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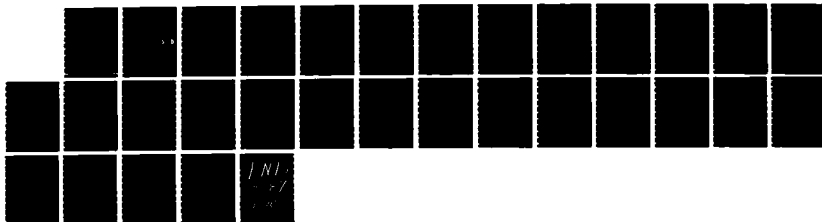
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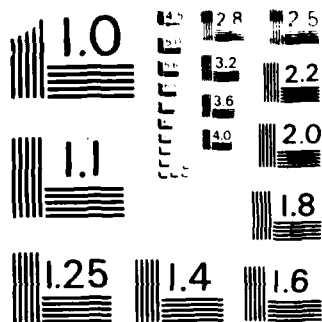
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MOLECULAR MODELING IN DRUG DESIGN FOR THE
DEVELOPMENT OF ORGANOPHOSPHORUS ANTIDOTES/PROPHYLACTICS

Final Report

R. Venkataraghavan, Ph.D.

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MOLECULAR MODELING IN DRUG DESIGN FOR THE DEVELOPMENT
OF ORGANOPHOSPHORUS ANTIDOTES/PROPHYLACTICS

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INTRODUCTION

Organophosphorus poisons consist of substituted phosphoric or phosphonic acids, coupled to a labile "leaving" group. They react with acetylcholinesterases with expulsion of the leaving group and acylation of a key serine residue at the active site of the enzyme, a process which leads to inactivation of the enzyme and which is essentially irreversible under physiological conditions.

Some of the approaches proposed to alleviate this problem are:

- 1) removal of the offending phosphorus residue, regenerating intact cholinesterase,
- 2) prior blockade of the active site with a less toxic, reversible agent, and
- 3) amelioration of the effects of excess acetyl choline by blockade of its receptor sites.

Our group has studied this problem using computer-assisted techniques. Specifically, our achievements can be broadly classified under the following major areas.

- A. Construction of a machine readable database of reactivator structures and their activities.
- B. Use of multidimensional statistical QSAR analysis techniques to suggest new structures for synthesis and evaluation.
- C. Application of quantum chemical techniques to design new variants of known reactivators to enhance their potency.
- D. Application of molecular modeling techniques to known antidotes and design of novel compounds for synthesis and testing for antidotal potency.
- E. Use of computer-assisted methods to determine the steric constraints at the active site of acetylcholinesterase.
- F. Application of distance geometry and conformational analysis methods to nicotinic agents to determine the molecular requirements at the binding site of the nicotinic acetylcholine receptor.
- G. Application of secondary structure prediction methods and

molecular modeling techniques to model the enzyme acetylcholinesterase.

H. Suggestion of some novel compounds for synthesis and testing for reactivating potency based on certain speculative ideas.

SUMMARY OF METHODS AND RESULTS

We give below, a brief summary of the methods used and the important results under the headings described in the Introduction.

(A) Construction of database: The open world literature was searched for data bearing on the reactivation in vitro of poisoned choline esterase. Those articles with sufficient data to permit comparisons among compounds were encoded. To this was added data made available to us through WRAIR, selecting those experiments that measured reactivation in vitro. The total data was built into a database consisting of three datasets, as follows:

Dataset ACHER contained 466 data points from actual experimental data on 228 compounds, together with identifying data as to the compound and the test employed, and certain indices of activity, generated as described below.

Dataset ACHLIB contained data on the source and the conditions of the test; it was linked to ACHER by the TEST identity.

Dataset CNWLN contained the Wiswesser line formulae for 258 compounds (those tested in ACHER above as well as those tested in vivo for which the the corresponding ACHVIV was never completed); it was linked to ACHER via the (arbitrary) compound no.

These datasets have been dumped onto magnetic tape, and are supplied to WRAIR under separate cover. The detailed descriptions of all the (fixed-length) fields in the appendix should allow reconstruction of the database using almost any database management system.

(B) Statistical studies: Because of the severely limited amount of data, several assumptions had to be made to obtain any comparative data at all. Thus, experiments using different poisons and different species of acetyl cholinesterase were pooled. The compounds used in a single test were ranked, and indices of activity were assigned both by using the crude ranking converted to a percentile, and by using the Fisher Normal score associated with the percentile. These indices were then averaged across all the tests in which a compound appeared, to obtain a mean index of activity for the compound. These indices were then

studied in relation to the chemical structures as resolved into their atom pairs, by the trend vector technique, as described in (25). Application of the resulting trend vectors to two large databases, the Fine Chemicals Directory of Commercially Available Organic Compounds (46000 compounds) and the EPA/SANSS Master file (170000 compounds), allowed us to choose and recommend for testing about 400 hitherto untested structures. These structures have been transmitted in detail in earlier reports (1,18). We present a few of them here (Fig 13), just to give examples of the sort of novel structure selected from the above two databases. It must be reemphasized that the statistical techniques used are intended to enrich the yield of screening, usually less than one percent in random screening. Even with fivefold enrichment, our lists should not be expected to contain more than two or three active compounds per hundred. Therefore the compounds shown are not to be considered as a "pick of the best", but rather as examples of the sort of structure found.

(C) Application of quantum chemical analysis: Most potent organophosphorus reactivators are pyridinium oximes. The active form of the oxime is the deprotonated oximate anion. The pKa of most pyridinium oximes lies slightly above the biological range. Hence these compounds are largely in the protonated form at biological pH. We used CNDO calculations to study the possibility of adding substituents to the pyridinium ring of 2-PAM to lower the pKa of the oxime group to the biological range. We fixed a variety of functional groups at all the available positions on the pyridinium ring and in each case calculated the difference in CNDO energy of the protonated and deprotonated forms. The results of these calculations are given in the 1st Annual Report (1) and reproduced here for convenience in Table 1.

Table 1

S.No.	Substituent	Position	Energy required to deprotonate oxime Kcal/mole
1	none	-	402.35
2	-CHO	6	400.45
3	-CHO	5	403.68
4	-CHO	4	405.84
5	-CN	6	400.56
6	-CN	5	395.76
7	-CN	4	397.40
8	-CN	3	396.32
9	-NO ₂	6	390.71
10	-NO ₂	5	394.12
11	-NO ₂	1	395.11
12	-NO ₂	3	397.24
13	-SO ₂ CH ₃	6	399.77

14	-SO ₂ CH ₃	5	395.62
15	-SO ₂ CH ₃	4	397.19
16	-CH ₃	6	405.94
17	-CH ₃	5	409.38
18	-CH ₃	4	410.18
19	-CH ₃	3	413.11

It can be seen that the 6-NO₂ analog of 2-PAM shows the lowest proton affinity. Other analogs with low proton affinities are, the 3- 4- and 5-NO₂, the 3- 4- and 5-CN and the 4- and 5-SO₂CH₃ compounds. We suggest that some of these analogs be synthesized and tested for their reactivating potency.

