Professional Paper

PYRIDINIUM, IMIDAZOLIUM AND QUINUCLIDINIUM COMPOUNDS: TOXICITY AND ANTIDOTAL EFFECTS AGAINST THE NERVE AGENTS TABUN AND SOMAN

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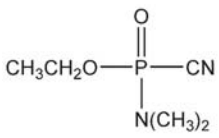
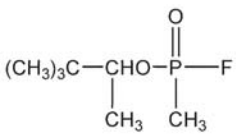
This paper discusses the toxicity and antidotal effects of 32 compounds. Screening studies have shown that these compounds combined with atropine are effective antidotes against the organophosphate nerve agents Tabun and/or Soman, having a therapeutic factor equal or greater than 2.0 when tested in mice or rats. We analysed the results of these studies, and recommend that these compounds should be studied in more detail simultaneously with conventional antidotes (PAM-2, HI-6, Toxogonin, TMB-4) in order to assess whether they could broaden the choice of compounds now available for the treatment of organophosphate poisoning.

KEY WORDS: *experimental poisoning; therapeutic factors; oximes; organophosphates*

Treatment of organophosphate (OP) poisoning is still a problem, particularly when the OP warfare nerve agents Sarin, Soman, Tabun and VX are concerned. The current standard treatment of OP poisoning includes atropine as an antimuscarinic drug and oximes as reactivators of inhibited acetylcholinesterase (AChE). The mono- and bis-pyridinium oximes PAM-2, Toxogonin, HI-6 and TMB-4 are conventional standard oximes used as reactivators of the inhibited AChE. While the conventional oximes have been considered sufficiently effective against Sarin and VX, they are rather ineffective against Tabun and Soman (cf.1).



Tabun



Soman

We have recently reviewed the synthesis and some biochemical properties of 158 compounds which had been prepared to test their interaction with native and phosphylated cholinesterases, and as antidotes against OP compounds (2). These compounds had been synthesized in Croatian laboratories over the past three decades. Only some compounds were studied in detail, while most were only screened for reactions with cholinesterases and as antidotes against OP warfare nerve agents in mice or rats.

Of 158 reviewed compounds, 28 were tested as antidotes against Tabun and 44 against Soman poisoning. Of those, we selected 32 compounds that showed a therapeutic effect in mice or rats, that is, a therapeutic factor equal or greater than 2.0. Here we present individual results obtained with these compounds (applied together with atropine), as well as data on their toxicity for the test animals. These data have not been summarised in our earlier review (2).

TESTING PROTOCOL

The acute toxicity and the antidotal effect of the compounds were tested in male albino mice (18 g

to 25 g b.w.) or rats (180 g to 200 g b.w.). The acute toxicity was expressed as the LD_{50} based on the 24-hour mortality. The antidotal effect was expressed as the therapeutic factor (TF) which is the ratio between the LD_{50} of the OP compound in the presence and in the absence of antidotes:

$TF = LD_{50}$(OP plus antidote) / LD_{50}(only OP)

The OPs Tabun or Soman were given subcutaneously. The studied compounds were applied intraperitoneally (i.p.) or intramuscularly (i.m.) together with 10 mg kg^{-1} atropine sulphate. The antidotes were applied within less than one minute after the OP compound. The LD_{50} values of the studied compounds and OPs were calculated from the results obtained with 4 to 6 different doses applied to 4 or 6 animals per dose.

TOXICITY AND ANTIDOTAL EFFECTS

The studied antidotes were mono- or bis-pyridinium (Py), imidazolium (Im) or quinuclidinium (Q) compounds, or compounds which contain two different moieties in the same molecule (PyIm, PyQ or ImQ). Their structures are given in Table 1.

