•0.041±0.003 (100)	
5	•Paraoxon ethyl inhibited Electric eel AChE. • Paraoxon methyl inhibited Electric eel AChE.	•68.68±0.0073 •66.88±0.0175	•0.047±0.0008 •0.065±0.0029	•0.68±0.003 •0.98±0.003	•0.98 •0.91	•39.5 •39	-	55
6	•Paraoxon ethyl inhibited Electric eel AChE. •Paraoxon methyl inhibited Electric eel AChE.	•422.20±0.1078 •346.60±0.0825	•0.096±0.1027 •0.062±0.0057	•0.23±0.006 •0.18±0.005	•0.97 •0.97	•27.0 •29	-	55
7	•Paraoxon ethyl inhibited Electric eel AChE. •Paraoxon methyl inhibited Electric eel AChE.	•877.70±0.4149 •237.40±0.0821	•0.107±0.0287 •0.037±0.0041	•0.12±0.008 •0.16±0.007	•0.95 •0.93	•21.0 •34	-	55
8	•Tabun-inhibited	56	0.120	•2142(human) •16000(rat)	-	-	-	53
24	•VX-inhibited •Sarin-inhibited •Cyclosarin-inhibited •Tabun-inhibited	•90±30 •160±20 •330±110 •110±40 •200±110	•0.17±0.03 •0.075±0.003 •0.06±0.01 •0.0033±0.0004 •0.07±0.02	•1890±410 •490±50 •180±40 •30±5 •340±100	-	•90 •100 •100 •80 •70	-	31

	•Paraoxon - inhibited (human AChE)							
25	•VX-inhibited •Sarin-inhibited •Cyclosarin-inhibited •Tabun-inhibited •Paraoxon - inhibited (human AChE)	•300±60 •270±90 •430±130 •410±280 •850±150	•0.68±0.07 •0.29±0.03 •0.09±0.01 •0.016±0.007 •0.36±0.03	•2270±240 •1080±290 •210±40 •40±10 •430±40	-	•100 •100 •100 •90 •80	-	31
26	•VX-inhibited •Sarin-inhibited •Cyclosarin-inhibited •Tabun-inhibited •Paraoxon - inhibited (human AChE)	•120±50 •220±60 •120±80 •310±100 •620±180	•0.57±0.08 •0.12±0.01 •0.04±0.01 •0.014±.001 •0.27±0.03	•4900±1250 •560±130 •320±140 •45±10 •440±80	-	•100 •100 •100 •80 •80	-	31
27	•VX-inhibited •Sarin-inhibited •Cyclosarin-inhibited •Tabun-inhibited •Paraoxon - inhibited (human AChE)	•10±3 •130±10 •120±100 •140±60 •190±70	•0.31±0.01 •0.180±0.005 •0.020±0.006 •0.014±0.002 •0.24±0.02	•30900±8100 •1380±60 •170±90 •100±40 •1300±350	-	•100 •90 •80 •80 •80	-	31
24	•VX-inhibited •Sarin-inhibited	•270 ±150 •- •270±200 •nd	• 0.05±0.01 •0.0022±0.0005 • 0.32±0.04 •nd	•180±50 •- •150±40 •nd	-	•90 •45 •90 •<10	-	31

	•Cyclosarin -inhibited •Tabun-inhibited •Paraoxon -inhibited (human AChE)	•140±40	•0.020±0.003	•140±30		•90		
25	•VX-inhibited •Sarin-inhibited •Cyclosarin -inhibited •Tabun-inhibited •Paraoxon -inhibited (human BChE)	•370±240 • - •810±200 •nd •1160±310	• 0.10±0.04 •0.005±0.001 •0.5±0.1 •nd •0.15±0.02	•270±70 •- •390±50 •nd •130±20	-	•100 •90 •90 •<10 •90	-	31
26	•VX-inhibited •Sarin-inhibited •Cyclosarin -inhibited •Tabun-inhibited •Paraoxon -inhibited (Human BChE)	•160±40 •- •790±420 •nd •250±80	•0.059±0.004 •0.0036±0.0004 •0.39±0.05 •nd •0.056±0.006	•360±65 •- •610±180 •nd •230±50	-	•80 •65 •90 •<20 •100	-	31
27	•VX-inhibited •Sarin-inhibited •Cyclosarin -inhibited •Tabun-inhibited •Paraoxon -inhibited (human BChE)	•130±30 •- •330±140 •nd •290±110	•0.096±0.007 •0.007±0.002 •0.32±0.07 •0.004±0.001 •0.075±0.01	•760±150 •- •560±80 •nd •260±70	-	•80 •80 •90 •40 •100	-	31