(D) Application of molecular modeling techniques: It was discovered that certain bis-quaternary oximes are very good reactivators of organophosphorus-inhibited AChE (2,3,4). Both 2- and 4-bispyridinium oximes are known to be good reactivators. It is reasonable to assume that in their active conformation, these two classes of compounds have a similar shape and also that their reactive functional groups are superposable. We used the distance geometry technique (5) (which is a powerful method for constructing 3-dimensional models starting from a set of distance constraints) to determine the probable active conformations of these classes of reactivators by superposing the two types of bispyridinium skeletons. In doing this, we assumed that the oxime groups as well as the nitrogen of the non-oxime ring of the two classes of molecules would be superposed. The superposed geometry presumably represents the bioactive shape of these compounds.

By examining the structure of the two superposed bispyridinium skeletons order to get an idea of the steric constraints on reactivators at the active site of AChE, we used the technique of active volume mapping (6). A set of 2- and 4-bispyridinium oximes of known reactivating potencies (7 actives and 3 inactives) were used. The actives are shown in Fig 2 and the inactives are shown in Fig 3. The conformations of the 2- and 4-bispyridinium skeletons were those obtained by distance geometry superposition as described in the previous section. We calculated the union of the volume of all the active compounds (shown in Fig 4) and calculated difference maps for the inactives (shown in Fig 5). These difference maps represent a negative image of the binding

region of AChE.

Using these maps the following tentative inferences were made in regard to substitution on the non-oxime ring. In the 2-oxime series any substituent in the 2-position in the non-oxime ring is sterically disallowed. In the 3- and 4- positions of the 2-oxime series and in the 3-position of the 4-oxime series a phenyl ring is allowed while a cyclohexyl ring is too bulky. Any bulky substituent is allowed in the 4-position of the 4-oxime series.

Since the dataset used for the above study was fairly small, these conclusions should be taken as tentative. However, they demonstrate the power and applicability of the method. As more data becomes available, we could improve these volume maps and use them to make more reliable predictions. These studies are described in the 1st annual report (1).

(F) Application of conformational analysis: The acetylcholine receptor (AChR) is a large multi-subunit transmembrane protein (7). The complete amino acid sequence of this protein has been deduced (8-11). There have been some attempts to build models for this protein (12,13). However, these models are at the level the gross overall shape of the molecule. There have been some successes in obtaining a low resolution structure for the model (14). A high resolution crystal structure of the molecule however, is at least a few years away. However, we have pharmacological data on several receptor agonists and antagonists. Using such data and the distance geometry technique, we have attempted to define a minimal set of requirements for nicotinic activity.

Almost all nicotinic agents have a charged atom such as nitrogen (which we call A) and an electronegative atom (which we call B) such as oxygen which can act as a hydrogen bond acceptor. We can also choose a third atom or point C which together with B defines the direction of a dipole. We used these three points A, B and C to define a three-point pharmacophore. We used a set of nicotinic agonists- nicotine, cytisine, ferruginine methiodide and muscarone, and superposed these three equivalent points using distance geometry. Figure 6 shows the four agonists used in the study. The points A, B and C are marked on each of the molecules. Only one set of interpoint distances was consistent with such a superposition, viz. $A-B = 4.8 \pm 0.2$ A, $B-C = 4.2 \pm 0.3$ A and $A-C = 1.2$ A. These points ABC define a 3-point pharmacophore for the nicotinic AChR.

The pharmacophore, as defined above, has no chirality. In other words, in three dimensions a molecule can always be made to fit a 3-point pharmacophore in two different ways. Cytisine is the only molecule of the above, which is strongly stereoselective. We used (-)-cytisine, an active chiral molecule

to suggest a 'chirality' requirement for nicotinic activity. This chirality requirement demands that the bulk of the molecule has a particular disposition relative to the pharmacophore triangle. Specifically, if the points A, B, and C are arranged counter-clockwise on the plane of the paper, the bulk of the molecule should be in front of the plane. Taken together with the 'chirality' requirement, there is only one way in which a molecule could be made to fit the pharmacophore. This pharmacophore defines the minimum requirement for nicotinic activity.

We tested the pharmacophore model against 3 nicotinic antagonists- strychnine, trimethaphan, and dihydro-erythroidine, and one agonist- trans-3-3'-bisQ, (Fig 7) and found that all these molecules fit the the pharmacophore model. These findings have been published elsewhere (15).

We have built a model for the presumptive active peptide segment of AChR following previously published guidelines (16). The model consists basically of an antiparallel beta sheet with a bend (Fig 6). We have tested this model and found that it fits our pharmacophore.

We have also built models for the peptide neurotoxin, conotoxin, which is a potent nicotinic binder and found that it can reach the pharmacophoric requirements (17). We also discovered some interesting structural homologies between snake venom long neurotoxins and conotoxin. We used these observations to design an 8-residue disulfide-bridged peptide as a possible nicotinic agent (18). The peptide has the following sequence-

NH₂-ALA-CYS-GLY-ARG-HIS-TYR-SER-CYS-COOH
:.....:

We recommend that this peptide be synthesized and tested for nicotinic binding activity. It is possible that such nicotinic binders (if they are antagonists) could be used as nerve gas antidotes, since they would bind to AChR and displace excess acetylcholine at the synapse. In fact there is one report in the patent literature regarding the use of detoxified snake venom as a nerve gas antidote (19).

(G) Application of secondary structure prediction methods: The enzyme acetylcholinesterase is a massive multi-subunit protein. The complete amino acid sequence has recently been published (20). We have used two methods of secondary structure prediction (21-23) on this sequence. Those segments which were strongly predicted by both the methods were selected. Given below is the entire amino acid sequence of *Torpedo californica* AChE with the

strongly predicted segments indicated.