Table 1 *Structure and Chemical Abstract Service Registry Number (CAS RN) of the compounds. References refer to the synthesis. Abbreviations and CAS RN are taken from Ref. (1).*

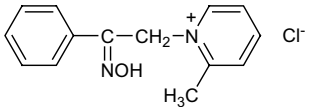
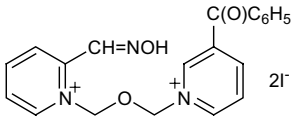
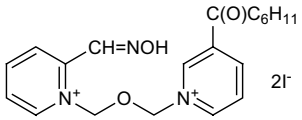
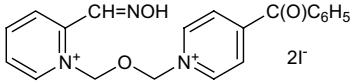
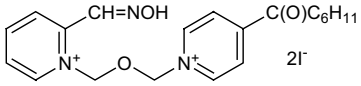
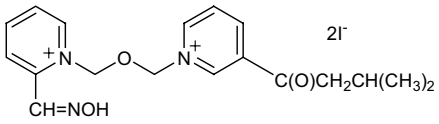
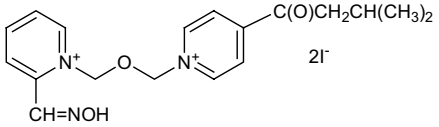
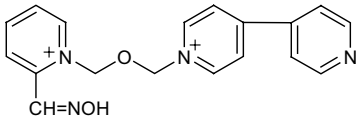
Compound	Abbreviation [CAS RN]	Refs.
	Py-2 [2676-84-8]	3
	Py_2-2 [65320-89-0]	4
	Py_2-4 [65320-92-5]	4
	Py_2-6 [65320-93-6]	4
	Py_2-8 [71752-87-9]	4
	Py_2-42 [78851-95-3]	5
	Py_2-43 [85126-23-4]	5
	Py_2-62 [95575-03-4]	6

Table 1 *continued*

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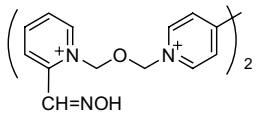
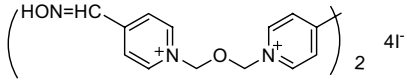
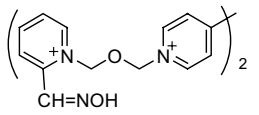
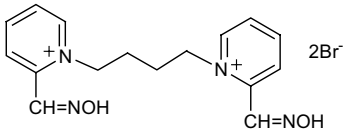
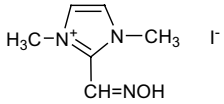
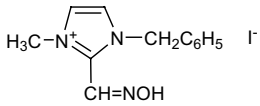
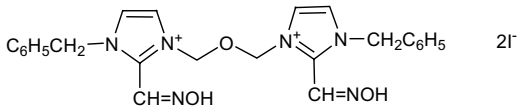
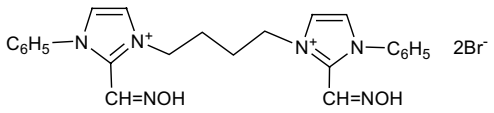
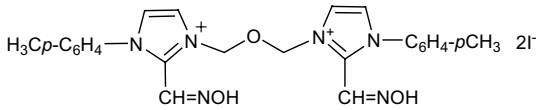
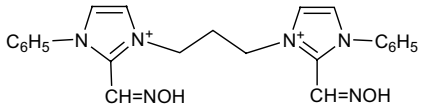
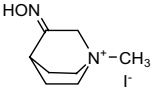
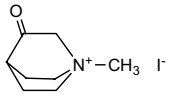
	Py_2-66 [95575-02-3]	6
	Py_2-67 [95575-08-9]	6
	Py_2-68 [95575-05-6]	6
	Py_2-87 [133325-76-5]	7
	Im-2 [43193-21-1]	8
	Im-3 [49702-55-8]	9
	Im_2-2 [138173-96-3]	9
	Im_2-13 [144310-45-2]	7
	Im_2-16 [160193-38-4]	10
	Im_2-25 [159980-41-3]	11
	Q-1 [192509-79-8]	12
	Q-2 [6659-51-4]	13