53	Sarin Cyclosarin VX Tabun Inhibited AChE	745 ± 425 80 ± 10 430 ± 80 40 ± 10	0.37 ± 0.14 0.49 ± 0.08 0.17 ± 0.02 0.0020 ± 0.0001	490 ± 100 2500 ± 500 820 ± 130 280 ± 120	-	80 100 100 80	-	58
54	Sarin Cyclosarin VX Tabun Inhibited AChE	1150 ± 640 80 ± 10 430 ± 80 40 ± 10	0.38 ± 0.16 0.027 ± 0.001 0.18 ± 0.02 0.017 ± 0.001	330 ± 50 340 ± 40 410 ± 40 470 ± 80	-	80 100 100 80	-	58
55	Sarin Cyclosarin VX Tabun Inhibited AChE	840 ± 195 160 ± 20 320 ± 60 40 ± 10	0.35 ± 0.06 0.040 ± 0.002 0.14 ± 0.01 0.021 ± 0.001	420 ± 30 240 ± 20 440 ± 40 560 ± 110	-	80 100 100 80	-	58
56	Sarin Cyclosarin VX Tabun Inhibited AChE	35 ± 10 160 ± 70 70 ± 20 nd	0.43 ± 0.04 4.2 ± 0.7 0.53 ± 0.05 nd	12000±2500 25900±6400 7660 ± 1280 Nd	-	80 100 100 20	-	58
57	Sarin Cyclosarin VX Tabun Inhibited AChE	50 ± 10 50 ± 10 40 ± 10 nd	0.20 ± 0.01 0.101 ± 0.004 0.18 ± 0.01 nd	3880 ± 430 2120 ± 230 4310 ± 840 Nd	-	80 80 60 20	-	58
58	Sarin Cyclosarin VX Tabun Inhibited AChE	60 ± 10 220 ± 30 10 ± 4 nd	0.17 ± 0.02 0.49 ± 0.04 0.059 ± 0.003 nd	2830 ± 390 2200 ± 190 6500 ± 2370 Nd	-	80 100 80 40	-	58

a= Not determined when [Reactivator]<<KD leading to a linear dependence between kobs and [Reactivator]: kobs=kr/KD*[Reactivator]. In this case, kr2=kr/KD, the slope of the line, is directly obtained by fitting. [36] (nd = not determined)

Table 6. *In Vitro* reactivation efficacy data in eel AChE, ADME toxicity, BE at active site of OP-inhibited AChE for above 10 non-oximes compared with 2-PAM[62]

Compound	Mol. Wt.	k_r ($mmol^{-1}$ min^{-1})	PSA	Clog P	Rat Oral LD_{50} (mg/kg)	BE (kcal/mol) OP-Inhibited AChE	BE (kcal/mol) Normal AChE
59	441.9	10.6	93.7	3.56	9560.0	-307.2	-311.5
60	424.6	2.3	73.9	0.91	2440.0	-363.9	-376.4
61	313.7	9.3	86.3	3.66	230.0	-302.4	-309.5
62	275.0	4.6	73.6	1.59	850.0	-322.4	-332.8
63	274.2	8.8	72.4	1.60	10000.0	-405.3	-399.3
64	322.4	5.2	86.3	3.05	1700.0	-405.3	-413.4
65	259.0	10.1	59.5	2.78	260.0	-398.3	-389.1
66	260.3	12.5	51.9	2.28	630.0	-409.8	-416.5
67	274.3	12.1	98.3	-0.035	9440.0	-326.3	-316.5
68	246.3	12.5	115.6	-0.68	4360.0	-406.7	-410.8
2-PAM	136.3	2.61	37.5	-3.66	477.4	-188.2	-189.7

Table 7. *In Vivo* efficacy of four selected non-oximes comparable to 2-PAM against DFP in guinea pigs[50]

Compound	Activity (U/ml) Blood	Activity (U/mg) Diaphragm	Activity (U/mg) Brain	Seizure Strength	Post-DFP Survival (hr)
59	0.223	3.61	15.9	Trace	24.0
60	0.109	3.18	17.6	Severe	24.0
61	0.106	1.58	7.75	Severe	6.5
62	0.179	1.92	7.54	Severe	6.3
2-PAM	0.231	6.59	17.0	Moderate	24.0

Table 8. Docking results for the complex HssAChE/paraoxon (POX) [57]