Strongly predicted secondary structural segments of
Torpedo californica Acetylcholinesterase

(KEY: ~~~~~ MEANS HELIX; ^^^^^ MEANS BETA SHEET. PRESUMPTIVE
 ACTIVE RESIDUES ARE MARKED BY ASTERISKS)

	ASP-ASP-	2
HIS-SER-GLU-LEU-LEU-VAL-ASN-THR-LYS-SER-GLY-LYS-VAL-MET-GLY-		17
THR-ARG-VAL-PRO-VAL-LEU-SER-SER-HIS-ILE-SER-ALA-PHE-LEU-GLY-		32
ILE-PRO-PHE-ALA-GLU-PRO-PRO-VAL-GLY-ASN-MET-ARG-PHE-ARG-ARG-		47
PRO-GLU-PRO-LYS-LYS-PRO-TRP-SER-GLY-VAL-TRP-ASN-ALA-SER-THR-		62
TYR-PRO-ASN-ASN-CYS-GLN-GLN-TYR-VAL-ASP-GLU-GLN-PHE-PRO-GLY-		77
PHE-SER-GLY-SER-GLU-MET-TRP-ASN-PRO-ASN-ARG-GLU-MET-SER-GLU-		92
ASP-CYS-LEU-TYR-LEU-ASN-ILE-TRP-VAL-PRO-SER-PRO-ARG-PRO-LYS-		107
97^^^^^^^^^^^^^^^^^101		
SER-THR-THR-VAL-MET-VAL-TRP-ILE-TYR-GLY-GLY-GLY-PHE-TYR-SER-		122
110^^^^^^^^^^^^^^^^^116		
GLY-SER-SER-THR-LEU-ASP-VAL-TYR-ASN-GLY-LYS-TYR-LEU-ALA-TYR-		137
THR-GLU-GLU-VAL-VAL-LEU-VAL-SER-LEU-SER-TYR-ARG-VAL-GLY-ALA-		152
PHE-GLY-PHE-LEU-ALA-LEU-HIS-GLY-SER-GLN-GLU-ALA-PRO-GLY-ASN-		167
VAL-GLY-LEU-LEU-ASP-GLN-ARG-MET-ALA-LEU-GLN-TRP-VAL-HIS-ASP-		182
ASN-ILE-GLN-PHE-PHE-GLY-GLY-ASP-PRO-LYS-THR-VAL-THR-ILE-PHE-		197
194^^^^^^^^^^^^^197		

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      *      *
GLY-GLU-SER-ALA-GLY-GLY-ALA-SER-VAL-GLY-MET-HIS-ILE-LEU-SER- 212
      207^^^^^^^^^^^^^^^^^211

PRO-GLY-SER-ARG-ASP-LEU-PHE-ARG-ARG-ALA-ILE-LEU-GLN-SER-GLY- 227

SER-PRO-ASN-CYS-PRO-TRP-ALA-SER-VAL-SER-VAL-ALA-GLU-GLY-ARG- 242

ARG-ARG-ALA-VAL-GLU-LEU-GLY-ARG-ASN-LEU-ASN-CYS-ASN-LEU-ASN- 257

SER-ASP-GLU-GLU-LEU-ILE-HIS-CYS-LEU-ARG-GLU-LYS-LYS-PRO-GLN- 272
      260~~~~~268

GLU-LEU-ILE-ASP-VAL-GLU-TRP-ASN-VAL-LEU-PRO-PHE-ASP-SER-ILE- 287

PHE-ARG-PHE-SER-PHE-VAL-PRO-VAL-ILE-ASP-GLY-GLU-PHE-PHE-PRO- 302
288^^^^^^^^^^^^^^^^^296

THR-SER-LEU-GLU-SER-MET-LEU-ASN-SER-GLY-ASN-PHE-LYS-LYS-THR- 317
      305~~~~~311

GLN-ILE-LEU-LEU-GLY-VAL-ASN-LYS-ASP-GLU-GLY-SER-PHE-PHE-LEU- 332
      319^^^^^^^^^^^^^324                      330^^^^^^^^^

LEU-TYR-GLY-ALA-PRO-GLY-PHE-SER-LYS-ASP-SER-GLU-SER-LYS-ILE- 347
^^^^^334

SER-ARG-GLU-ASP-PHE-MET-SER-GLY-VAL-LYS-LEU-SER-VAL-PRO-HIS- 362

ALA-ASN-ASP-LEU-GLY-LEU-ASP-ALA-VAL-THR-LEU-GLN-TYR-THR-ASP- 377

TRP-MET-ASP-ASP-ASN-ASN-GLY-ILE-LYS-ASN-ARG-ASP-GLY-LEU-ASP- 392

ASP-ILE-VAL-GLY-ASP-HIS-ASN-VAL-ILE-CYS-PRO-LEU-MET-HIS-PHE- 407
                        405~~~~~

VAL-ASN-LYS-TYR-THR-LYS-PHE-GLY-ASN-GLY-THR-TYR-LEU-TYR-PHE- 422
~~~~~410                      419^^^^^^^^^

PHE-ASN-HIS-ARG-ALA-SER-ASN-LEU-VAL-TRP-PRO-GLU-TRP-MET-GLY- 437
^^^^^424

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VAL-ILE-HIS-GLY-TYR-GLU-ILE-GLU-PHE-VAL-PHE-GLY-LEU-PRO-LEU- 452
      444~~~~~447
VAL-LYS-GLU-LEU-ASN-TYR-THR-ALA-GLU-GLU-GLU-ALA-LEU-SER-ARG- 467
      462~~~~~
ARG-ILE-MET-HIS-TYR-TRP-ALA-THR-PHE-ALA-LYS-THR-GLY-ASN-PRO- 482
~~~~~477
ASN-GLU-PRO-HIS-SER-GLN-GLU-SER-LYS-TRP-PRO-LEU-PHE-THR-THR- 497
LYS-GLU-GLN-LYS-PHE-ILE-ASP-LEU-ASN-THR-GLU-PRO-MET-LYS-VAL- 512
      509~~~~~
HIS-GLN-ARG-LEU-ARG-VAL-GLN-MET-CYS-VAL-PHE-TRP-ASN-GLN-PHE- 527
~~~~~516
LEU-PRO-LYS-LEU-LEU-ASN-ALA-THR-GLU-THR-ILE-ASP-GLU-ALA-GLU- 542
      538~~~~~
ARG-GLN-TRP-LYS-THR-GLU-PHE-HIS-ARG-TRP-SER-SER-TYR-MET-MET- 557
~~~~~550
HIS-TRP-LYS-ASN-GLN-PHE-ASP-HIS-TYR-SER-ARG-HIS-GLU-SER-CYS- 572
ALA-GLU-LEU- 575

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These predictions could be of use in further model building studies on the enzyme. These studies are reported in the last quarterly report (18).

We have also tried to build a speculative model for the active site sequence of the enzyme consistent with a set of postulated mechanisms of action (24). The model basically consists of an antiparallel beta sheet with a hairpin bend located at residues 203-206. The active residues are Ser 200, Glu 199 and His 209. A stereo pair view of this model is shown in Fig 8.

The anionic site consists of Glu 199 which provides a negatively charged region which can accept cationic head group of ACh. The esteratic site is composed His 209 which provides a hydrogen bond donor, and Ser 200 which is responsible for the transfer of the acetyl group. When a nerve agent like soman attacks the molecule a partial bond is formed between the 'onyl' group of the nerve gas and the imidazole proton of His 209. This decreases the electron density on the phosphorus atom of the

nerve agent and facilitates a nucleophilic attack by the serine hydroxyl. Figure 9 shows a soman molecule bound to the imidazole of His 209. It can be seen that the hydroxyl of Ser 200 is in a favorable orientation for nucleophilic attack on the phosphorus of soman. The mechanism of action of pyridinium oxime antidotes is supposed to be as follows. The anionic site represented by Glu 199 attracts and holds the positively charged pyridinium nitrogen. This allows the oximate anion to orient itself favorably to attack the phosphorus serine bond and displace the nerve gas. This is illustrated in Fig 10. Details of the model have been presented in the 1st Annual report (1).