Table 1 *continued*

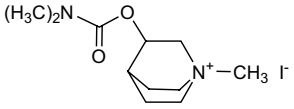
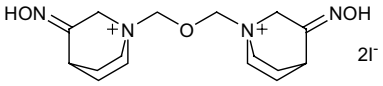
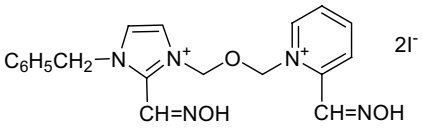
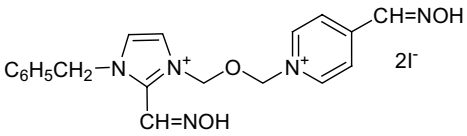
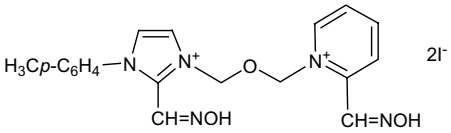
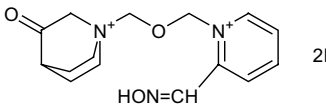
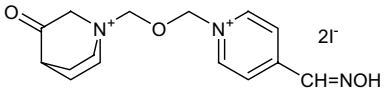
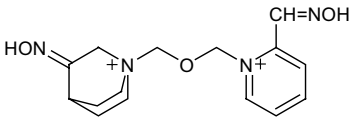
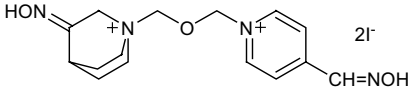
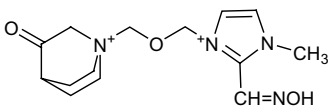
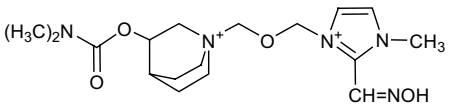
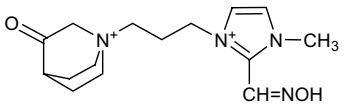
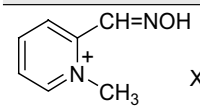
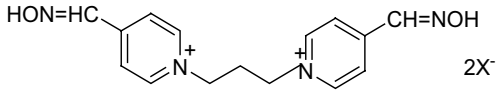
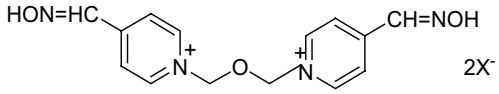
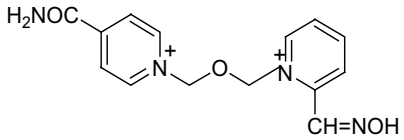
Compound	Abbreviation [CAS RN]	Refs.
	Q-4 [243663-66-3]	14
	Q_2-1 [192509-82-3]	12
	PyIm-5 [138174-02-4]	9
	PyIm-6 [138173-99-6]	9
	PyIm-13 [160193-39-5]	10
	PyQ-1 [192509-91-4]	12
	PyQ-2 [192509-92-5]	12
	PyQ-3 [192509-86-7]	12
	PyQ-4 [192509-89-0]	12
	ImQ-2 [208182-96-1]	13
	ImQ-4 [243663-68-5]	14
	ImQ-5 [208182-95-0]	13

Table 2 *Conventional oximes used as antidotes in the therapy of OP poisoning. X- stands for an anion.*

Compound	Abbreviation/Names
	PAM-2 Pralidoxime
	TMB-4 Trimedoxime
	Toxogonine Obidoxime
	HI-6

All compounds, except Q-2 and Q-4, are oximes. Two compounds, Q-4 and ImQ-4, are carbamates. The abbreviations used in this paper are taken from reference (2). For the sake of comparison the structures, abbreviations and names of the conventional antidotes are shown in Table 2.

