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SRI PROJECT PYU-4681

# NEW DRUGS FOR PRETREATMENT OF ORGANOPHOSPHONATE INTOXICATION

FINAL REPORT



Daniel W. Parish, Allen L. Dodge, and Marjorie M. Petesch



February 20, 1990

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U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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Forty-five 1-[(1-arylcycloalkyl)methyl]amines were submitted. Structural variables examined included the phenyl substituent (unsubstituted, 3-$OCH_3$, 3-OH, 3,4-$(OCH_3)_2$, 4-$CH_3$, and 4-$NO_2$), the cycloalkyl ring (cyclohexyl, cyclopentyl, cyclopropyl, and replacement of the cycloalkyl ring with two ethyl groups), the amine (pyrrolidine, piperidine, morpholine, diethylamine, and dimethylamine), the aryl group (substituted and unsubstituted phenyl, 2-thienyl, and 1-naphthyl), and protic verses quaternary (methyl) salts.

Twenty-nine dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates were submitted. Structural variables examined included the cycloalky ring (cyclohexyl, cyclopentyl, and cyclopropyl), the alkyl chain connecting the amino nitrogen to the ether oxygen (di- and trimethylene), the amine (pyrrolidine, piperidine, morpholine, diethylamine, and dimethylamine), and protic versus quaternary (methyl) salts.

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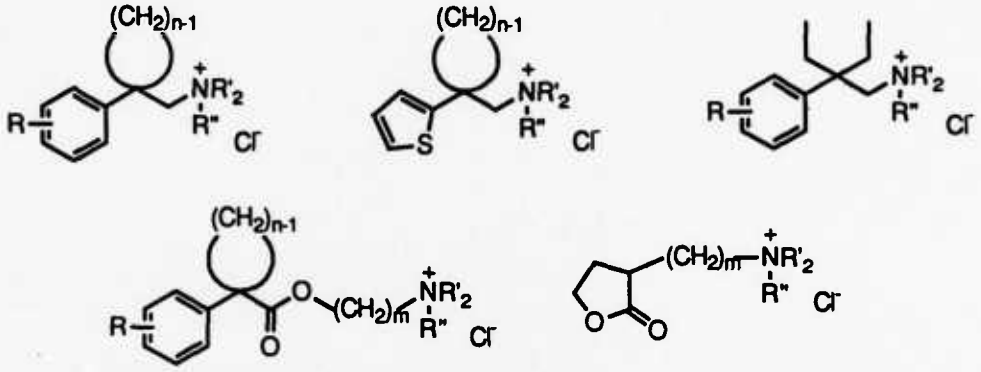

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R = $CH_2OCH_2(C_6H_5)$; n = 3 - 8

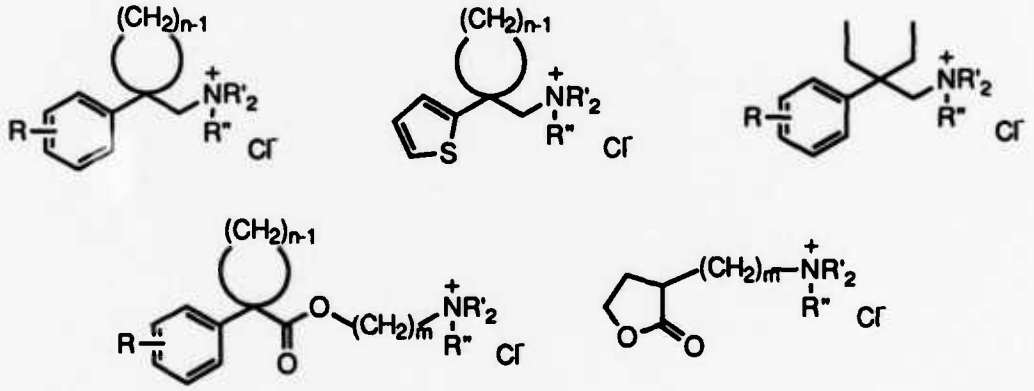
All compounds prepared under Contract DAMD17-88-C-8001 were submitted to MRDC for in vivo evaluation of their ability to provide pretreatment protection against soman (GD) in the mouse model. To date, we have received results for 48 compounds submitted under this contract. With the exception of PRE-064, all compounds tested as oral pretreatments had already been tested in the initial intramuscular (IM) pretreatment efficacy screen. Our 'hit rate' for passing the initial screen is very good, with eight of 25 1-[(1-arylcycloalkyl)-methyl]amines, one of two α,α-dialkylphenethylamines, four of six 1-[(1-(2-thienyl)cycloalkyl)methyl]amines, seven of 10 dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates, and three of four bis-quaternary bis(hetero-aryl)alkanes passing the initial IM pretreatment efficacy screen. In addition, seven of seven 1-[(1-arylcycloalkyl)-methyl]amines, one of one α,α-dialkylphenethylamines, one of one 1-[(1-(2-thienyl)cycloalkyl)methyl]amines, three of five dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates, and one of two bis-quaternary bis(hetero-aryl)alkanes passed the initial oral pretreatment efficacy screen against GD in the mouse.

The PCP receptor affinity was determined for many candidate pretreatment compounds by their ability to displace specific [$^3$H]TCP binding from guinea pig brain membranes. As expected, the 1-(2-arylcycloalkyl)-amines and dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates were completely inactive in the PCP assay. Some 1-[(1-arylcycloalkyl)methyl]amines do exhibit binding to the PCP receptor but with affinities lower than that of phencyclidine (PCP). Most important, there appears to be no correlation between PCP receptor affinity and pretreatment efficacy against GD.

## SUMMARY

This report summarizes the technical efforts undertaken for the U.S. Army Medical Research and Development Command (MRDC) under Contract DAMD17-88-C-8001, "New Drugs for Pretreatment of Organophosphonate Intoxication", and covers progress during the period 16 November 1987 through 15 November 1989.

Our work during this contract has focused on the synthesis of compounds having the general structures shown below. Eighty-four compounds were synthesized and submitted to MRDC; they are shown in Appendix A. In addition, two previously submitted 1-[(2-phenylmethyl)cycloalkyl]amines were resynthesized at the request of the Contracting Officers Representative (COR) for further in vivo testing.



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## ACKNOWLEDGMENTS

This work was supported by the U.S. Army Medical Research and Development Command under Contract DAMD17-88-C-8001. The authors gratefully acknowledge Drs. H. A. Musallam and R. Engle of the Walter Reed Army Institute of Research for their encouragement and support of this work, and we thank Major James R. Stewart and staff at the Institute of Chemical Defense for in vivo test results. We especially thank Drs. Tsung-Ping Su and Edward J. Cone of the National Institute on Drug Abuse's Addiction Research Center for determination of PCP receptor-binding affinities. We also thank Mses. Dorris L. Taylor and Mary Mulvehill of SRI for log P and solubility determinations.

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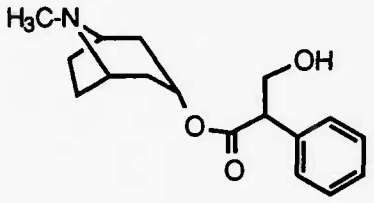


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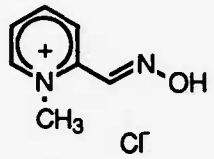


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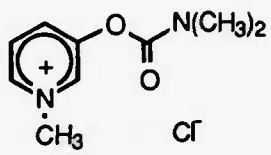


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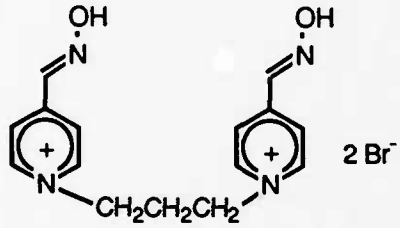
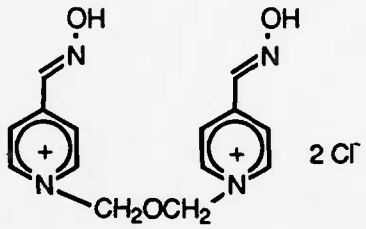



TMB-4

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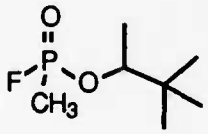


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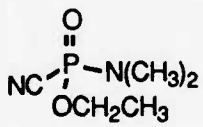
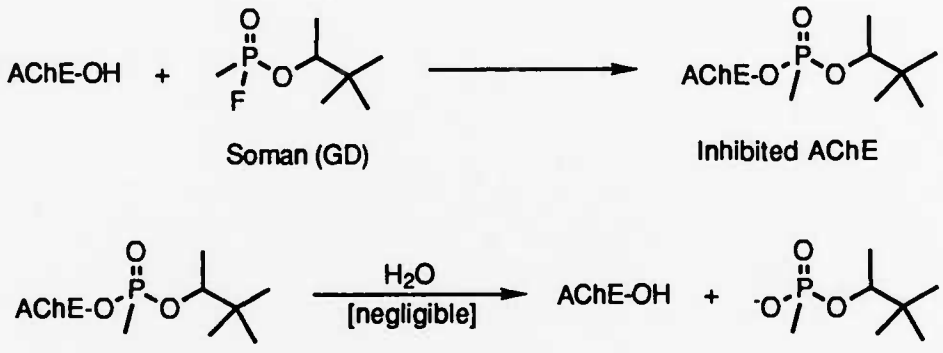