(H) Some novel thoughts and ideas for synthesis: We now present some speculative ideas and suggestions for synthesis and testing. We carried out computer searches for embedded oxime fragments in our own proprietary database of chemical compounds. We obtained several interesting fragments which we then used to design some novel compounds. Fig 11 shows four such compounds designed by us. Two of these compounds are seen to be N-oxides which are known to be 'soft' nucleophiles.

The idea of a 'soft' nucleophile can be carried much further. Thus, a reasonable explanation of the inability of the pyridinium oximes ($RCH=NOH$) to reactivate methylphosphonyl-(choline esterase) (the form encountered after choline esterase has been inactivated by SOMAN, which has then aged by loss of its pinacolyl group) is that the oximate anion is unable to approach the negatively charged phosphonate. A soft nucleophile, not bearing a negative charge, might still be nucleophilic enough to remove the phosphonyl group from serine. Accordingly, we proposed consideration of the corresponding hydrazones ($RCH=NNHR'$), as well as possible consideration of compounds containing $RCH=NSH$ or $RCH=NNHN=CHR$. These nucleophiles might be less charged than oximate, and should be tested for reactivation of Soman-inactivated enzyme. Even a low level of activity in such a system would be extremely encouraging. (We are aware that the hydrazine analog of 2-PAM (Fig 12) has been synthesized as the hydrate at WRAIR and is active in some system, but we have no details of further testing or synthesis along these lines.)

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APPENDIX 1 CHOLINESTERASE REGENERATION DATABASE

NAME	COLS	PURPOSE
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DATASET ACHER:

ARN	1-4	Arbitrary reference number identifying compound in this paper only.
ALIAS	5-16	Trivial name or alphabetic designation of compound
CN	17-20	Compound no. - identifies compound in entire data Links to dataset CNWLN.
TEST	21-24	Test no, of form IIPP, where II is number of reference and PP is 2-character abbreviation of poison used Link to dataset ACHLIB.
ACT	25-32	Activity (real no.) measure of compound activity direct or reciprocal units, chosen so as to associate higher numbers with better anti-nerve-gas activity
NDX1	33-40	Index-of-activity #1, real number giving the percentage of this compound among all compounds active in the test, or 0.0 for inactives. Higher numbers correspond higher activity.
NDX2	41-48	Index-of-activity #2, real number giving 5.0 + standard normal score corresponding to this compound among compounds tested in this particular test. Higher numbers correspond to higher activity.
TEMP	49-56	Temporary work field.
NOTE	57-76	Any further comments, not otherwise coded.

DATASET ACHLIB:

TEST	1-4	Same as TEST above, link to dataset ACHER.
SOURCE	5-19	Codon for the journal, as in Chem. Abstracts.
YEAR	20-23	Year of publication.
SPECIES	24-25	2-letter abbreviation of species of enzyme tested (HU = human, BO = bovine, EE = electric eel or torpedo).
PREP	26-40	Preparation tested (rbc, purified enzyme, etc).

POISON 41-50 Poison used.

MEASURE 51-170 What was actually measured in this test.

DATASET CNWLN:

CN 1-4 Same as CN above, link to dataset ACHER.

WLN 7-66 Wiswesser line notation for compound.

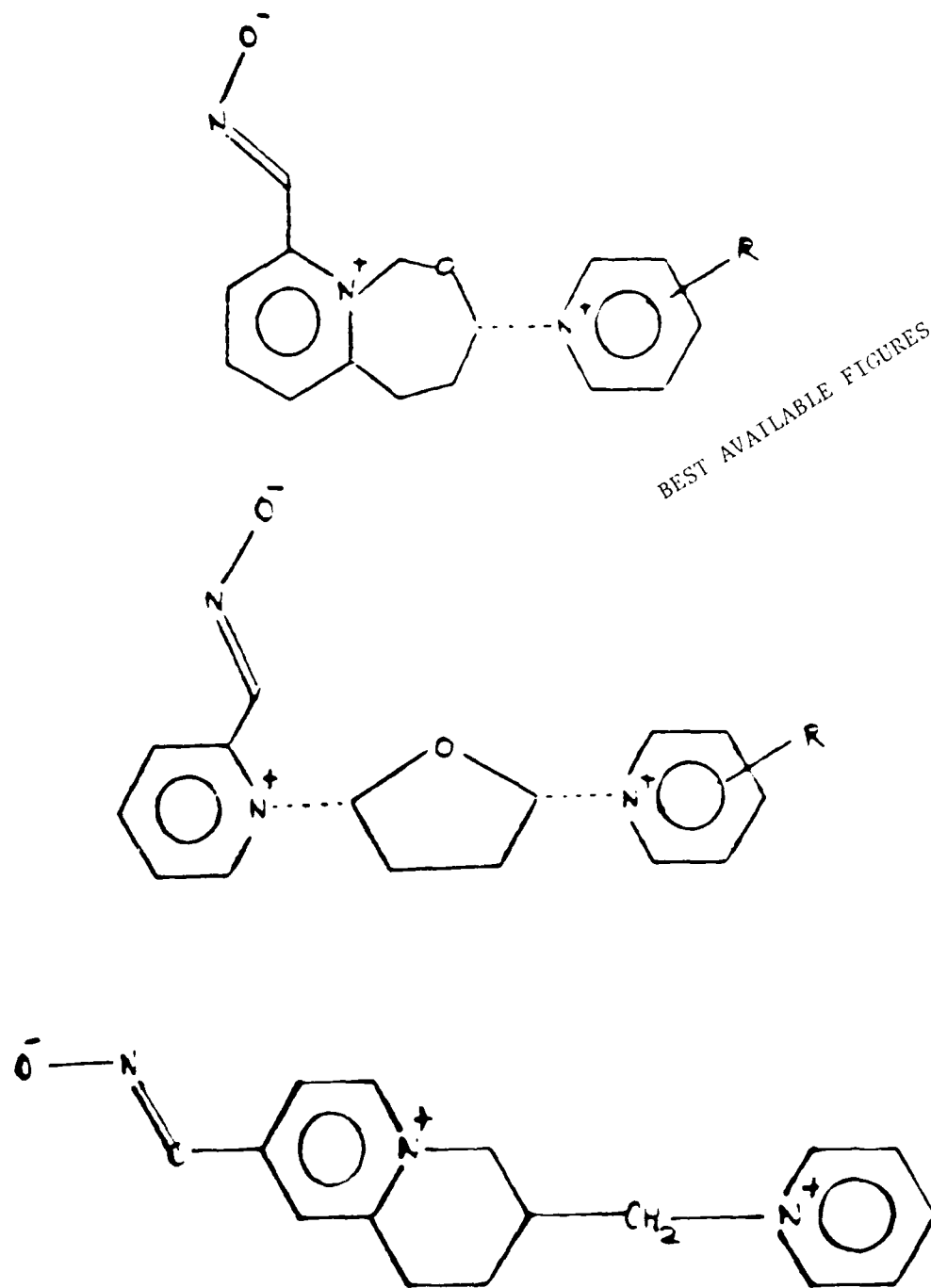


Figure 1. Rigidified bis-pyridinium compounds suggested for synthesis and testing. The three compounds shown here have, respectively, 7-membered, 5-membered and 6-membered rigidifying rings.