Table 3 *Acute toxicity (LD_{50}) of the compounds applied i.p. to mice or (*) rats*

Compound abbreviation	LD_{50}		Refs.
	mg kg^{-1}	μmol kg^{-1}	
Py-2	71(*)	271(*)	15
Py_2-2	250	404	16
Py_2-4	197	323	16
Py_2-6	191	309	16
Py_2-8	179	293	16
Py_2-42	170	292	5
Py_2-43	132	226	5
Py_2-87	33.4	70	17
Im-2	182	682	18
Im_2-13	4.7	8.2	19
Im_2-16	21	30	20
Im_2-25	4.7	8.2	18
Q-1	56	208	12
Q-2	56	210	18
Q-4	144	424	18
Q_2-1	224	388	12
PyIm-13	19	31	20
PyQ-1	>1000	>1830	12
PyQ-2	>200	>369	12
PyQ-3	>100	>179	12
PyQ-4	107	191	12
ImQ-2	283	775	18
ImQ-4	202	464	18
ImQ-5	225	498	13

The i.p. toxicity of 24 compounds is listed in Table 3. Expressed on a molar basis, LD_{50} ranged from 8 μmol kg^{-1} to about 1800 μmol kg^{-1}. The most toxic compounds were two bis-imidazolium compounds, Im_2-13 and Im_2-25. Their toxicities almost approached the molar toxicity of the nerve agents. Such high toxicities on mice were also reported for a series of other prepared bis-imidazolium compounds (11). The second highest toxicity reported was for Im_2-16 and PyIm-13, while all other compounds had LD_{50} above 200 μmol kg^{-1}. The LD_{50} of the conventional oximes, determined using the same protocol as reported for compounds in Table 3, were between 200 μmol kg^{-1} and 1900 μmol kg^{-1} (6, 15-17, 21, 22).

All 32 compounds were tested as antidotes against Soman, and 21 of those also against Tabun (Table 4). The best antidotal effect was reported for ImQ-4, which had TF values 5.3 and 4.3 against Soman and Tabun respectively. TF values between 3.0 and 3.4 against both Soman and Tabun were reported for Q-4 and Py_2-42. Four compounds (Im-3, Im_2-2, PyIm-5 and PyIm-6) had TF values between 3.6 and 4.9, but only against Tabun.

DISCUSSION

The major cause of OP toxicity is the phosphylation of serine in the catalytic site of acetylcholinesterase, whereby AChE becomes inhibited. The inhibited AChE can be reactivated by oximes which dephosphylate the enzyme. Oximes are therefore used as antidotes against OP poisoning. Protectors of AChE from OP

Table 4 *Therapeutic factor (TF) of the compounds evaluated in male mice or (*) rats poisoned by Tabun or Soman. Compounds were applied i.p. or (**) i.m.*