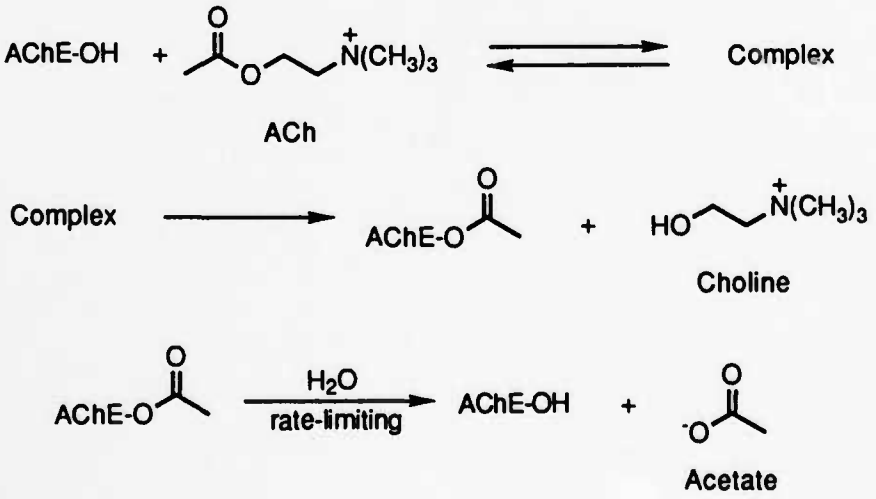

Tabun (GA)

# I INTRODUCTION

Organophosphorus (OP) pesticides and chemical warfare (CW) agents are potent inhibitors of synaptic acetylcholinesterase (AChE).[1] As shown schematically in Scheme 1, acylation of the active site serine hydroxyl of AChE by OP agents causes essentially irreversible inhibition of AChE, rendering it incapable of hydrolyzing acetylcholine (ACh). At sufficiently high doses of an OP agent, the buildup of ACh, caused by disruption of AChE function (Scheme 2), causes depression of the respiratory center in the brain and peripheral neuromuscular blockade, resulting in respiratory paralysis and death.[2]

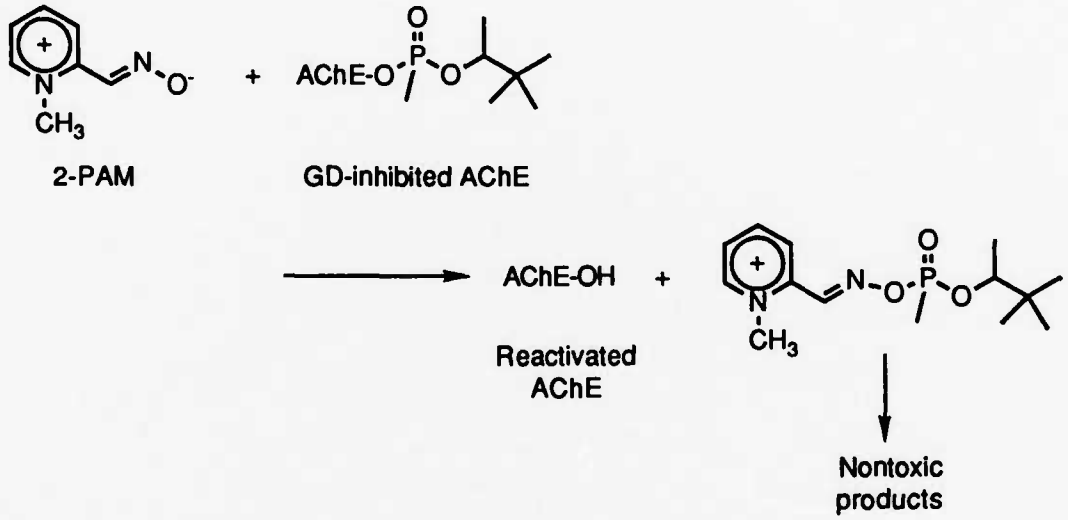



Scheme 1. Mechanism of soman toxicity.




Scheme 2. Function of acetylcholinesterase (AChE).

Standard therapy for poisoning by OP agents consists of coadministration of atropine and an AChE "reactivator".[3-5] Atropine, by blocking the muscarinic cholinergic receptors, antagonizes the peripheral parasympathetic effects of elevated ACh levels. As shown in Scheme 3, the "reactivator" functions by displacing the phosphonyl group from the AChE active site, regenerating (i.e., "reactivating") AChE's catalytic activity. Three such reactivators, pralidoxime chloride (2-PAM), TMB-4, and toxogonin,* effectively reverse intoxication symptoms in cases of pesticide or nerve agent poisoning and have found widespread application in managing OP poisoning. It is the nucleophilic oximate anion of these reactivators that displaces the phosphonyl group from the active site serine hydroxyl.



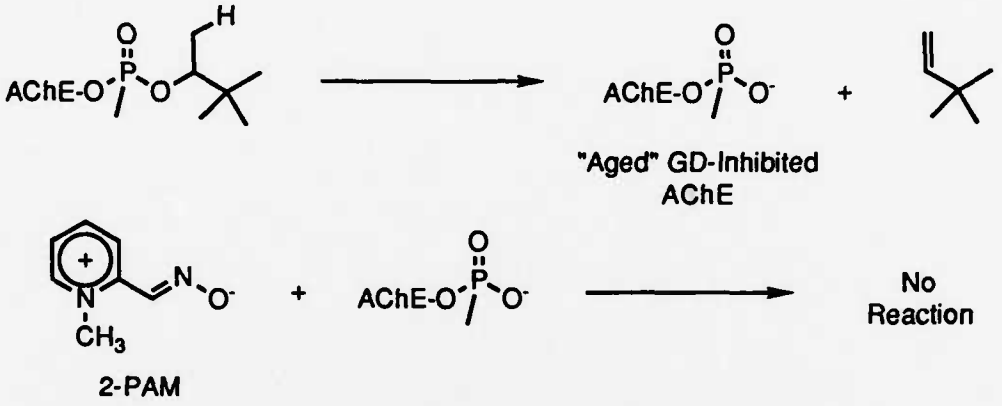

Scheme 3. "Reactivation" of GD-inhibited AChE.

Despite the general utility of the aforementioned oximes in treating cases of OP poisoning, a major limitation exists with respect to the CW agent soman (GD).[6,7] When administered in amounts over 1.2 times its median lethal dose ($LD_{50}$), intoxication is not effectively reversed by oxime reactivators.[8-10] Because GD is considered a principal threat agent,[11-13] development of improved methods for the treatment or pretreatment of poisoning by GD is imperative.

The ineffectiveness of oximes in treating GD intoxication is due to the rapid ($t_{1/2}$ << 10 min)[14] unimolecular dealkylation of GD-inhibited AChE to a species that is essentially inert to attack by oximate. This process has been termed "aging" and is shown

* See Glossary (pg xi) for structures not identified in the text.

schematically in Scheme 4. To protect effectively, against GD poisoning compounds must either retard the rate of aging or, better yet, substantially suppress phosphonylation of the enzyme. In 1946, Koster[15] demonstrated that prior administration of the carbamate physostigmine protects animals against the toxic effects of diisopropyl phosphonyl-fluoridate (DFP). A variety of carbamates were later shown to interfere with phosphonylation of AChE.[16-23]




Scheme 4. Aging of GD-inhibited AChE.

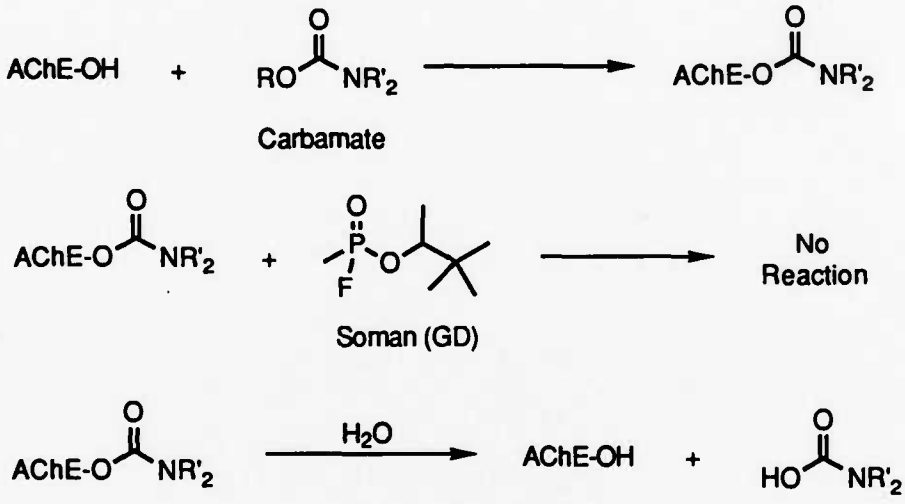
As shown in Scheme 5, the prophylactic activity of carbamates arises from their carbamoylation of the active site serine hydroxyl of AChE. The carbamoylated enzyme cannot be phosphonylated but is still hydrolyzed reasonably rapidly ($t_{1/2}$ = 30 min for $EOC(O)N(CH_3)_2$ at 30 °C)[24] to regenerate active AChE. Carbamates thus provide a "reactivatable" pool of AChE from which the level of AChE, depleted by OP agent exposure, can be replenished. Pretreatment with pyridostigmine, followed by treatment with atropine and 2-PAM, protects animals against the lethal effects of 2-8 times the $LD_{50}$ of GD.[16,17]