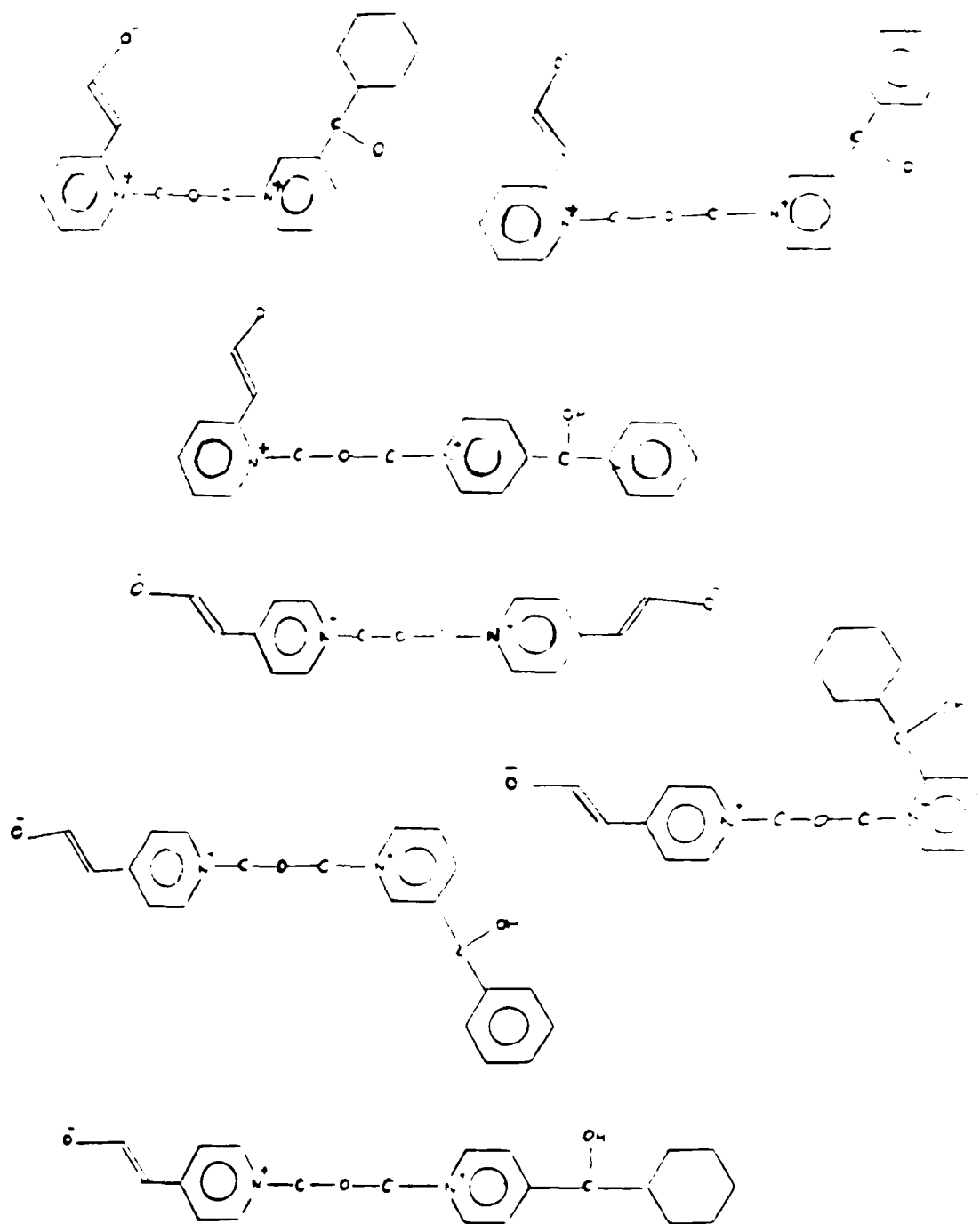


Figure 2. Active bis-pyridinium oximes used in our active volume mapping study.

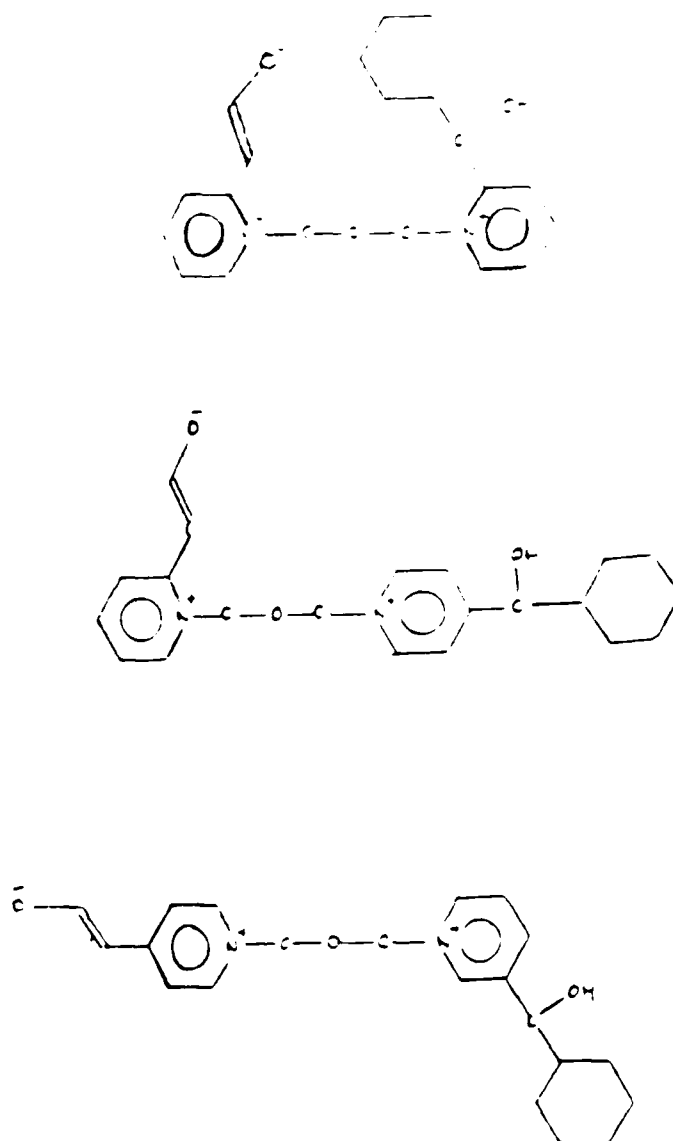


Figure 3. Inactive bis-pyridinium oximes used in our active volume mapping study.