Compound abbreviation	TF		Compound dose	Refs.
	Tabun	Soman		
Py-2	-	2.0 (*)	200 μmol kg^{-1}	15
Py_2-2	2.8	2.9	30 μmol kg^{-1}	16
Py_2-4	2.5	2.6	30 μmol kg^{-1}	16
Py_2-6	2.1	2.1	30 μmol kg^{-1}	16
Py_2-8	2.4	3.3	30 μmol kg^{-1}	16
Py_2-42	3.0	3.4	30 μmol kg^{-1}	5
Py_2-43	<2.0	2.3	30 μmol kg^{-1}	5
Py_2-62	<2.0	2.0	30 or 15 μmol kg^{-1}	6
Py_2-66	2.0	2.9	30 or 15 μmol kg^{-1}	6
Py_2-67	2.3	<2.0	30 μmol kg^{-1}	6
Py_2-68	2.2	2.9	30 μmol kg^{-1}	6
Py_2-87	2.4	2.5	1/4 LD_{50}	17
Im-2	<2.0	2.0	1/4 LD_{50}	18
Im-3	3.6 (*)(**)	<2.0 (*)(**)	30 μmol kg^{-1}	9
Im_2-2	4.9 (*)(**)	<2.0 (*)(**)	30 μmol kg^{-1}	9
Im_2-13	-	2.4	1/4 LD_{50}	19
Im_2-16	-	2.2	1/4 LD_{50}	20
Im_2-25	3.8	2.4	1/4 LD_{50}	18
Q-1	-	3.2	1/4 LD_{50}	12
Q-2	<2.0	2.3	1/4 LD_{50}	18
Q-4	3.2	3.2	1/4 LD_{50}	18
Q_2-1	-	3.3	1/4 LD_{50}	12
PyIm-5	4.2 (*)(**)	<2.0 (*)(**)	30 μmol kg^{-1}	9
PyIm-6	4.4 (*)(**)	<2.0 (*)(**)	30 μmol kg^{-1}	9
PyIm-13	-	2.0	1/4 LD_{50}	20
PyQ-1	-	2.7	50 μmol kg^{-1}	12
PyQ-2	-	3.8	50 μmol kg^{-1}	12
PyQ-3	-	2.5	50 μmol kg^{-1}	12
PyQ-4	-	2.8	1/4 LD_{50}	12
ImQ-2	2.4	2.8	1/4 LD_{50}	18
ImQ-4	4.3	5.3	1/4 LD_{50}	18
ImQ-5	-	2.4	1/4 LD_{50}	13

inhibition are carbamates which carbamoylate the catalytic-site serine of AChE. Unlike the phosphylated AChE conjugate, the carbamoylated conjugate is very unstable, but still enough stable to ensure the protection of AChE against OP. Some carbamates are therefore used as prophylaxis/preatreatment against OP poisoning. Current knowledge of prophylactic and therapeutic treatment of OP poisoning has been summarized in many reviews (cf. 1, 23-26).

Antidotes against OP poisoning were developed soon after the OP warfare nerve agents were synthesized. In the early 1950s, PAM-2 was prepared and studied as an antidote (cf. 27). Later, bis-pyridinium compounds were prepared with one or two oxime groups (HI-6, Toxogonin, TMB-4) (cf. 28), and were shown to be more effective than PAM-2. Grifantini et al. (29) introduced the imidazolium moiety into the oxime antidotes. During the 1980s, a series of quinuclidinium compounds, with or without an oxime group, were tested as antidotes due to the antimuscarinic properties of quinuclidinium (30, 31).

Compounds listed in Table 1 were described by their authors either as new compounds or as compounds analogous to those previously published. Some of those belong structurally to the series known under the abbreviations HGG, BDB, BMR, BMP or AB, according to the authors who prepared the compounds. In some papers the compounds were simply marked by capital letters or Roman numbers. In order to avoid ambiguity, we have not used the original abbreviations of the authors. Instead, in this paper we use abbreviations introduced in our previous review (2) that indicate the basic chemical structure which is pyridinium, imidazolium and quinuclidinium.

As shown in Table 4, the best antidotal effect was achieved with ImQ-4, which is a carbamoylated

quinuclidinium/imidazolium compound with an oxime group in the molecule. The corresponding ImQ-2 compound, which is not a carbamate, but has an oxime group, was much less effective against both Tabun and Soman. Compound Q-4, a carbamoylated quinuclidinium compound without an oxime group, was as good as its analogue Q-1, which has an oxime group instead of the carbamoyl group. However, Q-2, being no carbamate and having no oxime group, was ineffective against Tabun and only slightly effective against Soman. These results are in line with the known prophylactic properties of carbamates against OP poisoning.