However, several factors limit the use of carbamates as pretreatment drugs to be self-administered by combat troops:

- High acute toxicity; the $LD_{50}$ for pyridostigmine is 5.5 mg/kg (0.025 mmol/kg) by intramuscular (IM) injection in guinea pigs[16]
- High species dependence[16,17]
- Incompatibility with oxime therapy[25, 26]

Because the standard therapy for poisoning by OP agents is coadministration of atropine and an oxime reactivator,[3-5] it is likely that a person exposed to an OP will be

given an oxime as part of treatment. It is therefore critical that any prophylactic agent administered before exposure be compatible with the expected postexposure therapy. Displacement of the carbamoyl group from a carbamate-inhibited enzyme by an oxime results in formation of a carbamoylated oxime. One source of incompatibility between carbamates and oximes is the fact that these carbamoylated oximes are themselves potent inhibitors of AChE's hydrolytic activity.[27] A second potential source is that once a carbamate-inhibited enzyme is reactivated, it is then susceptible to (irreversible) reinhibition by residual OP in the system.




Scheme 5. Mechanism of carbamate prophylaxis.

Another factor complicating the development of improved carbamate pretreatment drugs is the relative insensitivity of their duration of protection to structural modifications in the molecule. This limitation of carbamates is a manifestation of their mode of action. Once carbamoylated, the enzyme is protected against phosphonylation for a length of time specified by bimolecular (time-dependent) reactions with water or other nucleophiles. Most of the carbamate molecule functions as a delivery system, and once the enzyme is carbamoylated this delivery system diffuses away and plays no further role in defense of the enzyme. Little opportunity remains for structural modification to influence the carbamate's duration of action, because only a small portion of the molecule is involved in protecting the enzyme.

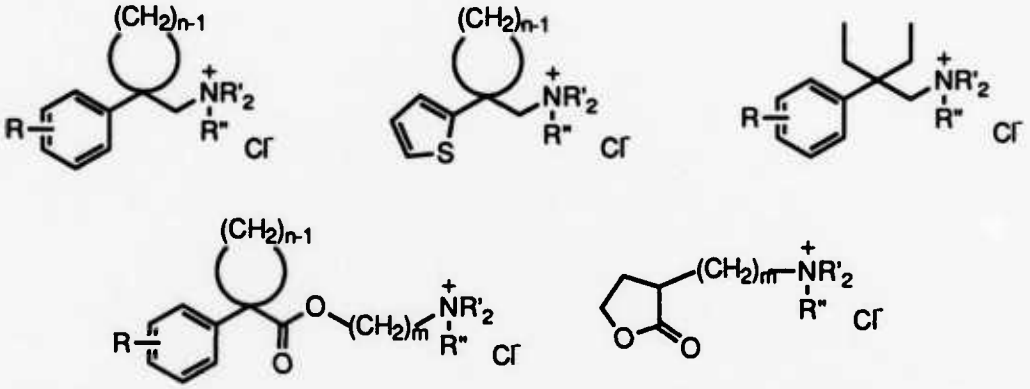
Reversible inhibitors, on the other hand, protect the enzyme via interactions with the entire pretreatment molecule. The onset or loss of inhibition is instantaneous because it involves no covalent bond-forming or bond-breaking processes. The duration of AChE

protection is, therefore, completely determined by the rate of absorption, distribution, and removal (by metabolism or excretion) of inhibitor. These pharmacodynamic properties are strongly influenced by structural modification; therefore, appropriate selection of functional groups should enable us to design pretreatment drugs that feature a broad range of biological half-lives.

The objective of our program is to develop safe and effective drugs for the pretreatment of GD poisoning. To date, we have focused on compound types that address the specific limitations of carbamate drugs discussed above. Two of these limitations are critical in a drug meant to be self-administered by personnel before actual exposure to GD: high toxicity with its corresponding risk of a performance decrement, and incompatibility with oxime therapy. As our pretreatment program has developed, we have identified several lead compounds that are superior to known carbamates with respect to efficacy and toxicity. During the period covered by this contract, we continued to evaluate the effects of structural modifications on these leads, began investigation of two additional structural families of potential pretreatment drugs, and directly addressed concerns that the 1-[(1-arylcycloalkyl)methyl]amines may cause PCP receptor-mediated behavioral effects.

## II CHEMISTRY

Our work during the period covered by this contract has focused on the synthesis of compounds having the general structures shown below. Eighty-four compounds were synthesized and submitted to the U.S Army Medical Research and Development Command (MRDC); they are shown in Appendix A. In addition, two previously submitted 1-[(2-phenylmethyl)cycloalkyl]amines were resynthesized at the request of the COR for further in vivo testing.



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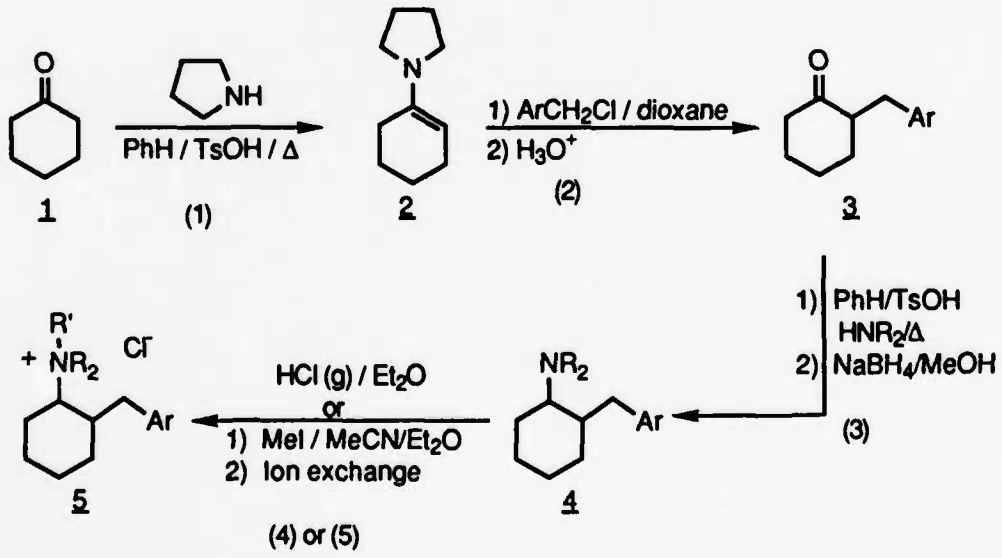
## 1-[(2-Phenylmethyl)cycloalkyl]amines

The general synthetic route shown in Scheme 6 was used to prepare the 1-[(2-phenylmethyl)cyclohexyl]amines, PRE-201 and -208, for resubmission.

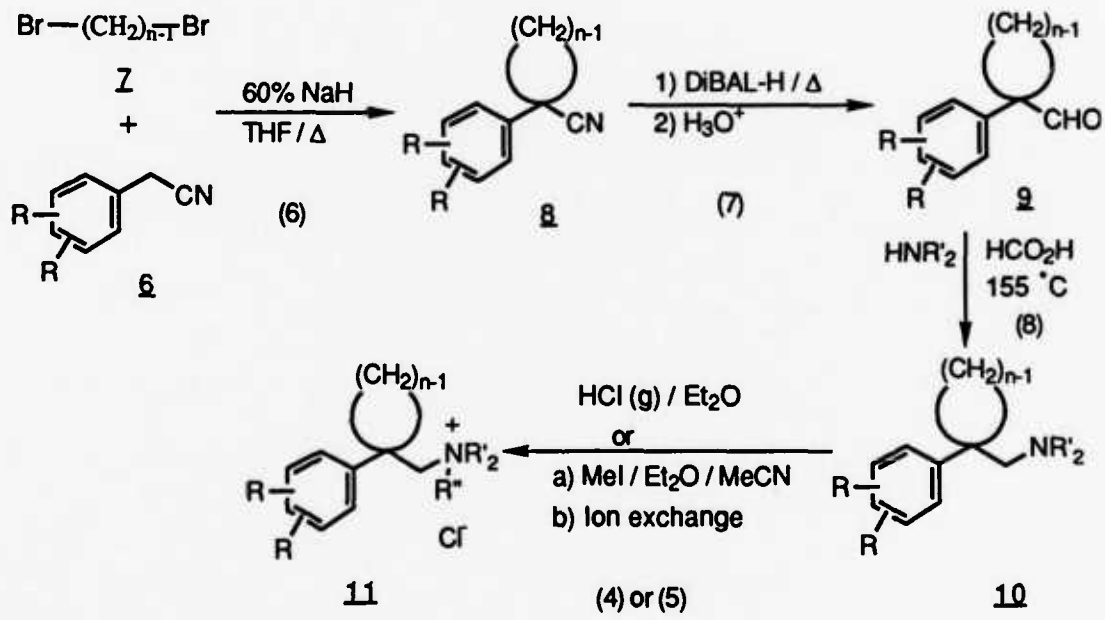



Scheme 6. Synthesis of 1-[(2-phenylmethyl)cycloalkyl]amines.