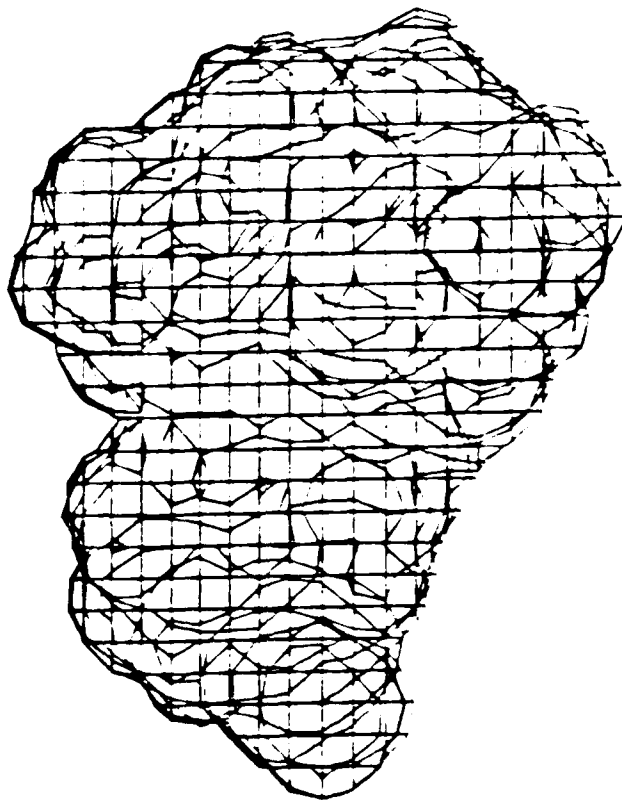


Figure 4. Chicken mesh type representation of the union of the volumes of the actives shown in Fig 2.

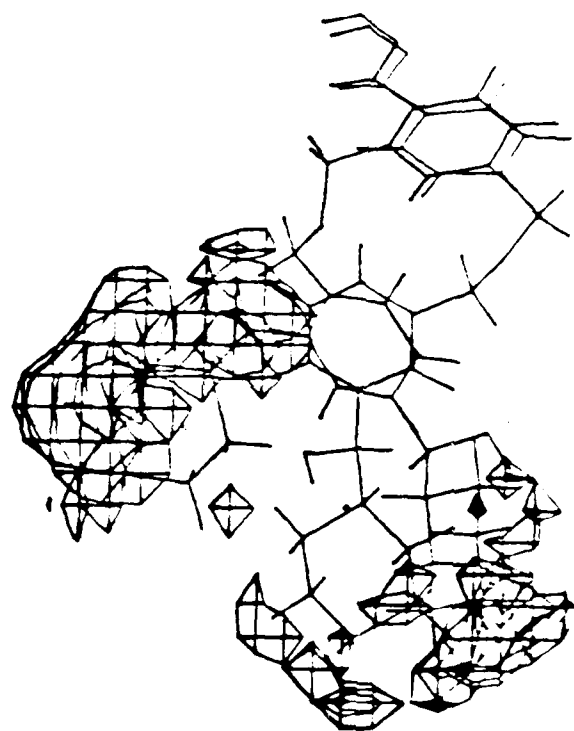
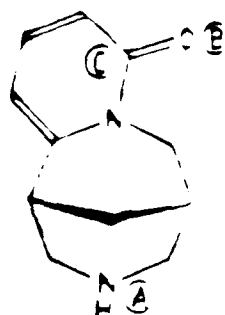
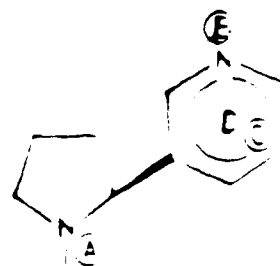


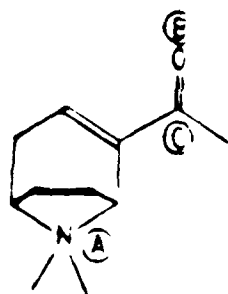
Figure 5. Chicken mesh type representation of the 'extra' volumes of the inactives shown in Fig 3.



(-)-CYTISINE



(-)-NICOTINE

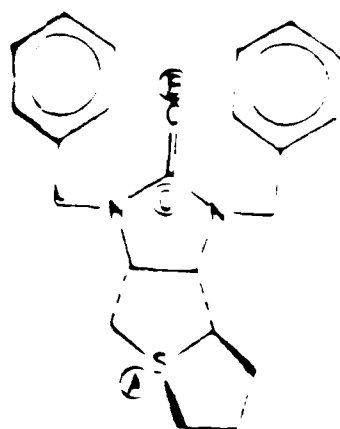


(-)-FERRUGININE
METHIODIDE

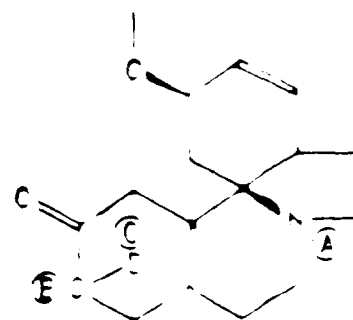


(-)-MUSCADONE

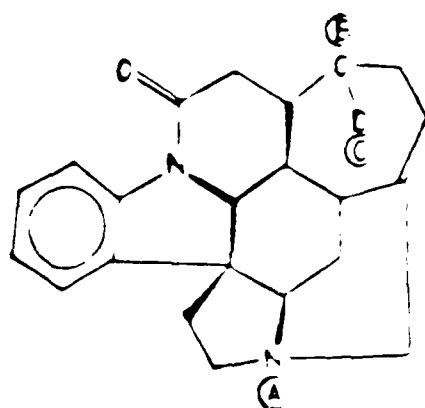
Figure 6. Nicotinic agonists used in our pharmacophore identification study.



1,1-DIMETHYL-4-PHENYL-5-PHENYL-2-PYRROLIDINECARBOXAMIDE



DIHYDRO-5-ERYTHROCHOLINE



STRYCHNINE

Figure 7. Nicotinic effectors used to test our nicotinic pharmacophore model.