Most TF values presented in Table 4 were evaluated with doses of antidotes that were not equitoxic (cf. Table 3 *vs*. Table 4). Only 14 compounds were applied at equitoxic doses, i.e. 1/4 of their LD_{50}. For eight compounds no LD_{50} was determined. All other compounds were applied at a given dose irrespective of their toxicity. Due to this fact, most TF values listed in Table 4 can only be considered as screening values. However, they do indicate that the tested compounds have an antidotal effect against Soman and/or Tabun.

Only several authors (6, 9, 16, 17, 18, 21) have tested the conventional antidotes (Table 2) simultaneously with the compounds listed in Table 1. They applied the testing protocol outlined in this paper. With one exception (17), conventional antidotes were applied at a given dose irrespective of their toxicity. PAM-2 was ineffective against both Tabun and Soman (9, 21). The highest reported TF values were 7.1 with TMB-4 against Tabun, and 4.7 with HI-6 against Soman; the applied dose of TMB-4 and HI-6 was 1/4 of their LD_{50} values (17). The next highest TF value against Tabun was 5.1 with TMB-4 (16, 21).

Only three studies (9, 13, 17) tested the effects of atropine given alone. The obtained TF values against Tabun and Soman with atropine alone ranged between 1.1 and 1.5. These results agree with other published data on the effect of atropine against Tabun and Soman. Those TF values ranged from 0.9 to less than 1.6, when OPs were applied s.c. and atropine i.p. or i.m. to mice or rats (cf. 23). Therefore we took TF=2.0 as the cut-off value when stating that a compound (applied with atropine) has a positive therapeutic effect.

The antidotal properties of the studied compounds might be attributed to several different effects. Compounds bearing an oxime group are reactivators of the phosphylated AChE. These compounds also bind reversibly to AChE, whereby the enzyme is protected from OPs. Carbamates are well known protectors of AChE, and are therefore recommended for pre-treatment against OPs. Atropine, which was given together with the studied compounds, is an antimuscarinic drug. Quinuclidinium compounds also have antimuscarinic properties that might have contributed to their antidotal effects. For the quinuclidinium compound that has both a carbamate and an oxime group (ImQ-4) it is hard to know which of the two groups contributed mainly to the therapeutic effect.

The testing protocol used in the described studies includes probably both the prophylactic and the therapeutic effects, because the antidotes were given immediately after the OPs. By modifying the protocol, it would probably be possible to test these two effects separately. We suggest more detailed studies of the compounds presented in this paper and of the conventional antidotes in order to show whether the studied compounds are more effective than the conventional antidotes. Comparative studies of two groups of compounds should be done under the same experimental conditions concerning doses, routes of application, animals, and other details of the protocol. If the compounds discussed in this paper prove more adequate, this might broaden the choice of antidotes against Tabun and Soman poisoning.

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Sažetak

PIRIDINIJEVI, IMIDAZOLIJEVI I KINUKLIDINIJEVI SPOJEVI: TOKSIČNOST I PROTUOTROVNO DJELOVANJE NASPRAM NERVNIM OTROVIMA TABUNU I SOMANU

U ovom su radu opisani toksičnost i protuotrovno djelovanje 32-ju spojeva (antidota) koji su se prema literaturnim podacima pokazali djelotvornima (kada se primijene uz atropin) pri eksperimentalnom trovanju životinja organofosfornim spojevima tabunom i somanom. Terapijski faktor, tj. omjer LD_{50} organofosfornog spoja u prisutnosti i odsutnosti tih antidota bio je jednak ili veći od 2.0 kada su spojevi testirani na miševima ili štakorima. Predlaže se da se ovi spojevi detaljnije istraže usporedo s konvencionalnim antidotima (PAM-2, HI-6, toksogonin, TMB-4) da bi se vidjelo bi li oni mogli proširiti izbor spojeva koji su danas na raspolaganju u terapiji i prevenciji otrovanja organofosfatima.

KLJUČNE RIJEČI: *eksperimentalno trovanje; oksimi; organofosforni spojevi; terapijski faktor*

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