As shown in Scheme 6, cyclohexanone 1 and pyrrolidine are reacted in refluxing benzene to form the enamine 2. Monoalkylation of 2 with a substituted benzyl halide, followed by aqueous hydrolysis, provides the functionalized ketone 3. In the case of the pyrrolidine-containing amines, the initial alkylation product of enamine 2 can be directly reduced to yield the desired parent compound 4. For the other amines, ketone 3 and the desired amine are reacted in benzene containing a catalytic amount of p-toluenesulfonic acid (TsOH), followed by reduction with sodium borohydride in chilled methanol, to provide amine 4. Treatment of amine 4 with hydrogen chloride gas (4) or methyl iodide, followed by ion exchange (5), provides the desired amine salts 5.

## 1-[(1-Arylcycloalkyl)methyl]amines.

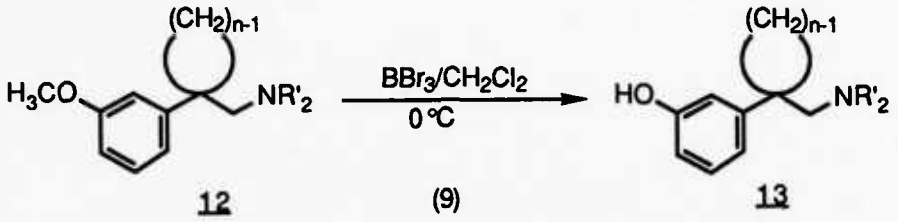
The general synthetic route shown in Scheme 7 was used to prepare the new 1-[(1-arylcycloalkyl)methyl]amines.




Scheme 7. Synthesis of 1-[(1-arylcycloalkyl)methyl]amines.

As shown in Scheme 7, treatment of substituted phenylacetonitrile 6 with either a 1,5- or 1,4-dihaloalkane 7 in refluxing tetrahydrofuran (THF) containing sodium hydride (6) yields arylcycloalkanecarbonitrile 8. Reduction of 8 with diisobutylaluminum hydride (DiBAL-H) followed by hydrolysis (7) yields carboxaldehyde 9, which is then converted to 1-[(1-arylcycloalkyl)methyl]amine 10 by heating with an amine in formic acid (8).

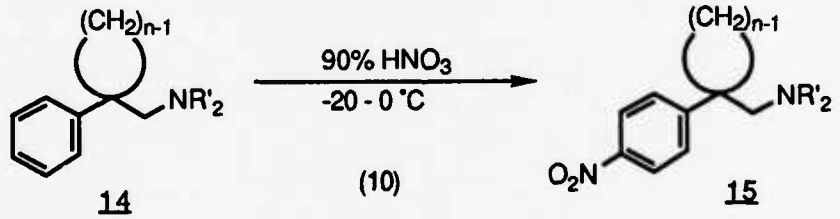
Amine 10 is then converted to its respective hydrochloride and methochloride salts 11 by standard procedures.




12 (9) 13

Scheme 8. Synthesis of 1-[(1-(3-hydroxyphenyl)cycloalkyl)methyl]amines.

The 1-[(1-(3-hydroxyphenyl)cycloalkyl)methyl]amines 13 were prepared by demethylation of the corresponding 1-[(1-(3-methoxyphenyl)cycloalkyl)methyl]amines 12. As shown in Scheme 8, the demethylation is accomplished by treatment of amine 12 with $BBr_3$ in $CH_2CH_2$ at 0 °C. The 1-[(1-(4-nitrophenyl)cycloalkyl)methyl]amines 15 were prepared by nitration of the corresponding 1-[(1-phenylcycloalkyl)methyl]amine 14 in nitric acid at -20 °C, as shown in Scheme 9. The 1-[(1-(1-naphthyl)cycloalkyl)methyl]amines and 1-[(1-(2-thienyl)cycloalkyl)methyl]amines were prepared using the route shown in Scheme 7, by substituting 1-naphthylacetonitrile or 2-thienylacetonitrile, respectively, in place of phenylacetonitrile 6. Synthesis of the 1-[(1-arylcyclopropyl)methyl]amines started from 1-phenyl-1-cyclopropanecarbonitrile, which is commercially available.




14 (10) 15

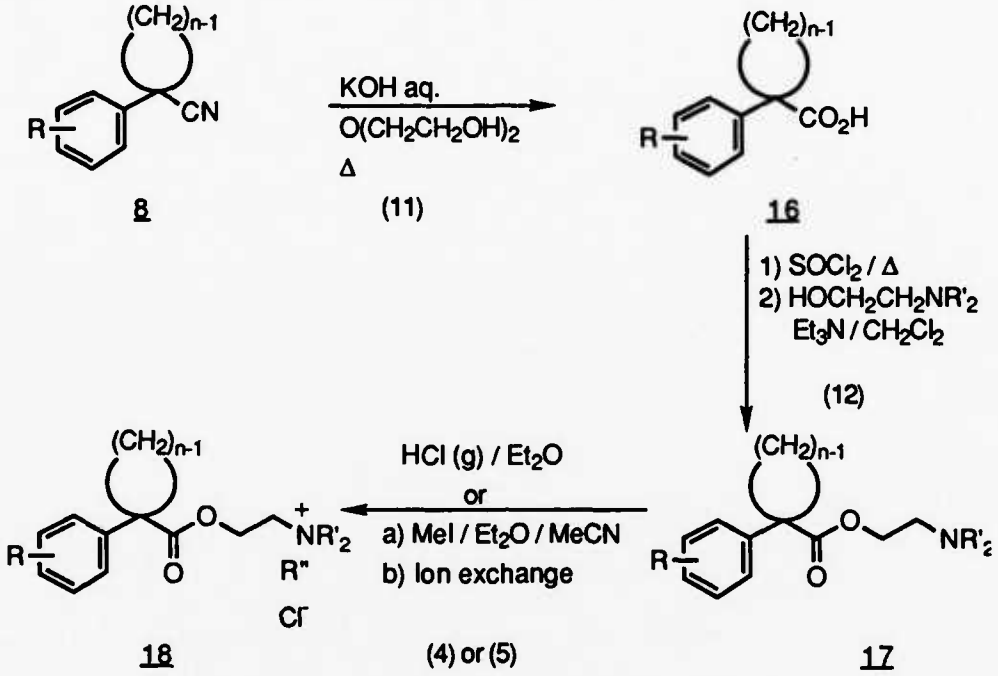
Scheme 9. Synthesis of 1-[(1-(4-nitrophenyl)cycloalkyl)methyl]amines.

## α,α-Dialkylphenethylamines

The general synthetic route shown in Scheme 7 was used to prepare the α,α-dialkylphenethylamines by substituting two equivalents of a monohaloalkane in place of the typical one equivalent of a dihaloalkane 7, in reaction (6). These compounds contain two ethyl groups in place of the spirocycloalkyl ring of the parent 1-[(1-arylcycloalkyl)methyl]-amine.

## Dialkylaminoalkyl 1-Phenylcycloalkane-1-carboxylates

The general synthetic route shown in Scheme 10 was used to prepare the new dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates.

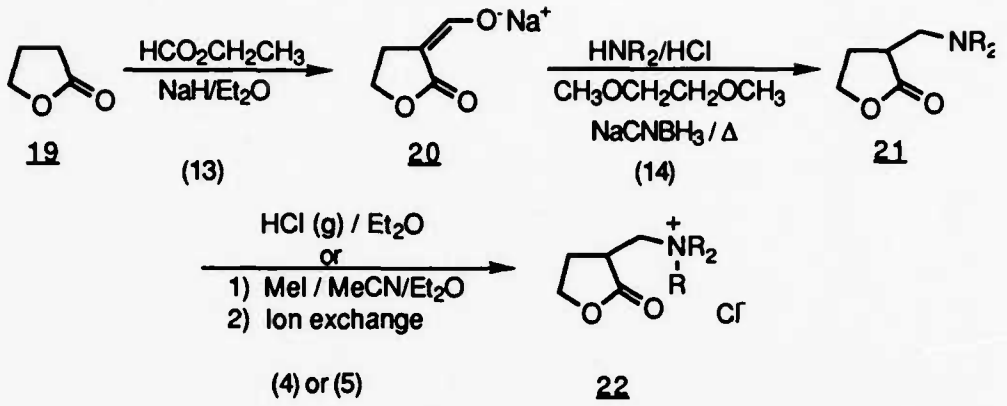



Scheme 10. Synthesis of dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates.

Arylcycloalkanecarbonitrile 8 is hydrolyzed by being heated in 2-hydroxyethyl ether containing 40% potassium hydroxide (KOH) aqueous (11) to yield carboxylic acid 16. Carboxylic acid 16 is refluxed in $SOCl_2$ to provide the acid chloride, which is converted to ester 17 by reaction with a dialkylaminoalkanol in $CH_2Cl_2$ containing $Et_3N$ (12). The amino ester is then converted to the hydrochloride and methochloride salts 18 by standard methods.