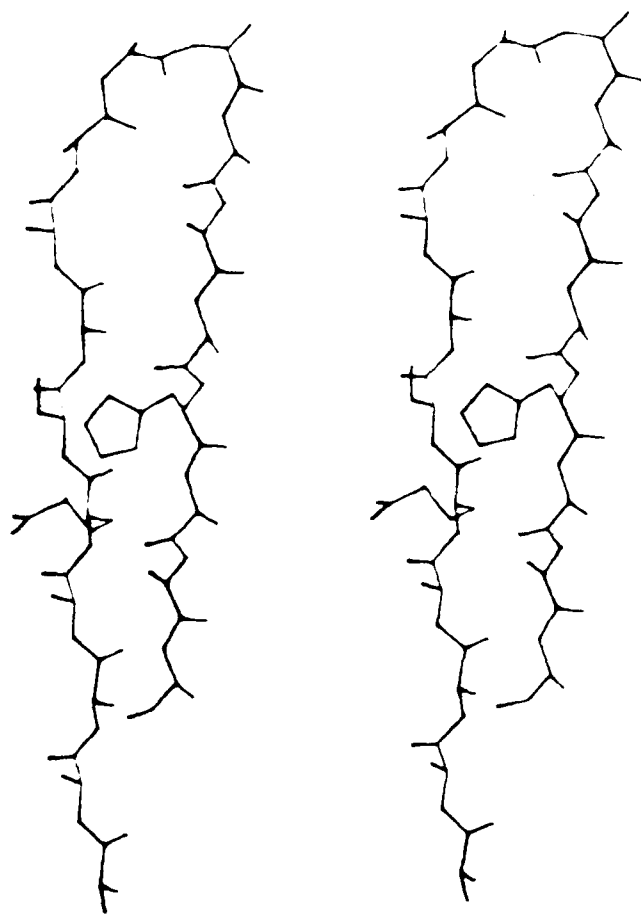


Figure 8. Stereo-pair view of the model for the presumptive active site region of acetylcholinesterase. All the side chains except those required to illustrate the postulated mechanism of action have been made Ala for clarity.

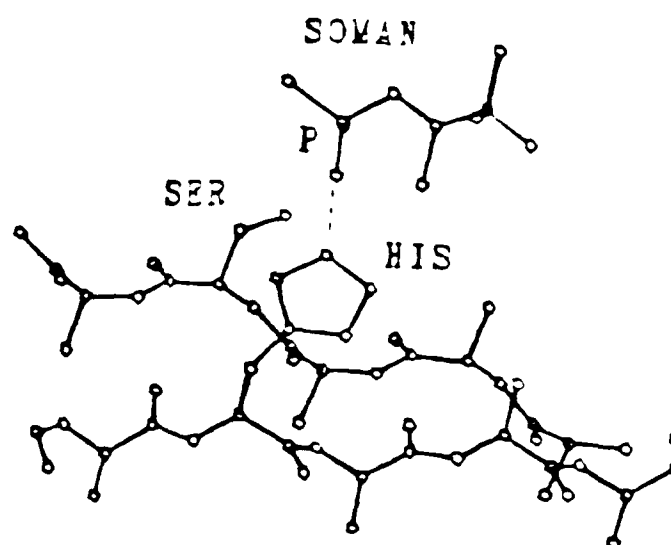


Figure 9. View of a portion of the active site of AChE showing the imidazole proton of His 209 bound to the 'onyl' group of a soman molecule.

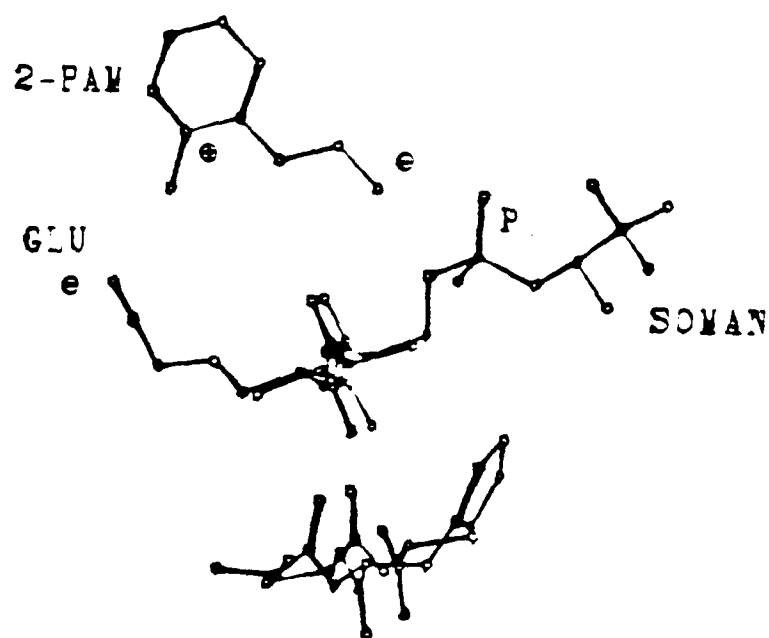


Figure 10. View of a portion of the active site of soman-AChE with 2-PAM bound making an attack on the phosphorus-serine bond. Note the positively charged pyridinium nitrogen of 2-PAM is in close proximity to the negatively charged side chain of Glu 199.