Oxime	The Best Pose (↓dOP*/↑θOPO*)6					
	dOP (Å)	Angle OPO	Energy of Interaction (kcal/mol)	Energy of H-bond (kcal/mol)	Interactions: H-bond	Interactions: Hydrophobic (π–π)
Pralidoxime	8.644 5.600	153.35◦ 148.21◦	−73.444 −57.770	−5.153 −2.370	Tyr124, Val294/Phe295, Phe295/Arg296 Thr120	Tyr72, Tyr124, Trp286, Phe295, Phe297, Tyr337, Phe338, Tyr341 Phe118, Phe329, Tyr332
Obidoxime	4.260 5.623	155.00◦ 168.15◦	−105.013 −135.823	−4.941 −9.600	Tyr124, Tyr337 Ser203–POX	Tyr72, Trp86, Tyr124, Trp286,

					Gly115/Gly116, Tyr128, Tyr332	Phe295, Phe297, Tyr337, Phe338, Tyr341, His447 Phe73, Trp82, Tyr114, Tyr128, Phe329, Tyr332, Trp430, Tyr440, His438
HI-6	7.102 5.469	147.64◦ 140.81◦	−135.261 −126.712	−6.397 −4.851	Tyr124, Val294/Phe295, Val282/Asn283 Thr120, His438/Gly439	Tyr72, Trp86, Tyr124, His284, Trp286, Phe295, Phe297, Tyr337, Phe338, Tyr341 Trp82, Phe118, Phe329, Tyr332, Trp430, Tyr440, His438
K131	4.111 5.587	144.47◦ 146.97◦	−136.854 −118.023	−2.500 −2.859	Ser203–POX Thr120	Tyr72, Tyr124, His284, Trp286, His287, Phe295, Phe297, Tyr337, Phe338, Tyr341, His447 Trp82, Phe329, Tyr332, His438
K142	3.864 5.172	141.70◦ 144.04◦	−129.978 −115.435	−3.586 −2.431	Tyr72, Ser203–POX Thr120	His287, Phe295,Phe297,Tyr337,Phe338, Tyr341 Trp82, Phe118, Phe329, Tyr332, His438
K153	6.777 5.414	147.81◦ 133.13◦	−119.168 −109.310	−2.445 −3.860	Val294/Phe295 Thr120	Tyr72, Tyr124, His284, Trp286, His287, Phe295, Phe297, Phe338, Tyr341 Trp82, Phe118, Phe329, Tyr332

*dOP = distance POP − OSer203; ** θOPO = angle Oox − POP − OSer203

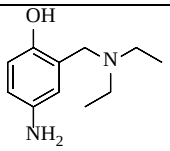
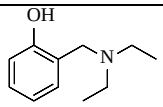
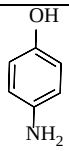
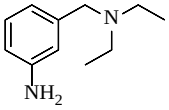
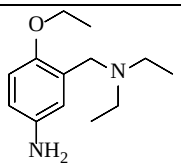
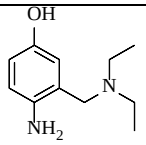
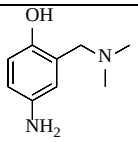
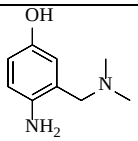
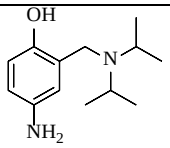
Table 9. *In silico* data: Dissociation constants (pK_a) for the oxime group (=N-OH), the hydroxy group (-OH), the nitrogen atom (R=N-R') in the pyridinium ring, and the tertiary amine of the substituent (R3-NH^+)

Oxime	***In silico* pK$_a$**				***In vitro* pK$_a$ [360 nm]**	
	=N-OH	**-OH**	**R=N-R'**	**R3-NH+**	**pK$_{a1}$**	**pK$_{a2}$**
24	8.10	9.82	3.41	10.49	8.01±0.04	nd
25	8.33	10.33	3.29	7.32	8.08±0.04	10.530.21
26	8.37	10.33	3.41	7.50	8.03±0.06	nd
27	8.52	10.33	3.44	7.89	8.20±0.06	10.44±0.27

Table 10. Reactivation rates for shown reactivators[72]

Reactivator	**K$_{r2}$ (M^{-1}min^{-1})**					
	GA	**GB**	**GD**	**GF**	**VX**	**VR**
2-PAM	7.0±4.4	81.0±16	17.6±16	18.4±4.2	121±29	46±1.2
ADOC	4.5±3.3	45.4±7.2	5.6±4.1	40.5±29	266±109	719±386