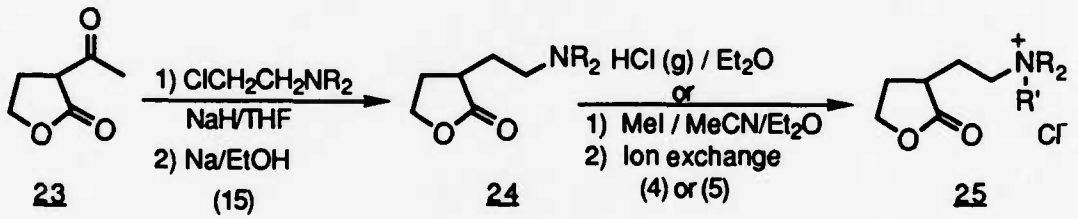
## 3-Dialkylaminoalkyl-4,5-dihydro-2(3H)-furanones

The general synthetic routes shown in Schemes 11 and 12 were used to prepare the new lactone-containing acetylcholine analogs: the 3-dialkylaminomethyl-4,5-dihydro-2(3H)-furanones (Scheme 11) and 3-dialkylaminoethyl-4,5-dihydro-2(3H)-furanones (Scheme 12).




Scheme 11. Synthesis of 3-dialkylaminomethyl-4,5-dihydro-2(3H)-furanones.

As shown in Scheme 11, γ-butyrolactone 19 is treated with ethyl formate and sodium hydride in $Et_2O$ (13) to provide the sodium salt of α-formyl-γ–butyrolactone 20. Reaction of 20 with an amine hydrochloride salt and sodium cyanoborohydride in dimethoxyethane yields the parent 3-dialkylaminomethyl-4,5-dihydro-2(3H)-furanone 21, which is then converted to the desired salts by standard methods.



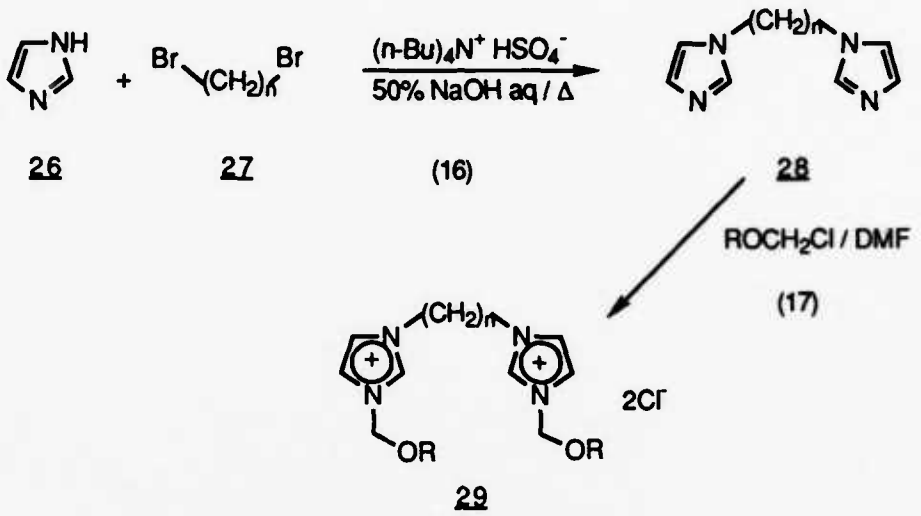

Scheme 12. Synthesis of 3-dialkylaminoethyl-4,5-dihydro-2(3H)-furanones.

As shown in Scheme 12, α-acetyl-γ-butyrolactone 23 is heated with sodium hydride and a dialkylaminoethyl chloride, followed by deacetylation in sodium ethoxide/ethanol (15) to provide the parent 3-dialkylaminoethyl-4,5-dihydro-2(3H)-furanone 24 which is then converted to the desired salts 25 by standard methods.

## Bis-Quaternary Bis(heteroaryl)alkanes

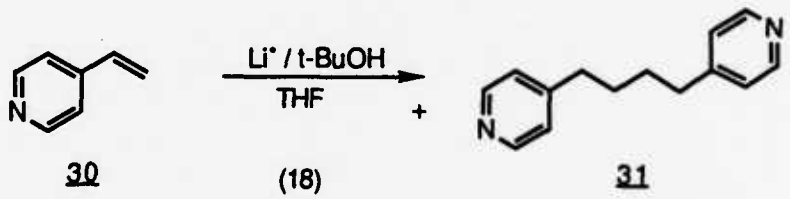
The general synthetic route shown in Scheme 13 was used to prepare new symmetrical bis-quaternary bis(imidazolium)alkanes. Imidazole 26 (2 equivalents) is reacted with dihaloalkane 27 in 50% sodium hydroxide (NaOH) aqueous containing a

phase-transfer catalyst to provide the bis(imidazolyl)alkane 28. Quaternization of 28 with a chloromethyl ether in dimethylformamide (17) yields the desired bis-quaternary salts 29.



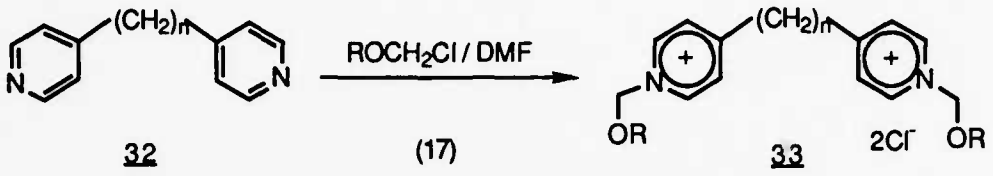

Scheme 13. Synthesis of bis-quaternary bis(imidazolium)alkanes.

Bis(4-pyridyl)-ethanes and -propanes are commercially available, and the bis(4-pyridyl)butane 31 is prepared as shown in Scheme 14.




Scheme 14. Synthesis of bis(pyridyl)butane.

4-Vinylpyridine 30 is treated with lithium metal in t-butanol/tetrahydrofuran (THF) at room temperature (18) to provide 1,4-bis(4-pyridyl)butane 31. As shown in Scheme 15, bis(4-pyridyl)alkane 32 is then treated with a chloromethyl ether in dimethylformamide (DMF) (17) to provide the symmetrical bis-quaternary bis(4-pyridinium)alkane 33.




32 (17) 33

Scheme 15. Synthesis of bis-quaternary bis(pyridinium)alkanes.

Selected physical data for all new compounds submitted under this contract are shown in Appendix B.

# III BIOLOGICAL RESULTS AND DISCUSSION

## Initial Pretreatment Efficacy Against GD (In Vivo)

All compounds prepared under this contract were have been submitted to MRDC for in vivo evaluation of their ability to provide pretreatment protection against GD in the mouse model. To date, we have received results for 48 compounds submitted under this contract. With the exception of PRE-064, all compounds tested as oral pretreatments had already been tested in the initial IM pretreatment efficacy screen. Our "hit rate" for passing the initial screen is very good, with eight of 25 1-[(1-arylcycloalkyl)methyl]amines, one of two α,α-dialkylphenethylamines, four of six 1-[(1-(2-thienyl)cycloalkyl)methyl]amines, seven of 10 dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates, and three of four bis-quaternary bis(heteroaryl)alkanes passing the initial IM pretreatment efficacy screen. In addition, seven of seven 1-[(1-arylcycloalkyl)methyl]amines, one of one α,α-dialkyl-phenethylamines, one of one 1-[(1-(2-thienyl)cycloalkyl)methyl]amines, three of five dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates, and one of two bis-quaternary bis(heteroaryl)alkanes passed the initial oral pretreatment efficacy screen against GD in the mouse.

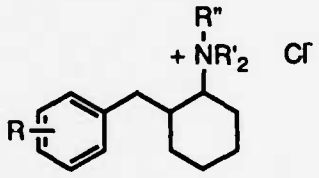
The discussions that follow will concentrate on the in vivo results of compounds submitted under this contract, with occasional reference to compounds submitted under previous contracts. For the sake of completeness, however, the most recent data for all compounds submitted under our pretreatment program, encompassing USAMRDC Contracts DAMD17-83-C-3106, DAMD17-85-C-5148, and DAMD17-88-C-8001, are listed in Appendix C.

PRE-201 and -208, compounds resynthesized at the request of the COR, were previously shown to be the most promising leads in the 1-[(2-phenylmethyl)cycloalkyl]-amine family. Although these compounds are significantly less effective as pretreatments against GD than are the parent 1-(2-arylcycloalkyl)amines, of which they are homologs, they are also substantially less toxic. Both PRE-201 and -208 are quaternary salts, which greatly reduces their ability to penetrate the central nervous system (CNS), with a corresponding reduction in the risk of CNS-mediated performance decrements. The issue of CNS-mediated performance decrements is especially relevant for a drug meant to be taken before actual GD exposure, and it is appropriately of great concern to the MRDC.

In the initial oral pretreatment efficacy screen (Table 1), PRE-201 at a dose of 1/4 its $LD_{50}$ is effective when administered either 30 or 120 min before GD challenge. It also shows some activity at a dose of 1/16 $LD_{50}$ when administered 30 min before GD exposure, yielding an IM minimum effective dose (MED) of 1/16 $LD_{50}$, but is completely ineffective at 120 min and at lower doses. Orally administered PRE-208, at a dose of 1/4 $LD_{50}$, is very effective when given 30 min before GD challenge but ineffective at 120 min and at lower doses, yielding an oral MED of 1/4 $LD_{50}$. Also, behavioral deficit free dose (BDFD) evaluation showed PRE-208 does not affect performance at a dose equivalent to 1/4 its $LD_{50}$.