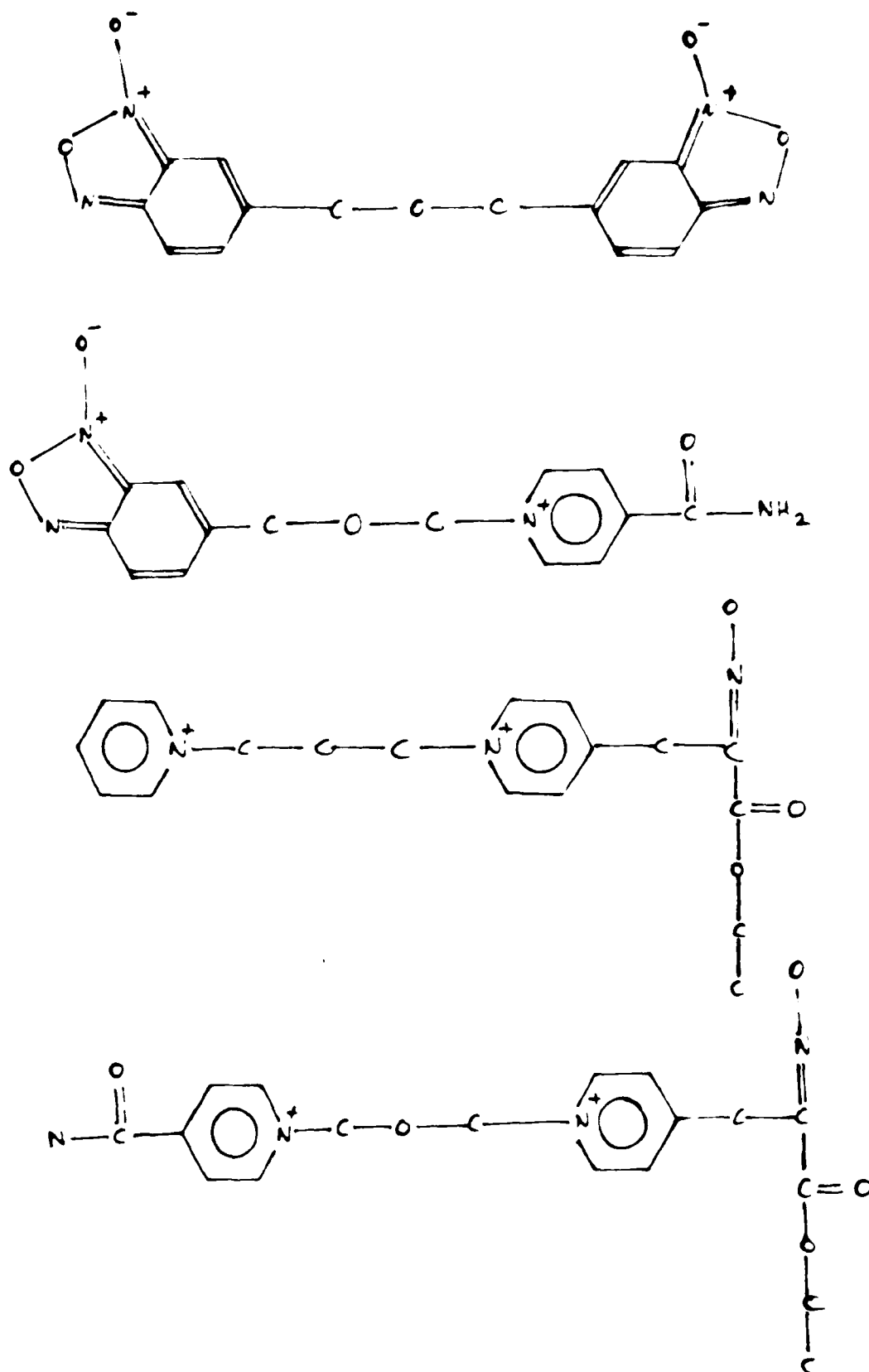


Figure 11. Novel compounds with embedded oxime fragments designed as candidate reactivators.

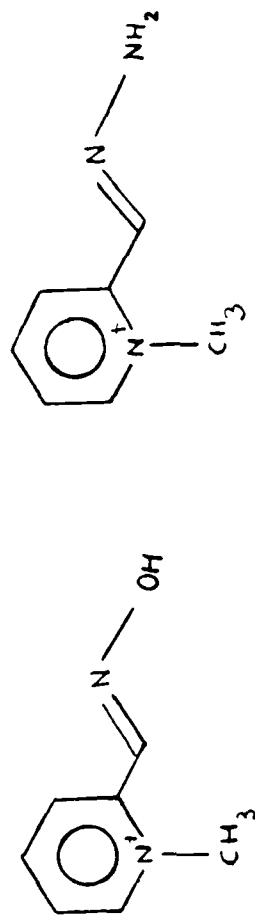


Figure 12. 2-PAM and its Hydrazine analog.

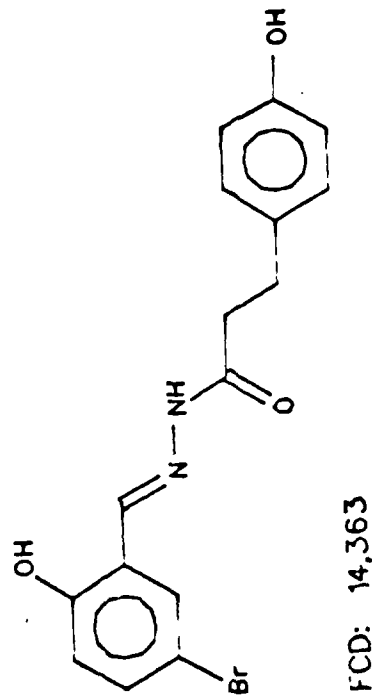
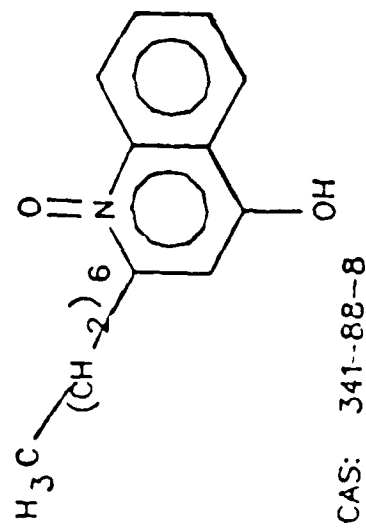
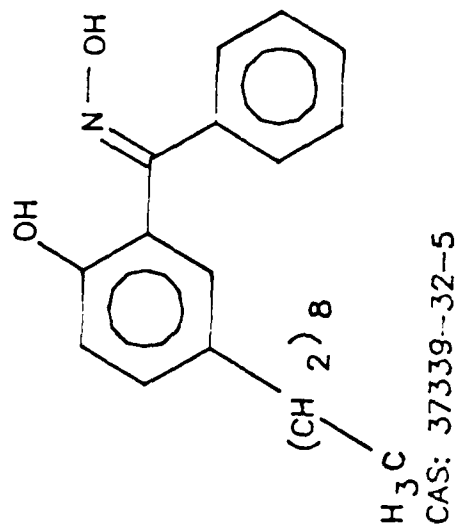
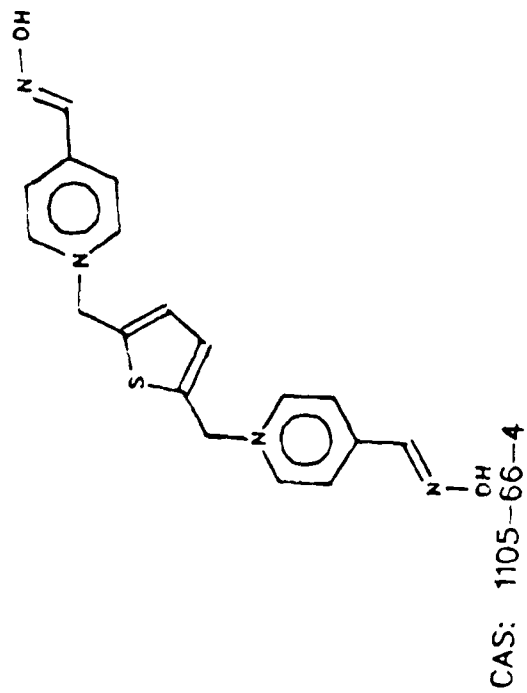


Figure 13. Classes of compounds from statistical structure-activity studies.

END

3-87

DTIC