Table 11. Reactivation potency of various substituents against OP-inhibited AChE [71]

Compound		GB	GF	VX	VR	Inhibition of RHuAChE @1mM	Hammett Values[72]
	Spontaneous Reactivation ($t_{1/2}$ in days)	2.01	1.25	1.18	0.35		
ADOC		361	164	1069	10723	60%	----
87		1.51	1.54	1.87	3.65	0%	----
88		2.24	1.48	2.24	14.3	0%	----
89		0.98	0.93	0.97	0.96	0%	----
90		1.54	0.89	1.11	1.25	5%	----
91		1.97	1.80	2.76	4.06	1%	-----
92		----	----	----	----	95%	-----
93		2.13	1.96	2.72	5.65	18%	----
94		----	----	----	----	94%	----

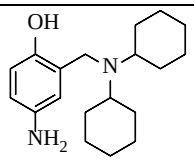
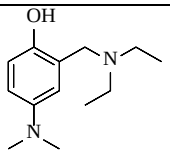
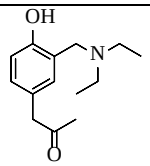
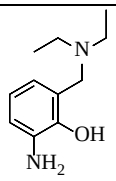
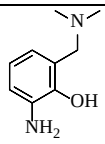
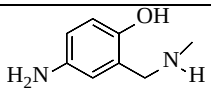
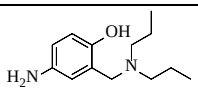
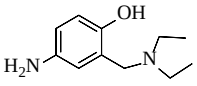
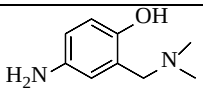
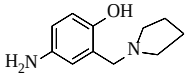
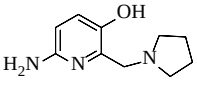
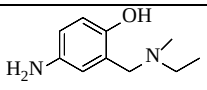
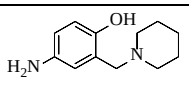
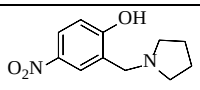
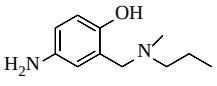
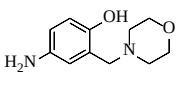
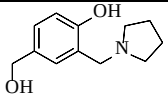
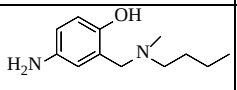
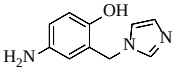
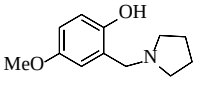
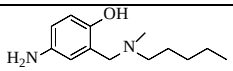
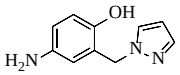
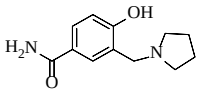
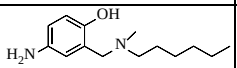
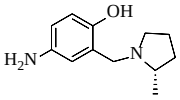
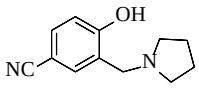
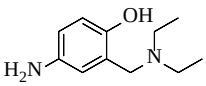
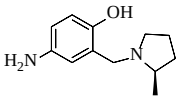
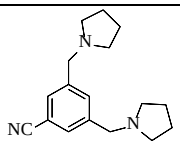
95		0.88	0.74	1.09	0.93	9%	----
96		6.15	3.07	16.5	32.7	0%	-0.83
97		3.85	1.72	6.95	19.0	0%	0.00
98		1.43	1.09	1.24	1.65	35%	N/A
99		1.70	1.30	1.61	1.59	43%	N/A

Table 12. The inhibition of native human AChE by non-oxime compounds was tested with 11 concentration (1-1000uM) in duplicate. [Compound 100-113[72] and compound 114-123[71]]

Compound	**Structure**	**IC_{50} (μM) ± SD**	**Compound**	**Structure**	**IC_{50} (μM) ± SD**	**Compound**	**Structure**	**IC_{50} (μM) ± SD**
100		333.5 ± 18.1	**108**		131.1±1.4	**116**		973±27
101		1536.5±604.6	**109**		6.3±0.0	**117**		135±4.5
102		965.1±134.0	**110**		456.0±4.0	**118**		300.5±14.9
103		1151.0±53.0	**111**		270.6±0.2	**119**		>1000
104		125.2±2.4	**112**		482.5±63.1	**120**		>1000

105		805.1±68.0	**113**		844.5±28.0	**121**		>1000
106		1053.5±28.5	**114**		9.21±0.03	**122**		>1000
107		48.3±0.2	**115**		42.7±0.8	**123**		>1000