Table 1*

INITIAL ORAL PRETREATMENT EFFICACY OF
1-[(2-PHENYLMETHYL)CYCLOALKYL)]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | Oral $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-201 | Pyrrolidine | H | $CH_3$ | 3.25 | 0 | 4 | 5 | 0 | 3 | 5 | 0.20 |
| PRE-208 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | >3.09 | 0 | 0 | 8 | 1 | 1 | 0 | 0.77 |

*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated.

As under the previous contracts, the 1-[(1-arylcycloalkyl)methyl]amine family has continued to provide some of our most promising lead compounds. As this contract began, our most viable candidate in this family was PRE-028. As an IM pretreatment (Table 2), PRE-028 is effective at both 15- and 60-min pretreatment times at a dose of 1/16 its $LD_{50}$; which is also its IM MED. PRE-028's toxicity is good, and BDFD evaluation shows doses of 0.38 $LD_{50}$ do not affect performance. As an oral pretreatment (Table 3), PRE-028 is effective at both 30 and 120 min but only at a dose of 1/4 its $LD_{50}$. Its oral toxicity is low, but the oral MED is 1/4 its $LD_{50}$.

At the 1989 Medical Defense Bioscience Review, the MRDC announced its new priorities in the area of OP pretreatment drug development. The goal was to explicitly exclude any compounds with unhindered access to the CNS because of their perceived risk

for causing centrally mediated performance decrements: Therefore, the MRDC would no longer consider any nonquaternary compounds for development as pretreatment drugs. Unfortunately, PRE-028 is a protic salt and, therefore, falls into this category. PRE-029, the methyl-quaternized analog of PRE-028, had also been prepared, but it is effective as an IM pretreatment only at 1/4 $LD_{50}$. PRE-029's oral toxicity is much lower than that of PRE-028, and its oral MED is 1/16 its $LD_{50}$; but its oral pretreatment efficacy at 1/4 $LD_{50}$ and 120 min pretreatment time is not nearly as attractive as that of PRE-028.

The most promising quaternized (methyl chlorides) 1-[(1-arylcycloalkyl)methyl]-amines, submitted under previous contracts, are PRE-041 and -046. As an IM pretreatment, PRE-041 is effective at both 15- and 60-min pretreatment times when administered at a dose of 1/4 its $LD_{50}$. It is also effective at 60 min pretreatment, when administered at a dose of 1/16 its $LD_{50}$. The toxicity of PRE-041 is not high, and its IM MED is 1/16 its $LD_{50}$. Also, BDFD evaluation showed that doses of 1/4 $LD_{50}$ do not affect performance. Unfortunately, we never received the results for PRE-041 in the initial oral pretreatment efficacy screen, so we cannot comment on its potential in this regard.

PRE-046, although barely passing the initial IM pretreatment efficacy screen, looks much more promising when administered orally. As an oral pretreatment, PRE-046 is effective at both 30 and 120 min when administered at a dose of 1/4 its $LD_{50}$. It was also very effective at 30 min at a dose of 1/16 $LD_{50}$. Its toxicity is low, and its oral MED is 1/16 its $LD_{50}$. PRE-046 was not evaluated in the BDFD screen.

Of the 1-[(1-arylcycloalkyl)methyl]amines submitted under this contract, PRE-067 is the most promising compound in terms of pretreatment efficacy. It is effective as an IM pretreatment when administered at 15- and 60-min pretreatment times at a dose of 1/4 $LD_{50}$. It is also effective at 15-min pretreatment times at a dose of 1/16 $LD_{50}$. The toxicity of PRE-067 is higher than we would like, but its IM MED is still 1/16 its $LD_{50}$.

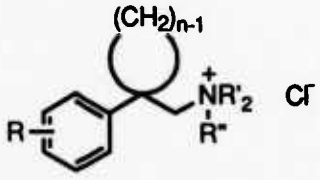
As an oral pretreatment, PRE-067 looks very good. It is very effective when administered at 30- and 120-min pretreatment times at a dose of 1/4 $LD_{50}$. It is also very effective at a 30 min pretreatment time at a dose of 1/16 $LD_{50}$. As with IM administration, the oral toxicity is somewhat higher than we would like, but its oral MED is 1/16 its $LD_{50}$. Unfortunately, because PRE-067 is a protic salt and, therefore, readily able to penetrate the CNS, it will be precluded from further development by virtue of the MRDC's pretreatment priorities.

None of the quaternary 1-[(1-arylcycloalkyl)methyl]amines submitted on this contract for which we have received in vivo efficacy data are as orally effective as PRE-

067. As an IM pretreatment, PRE-071 is effective at a 15-min pretreatment time at a dose of 1/16 $LD_{50}$. It is also effective at a 60-min pretreatment time when administered at a dose of 1/4 $LD_{50}$. Its IM toxicity is very low, and its IM MED is 1/16 its IM $LD_{50}$. As an oral pretreatment it is effective at both 30- and 120-min pretreatment times but only at a dose of 1/4 $LD_{50}$. Its oral toxicity is low, but its oral MED is only 1/4 its $LD_{50}$.

Table 2*

INITIAL IM PRETREATMENT EFFICACY OF
1-[(1-ARYLCYCLOALKYL)METHYL]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | n | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-028 | Pyrrolidine | 3-OH | H | 6 | >0.51 | 1 | 7 | 7 | 1 | 6 | 8 | - |
| PRE-029 | Pyrrolidine | 3-OH | $CH_3$ | 6 | 0.32 | 0 | 0 | 8 | 0 | 0 | 5 | - |
| PRE-041 | Piperidine | H | $CH_3$ | 5 | 0.26 | 0 | 1 | 6 | 1 | 7 | 9 | 0.02 |
| PRE-046 | Piperidine | 3-$OCH_3$ | $CH_3$ | 6 | 0.29 | 2 | 2 | 3 | 0 | 1 | 4 | - |
| PRE-062 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 5 | 0.17 | 1 | 4 | 10 | 0 | 2 | 2 | 0.01 |
| **PRE-063** | **Piperidine** | **3-$OCH_3$** | **H** | **5** | **0.32** | **3** | **2** | **3** | **0** | **5** | **0** | **0.02** |
| **PRE-065** | **Morpholine** | **3-$OCH_3$** | **H** | **5** | **>0.61** | **1** | **0** | **1** | **0** | **0** | **0** | **-** |
| **PRE-067** | **Pyrrolidine** | **3-OH** | **H** | **5** | **0.11** | **1** | **7** | **8** | **1** | **1** | **6** | **0.01** |
| **PRE-069** | **Piperidine** | **4-$CH_3$** | **$CH_3$** | **6** | **0.16** | **1** | **3** | **8** | **0** | **0** | **1** | **0.04** |
| **PRE-071** | **Morpholine** | **3-$OCH_3$** | **$CH_3$** | **5** | **>1.23** | **3** | **7** | **1** | **0** | **1** | **7** | **0.08** |
| **PRE-073** | **$N(CH_3)_2$** | **3-OH** | **H** | **6** | **1.01** | **4** | **3** | **6** | **0** | **1** | **1** | **0.02** |
| **PRE-081** | **Piperidine** | **3,4-$(OCH_3)_2$** | **$CH_3$** | **6** | **>1.06** | **3** | **3** | **1** | **2** | **5** | **0** | **0.07** |
| **PRE-130** | **Pyrrolidine** | **4-$NO_2$** | **$CH_3$** | **6** | **0.54** | **0** | **0** | **3** | **3** | **2** | **7** | **0.13** |
| **PRE-133** | **Piperidine** | **H** | **$CH_3$** | **3** | **0.18** | **0** | **3** | **6** | **3** | **2** | **5** | **0.05** |

*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. Compounds shown in boldface were submitted under Contract DAMD17-88-C-8001.

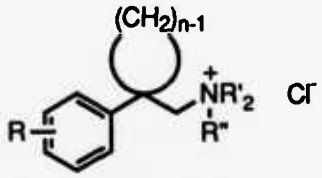
Tables 2 and 3 show that most the 1-[(1-arylcycloalkyl)methyl]amines that passed the initial pretreatment efficacy screens are substituted with oxygen-containing phenyl substituents. This observation supports our conclusion from previous contracts that such

substituents are beneficial for enhancing the pretreatment efficacy of 1-[(1-arylcycloalkyl)-methyl]amines against GD.

The two most promising oral pretreatment candidates found under the previous contract contained cyclohexane rings, whereas those identified under this contract are cyclopentane derivatives. Because the interaction of arylcycloalkylamines (PCP analogs) with the PCP receptor is attenuated when the cycloalkyl ring size deviates from cyclohexyl,[28] this is an important observation since we want to avoid such interactions. A related observation is that the cyclopropane derivative PRE-133 also shows IM efficacy

Table 3*

INITIAL ORAL PRETREATMENT EFFICACY OF
1-[(1-ARYLCYCLOALKYL)METHYL]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | n | Oral $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-028 | Pyrrolidine | 3-OH | H | 6 | 2.01 | 0 | 3 | 7 | 0 | 2 | 9 | 0.51 |
| PRE-029 | Pyrrolidine | 3-OH | $CH_3$ | 6 | >3.23 | 2 | 3 | 6 | 0 | 4 | 4 | 0.20 |
| PRE-046 | Piperidine | 3-$OCH_3$ | $CH_3$ | 6 | 2.96 | 1 | 8 | 6 | 1 | 1 | 7 | 0.18 |
| PRE-061 | Pyrrolidine | 3-$OCH_3$ | H | 5 | 0.66 | 0 | 0 | 7 | 0 | 0 | 5 | 0.16 |
| **PRE-063** | **Piperidine** | **3-$OCH_3$** | **H** | **5** | **1.55** | **0** | **1** | **3** | **1** | **0** | **6** | **0.39** |
| **PRE-064** | **Piperidine** | **3-$OCH_3$** | **$CH_3$** | **5** | **2.51** | **2** | **3** | **5** | **1** | **3** | **2** | **0.63** |
| **PRE-067** | **Pyrrolidine** | **3-OH** | **H** | **5** | **1.01** | **0** | **9** | **8** | **0** | **3** | **9** | **0.06** |
| **PRE-069** | **Piperidine** | **4-$CH_3$** | **$CH_3$** | **6** | **>2.72** | **2** | **2** | **4** | **0** | **1** | **3** | **0.68** |
| **PRE-071** | **Morpholine** | **3-$OCH_3$** | **$CH_3$** | **5** | **>3.07** | **0** | **0** | **4** | **0** | **0** | **6** | **0.77** |
| **PRE-073** | **$N(CH_3)_2$** | **3-OH** | **H** | **6** | **1.51** | **1** | **2** | **2** | **1** | **1** | **5** | **0.38** |
| **PRE-081** | **Piperidine** | **3,4-$(OCH_3)_2$** | **$CH_3$** | **6** | **>2.65** | **0** | **3** | **2** | **0** | **1** | **7** | **0.66** |

*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. Compounds shown in boldface were submitted under Contract DAMD17-88-C-8001.

against GD, both at 15- and 60-min pretreatment times, when administered at a dose of 1/4 $LD_{50}$. These observations are consistent with the fact that the pretreatment efficacy of the

1-[(1-arylcycloalkyl)methyl]amines' against GD is not a function of PCP receptor interactions.

It appears clear that the derivatives of the cyclic amines pyrrolidine, piperidine, and morpholine are more likely to be effective against GD poisoning than are the derivatives of the acyclic diethylamine and dimethylamine. In only one case in which an acyclic amine was substituted for a cyclic amine, PRE-073 for PRE-028, did the resulting compound save more than four animals at a single dose/pretreatment time point, and it still does not look especially promising. It is interesting to note that PRE-073 contains a 3-hydroxy group on the phenyl ring.

Among the protic salts, pyrrolidine seems to be the cyclic amine of choice, appearing in both PRE-028 and -067. The choice of amine in the quaternary analogs, however, is not so clear, with pyrrolidine, piperidine, and morpholine all appearing among the better compounds. The choice between quaternary and protic salt is also not clear. Although in some cases quaternization clearly compromises antidotal efficacy ( e.g., quaternization of PRE-028 to yield PRE-029), in other cases it just as clearly enhances it (e.g., quaternization of PRE-065 to yield PRE-071). At this point, the superiority of quaternary over protic salts as pretreatment antidotes has been rendered academic. The Army's decision to de-emphasize all nonquaternary pretreatment compounds negates the need to address this question within the scope of our investigation.

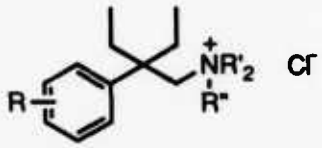
Although the 1-[(1-arylcycloalkyl)methyl]amines have continued to provide us with interesting leads, persistent concerns remain about their potential for producing CNS-mediated behavioral effects. The most specific concern has been for their potential to cause performance decrements via interactions with centrally located PCP receptors. To address this issue directly, a large number of the 1-[(1-arylcycloalkyl)methyl]amines were screened for PCP receptor affinity during the period covered by this contract; the assay results are presented in a later section. In spite of our efforts to dispel these concerns, their tenacity has led the MRDC to completely de-emphasize the 1-[(1-arylcycloalkyl)methyl]amines for now.

We submitted several α,α-dialkylphenethylamines, analogs of the 1-[(1-arylcycloalkyl)methyl]amines in which the cycloalkyl ring has been replaced by two alkyl groups, to determine whether the cycloalkyl ring is necessary for prophylactic activity against GD. Also, the lack of a cycloalkyl ring would be expected to eliminate affinity for the PCP receptor. Although five α,α-dialkylphenethylamines were submitted, only two were evaluated against GD (Table 4). PRE-077 shows activity against GD in both the IM and

oral pretreatment efficacy screen. The IM toxicity of PRE-077 is low, but as an IM pretreatment it is effective only when administered 60 min before GD challenge at a dose of 1/4 its $LD_{50}$; its IM MED is 1/4 $LD_{50}$. PRE-077 looks better as an oral pretreatment, however, being effective at a dose of 1/4 $LD_{50}$ at both 30- and 120-min pretreatment times. PRE-077 also starts to show activity at 1/16 $LD_{50}$ with a 30-min pretreatment time, yielding an oral MED of 1/16 its $LD_{50}$.

Table 4*

INITIAL IM AND ORAL PRETREATMENT EFFICACY OF
α,α-DIALKYLPHENETHYLAMINES AGAINST 2 x LD50 GD IN THE MOUSE




| SRI Code No. | NR'2 | R | R" | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-077** | **Piperidine** | **H** | **H** | **1.75** | **0** | **1** | **0** | **0** | **2** | **6** | **0.35** |

| | | | | Oral $LD_{50}$ (mmol/kg) | 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-077** | **Piperidine** | **H** | **H** | **2.53** | **0** | **4** | **5** | **1** | **3** | **6** | **0.16** |

*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. Compounds shown in boldface were submitted under Contract DAMD17-88-C-8001.

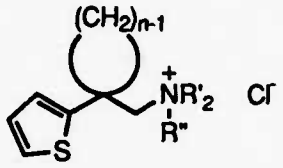
As described earlier, 1-[(1-arylcycloalkyl)methyl]amines with hydroxy- and methoxy-substituted phenyl groups exhibit enhanced prophylactic efficacy against GD. Since hydroxy and methoxy groups are electron-donating by resonance, one possible role these substituents might play is to increase the electron density of the aromatic phenyl ring, leading to enhanced interactions with appropriate acceptor sites within the AChE active site. If this is indeed the case, we expect that replacement of the phenyl group (of the 1-[(1-aryl-cycloalkyl)methyl]amine) with thiophene should yield active compounds.

The 1-[(1-(2-thienyl)cycloalkyl)methyl]amines do, in fact, exhibit activity against GD (Table 5); four of six compounds submitted passed the initial IM pretreatment efficacy screens. PRE-092 is the only compound with an IM MED less than 1/4 $LD_{50}$. Its IM toxicity is good and it is effective at 1/16 its $LD_{50}$, although only at the 15-min pretreatment time. PRE-088 was also evaluated in the initial oral pretreatment efficacy screen. Its

toxicity appears low, and it is effective at both 30- and 120-min pretreatment times but only at 1/4 its $LD_{50}$, which is also its oral MED. The quaternary analogs PRE-127 and -131 are effective at both 15 and 60 min, but their toxicities are high and, like PRE-088, they are effective only at doses of 1/4 $LD_{50}$, which also correspond to their IM MEDs.

Table 5*

INITIAL IM AND ORAL PRETREATMENT EFFICACY OF 1-[(1-(2-THIENYL)CYCLOALKYL)METHYL]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R" | n | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 1/16 | 1/4 | 60 min 1/64 | 1/16 | 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-088** | **Piperidine** | **H** | **6** | **>1.13** | **[0** | **1** | **6** | **0** | **0** | **3][a]** | **0.33** |
| **PRE-092** | **$NEt_2$** | **H** | **6** | **1.25** | **2** | **6** | **4** | **0** | **0** | **2** | **0.08** |
| **PRE-127** | **Pyrrolidine** | **$CH_3$** | **6** | **0.20** | **0** | **1** | **4** | **1** | **2** | **4** | **0.05** |
| **PRE-131** | **Piperidine** | **$CH_3$** | **6** | **0.16** | **0** | **0** | **4** | **1** | **0** | **4** | **0.04** |

| | | | | Oral $LD_{50}$ (mmol/kg) | 30 min 1/64 | 1/16 | 1/4 | 120 min 1/64 | 1/16 | 1/4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-088** | **Piperidine** | **H** | **6** | **3.17** | **0** | **0** | **5** | **1** | **1** | **7** | **0.79** |

*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. Compounds shown in boldface were submitted under Contract DAMD17-88-C-8001.

[a]Doses evaluated were 1/3, 1/12, and 1/48 $LD_{50}$.

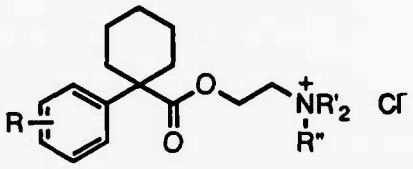
In light of the general de-emphasis of the 1-[(1-arylcycloalkyl)methyl]amines, it is unlikely that more α,α-dialkylphenethylamines or 1-[(1-(2-thienyl)cycloalkyl)methyl]-amines will be prepared or evaluated, as they are no longer within the scope of our investigation.

The dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates are clearly the most exciting new group of compounds we have identified under the present contract. PRE-086 is the most promising IM pretreatment lead (Table 6); it is a quaternary compound, its toxicity is low, it is extremely effective when administered 15 min before GD exposure,

and its IM MED is 1/64 its $LD_{50}$. PRE-086 is also effective at a 60-min pretreatment time, although only at a dose of 1/4 $LD_{50}$. Unfortunately, we have not received data for the initial oral pretreatment efficacy screen of PRE-086 and therefore are unable to comment directly on its potential as an oral pretreatment candidate.

Table 6*

INITIAL IM PRETREATMENT EFFICACY OF
DIALKYLAMINOALKYL 1-PHENYLCYCLOALKANE-1-CARBOXYLATES
AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-078** | **$N(CH_3)_2$** | **H** | **H** | **>0.91** | **[2** | **0** | **6** | **0** | **0** | **0]**[a] | **0.32** |
| **PRE-079** | **Pyrrolidine** | **H** | **H** | **>1.04** | **0** | **0** | **6** | **0** | **0** | **4** | **0.30** |
| **PRE-083** | **$NEt_2$** | **H** | **H** | **>0.54** | **[0** | **5** | **9** | **1** | **2** | **10]**[b] | **0.07** |
| **PRE-086** | **$N(CH_3)_2$** | **H** | **$CH_3$** | **0.65** | **4** | **10** | **10** | **0** | **0** | **5** | **0.01** |
| **PRE-087** | **Pyrrolidine** | **H** | **$CH_3$** | **0.41** | **0** | **3** | **5** | **1** | **1** | **7** | **0.10** |
| **PRE-089** | **Piperidine** | **H** | **$CH_3$** | **0.49** | **0** | **2** | **0** | **2** | **2** | **6** | **0.12** |
| **PRE-090** | **$NEt_2$** | **H** | **$CH_3$** | **0.57** | **0** | **0** | **1** | **0** | **4** | **6** | **0.04** |

*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. Compounds shown in boldface were submitted under Contract DAMD17-88-C-8001.

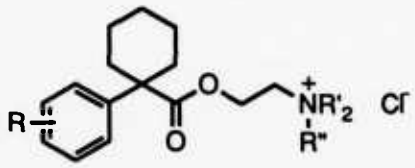
[a]Doses evaluated were 1/3, 1/12, and 1/48 $LD_{50}$.

[b]Doses evaluated were 1/2, 1/8, and 1/32 $LD_{50}$.

PRE-083 is very effective in the initial IM pretreatment efficacy screen at both 15- and 60-min pretreatment times when administered at a dose of 1/2 its $LD_{50}$. It is inferior to PRE-086, however, in two important regards. It is a protic salt, and although dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates failed to bind to the PCP receptor in our in vitro receptor binding assay, the potential consequences of its ready penetration of the CNS would definitely become an issue. The toxicity of PRE-083 is low, but it is most effective when administered at a dose of 1/2 its $LD_{50}$; its MED is 1/8 $LD_{50}$.

Table 7*

INITIAL ORAL PRETREATMENT EFFICACY OF
DIALKYLAMINOALKYL 1-PHENYLCYCLOALKANE-1-CARBOXYLATES
AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | IM $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-078** | **$N(CH_3)_2$** | **H** | **H** | **>3.21** | **0** | **1** | **4** | **0** | **0** | **0** | **0.80** |
| **PRE-087** | **Pyrrolidine** | **H** | **$CH_3$** | **2.33** | **[** | | | | | **]a** | **0.58** |
| **PRE-090** | **$NEt_2$** | **H** | **$CH_3$** | **>2.83** | **1** | **1** | **4** | **0** | **2** | **4** | **0.71** |

*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. Compounds shown in boldface were submitted under Contract DAMD17-88-C-8001.

[a]No data sheet received.

The results of those dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates evaluated in the initial oral pretreatment efficacy screen have been disappointing (Table 7). Although three of the five compounds passed this initial screen, all had MEDs of 1/4 their respective $LD_{50}$s. We are especially interested in the oral pretreatment test results for PRE-086 and -083, but we have received no data at the time of this writing.

Unlike the case with the 1-[(1-arylcycloalkyl)methyl]amines, derivatives of the acyclic amines diethylamine and dimethylamine appear to provide the most efficacious dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates. Similar to the case with 1-[(1-arylcycloalkyl)methyl]amines, however, quaternization does not produce a uniform effect. For example, while the quaternary analog of PRE-078, PRE-086, is clearly more effective than PRE-078 as a prophylactic agent, the pretreatment efficacy of PRE-090, the quaternary analog of PRE-083, is compromised by this modification.

Under Contract DAMD17-85-C-5148 we observed that the typical bis-quaternary bis(heteroaryl)alkane is relatively toxic, quite effective against GD in the initial IM pretreatment efficacy screen, and far less effective in the initial oral pretreatment efficacy screen. True to this pattern, three of the four bis-quaternary bis(heteroaryl)alkanes submitted are very effective in the initial IM pretreatment efficacy screen (Table 8), all with

IM MEDs of 1/16 their respective $LD_{50}$s. Two of the compounds are effective at both 15 and 60 min; PRE-123, the most promising lead, has an MED of 1/64 its $LD_{50}$ at both time points. PRE-126 is also effective at both pretreatment times but with an MED of 1/16 its $LD_{50}$. Also true to form, PRE-123 is far less effective as an orally administered pretreatment. Although its MED of 1/16 $LD_{50}$ looks good, it is effective only at the 60-min pretreatment time.

Table 8*

INITIAL IM AND ORAL PRETREATMENT EFFICACY OF BIS-QUATERNARY BIS(HETEROARYL)ALKANES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE


| SRI Code No. | Amine | R | n | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-123** | **Pyridine** | **-$CH_2OCH_2Ph$** | **4** | **0.15** | **6** | **5** | **0** | **6** | **10** | **5** | **0.002** |
| **PRE-125** | **Pyridine** | **-$CH_2OCH_2Ph$** | **2** | **0.17** | **1** | **2** | **2** | **1** | **4** | **9** | **0.01** |
| **PRE-126** | **Imidazole** | **-$CH_2OCH_2Ph$** | **6** | **0.14** | **3** | **7** | **9** | **0** | **5** | **8** | **0.01** |
| | | | | Oral $LD_{50}$ (mmol/kg) | 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | |
| **PRE-123** | **Pyridine** | **-$CH_2OCH_2Ph$** | **4** | **0.59** | **0** | **0** | **2** | **2** | **4** | **5** | **0.04** |

*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. Compounds shown in boldface were submitted under Contract DAMD17-88-C-8001.

As revealed by their activity in the initial IM pretreatment efficacy screens, the bis-quaternary bis(heteroaryl)alkanes look very promising as pretreatments against GD poisoning. Because the compounds are clearly effective once they have gained access to the system, their disappointing performance in the initial oral pretreatment screen must be due to their inability to reach the requisite site of action. Two factors that might hinder their access are the potential instability of the aminal moiety to gastric conditions, resulting in cleavage of the quaternizing groups and destruction of the pretreatment molecule, or poor absorption of the bis-quaternary compound from the intestinal tract. The first factor can be directly addressed by quaternizing the bis(heteroaryl)alkanes with groups that provide a

more stable pretreatment compound. The poor absorption might potentially be addressed by the design of pro-drug versions of the bis-quaternary bis(heteroaryl)alkanes, (i.e., drugs that can conveniently penetrate from the gut and then be converted to the active bis-quaternary species).

## PCP Receptor-Binding Affinity (In Vitro)

An issue raised early in our investigation of the 1-[(1-arylcycloalkyl)methyl]amines as potential pretreatment drugs was the possibility that these compounds might induce undesirable PCP-like behavioral effects. We interpreted available structure-activity relationship (SAR) data of PCP (1-(1-phenylcyclohexyl)piperidine) and its analogs to indicate that the structural difference between the 1-[(1-arylcycloalkyl)methyl]amines and PCP would be enough to eliminate or substantially attenuate any PCP receptor-mediated behavioral effects. Because the PCP receptor affinity of 1-[(1-arylcycloalkyl)methyl]-amines had never been determined, nor had their ability to produce PCP-like behavioral effects, we had no published evidence to corroborate our initial position. We therefore arranged to have the PCP receptor affinities of the 1-[(1-arylcycloalkyl)methyl]amines determined, as well as those of several 1-(2-arylcycloalkyl)amines and dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates.

There is an important mechanistic question underlying the potential for the 1-[(1-arylcycloalkyl)methyl]amines to produce PCP receptor-mediated behavioral effects. Is the efficacy of the 1-[(1-arylcycloalkyl)methyl]amines against GD a function of interactions with AChE, which result in inhibition of phosphonylation or retardation of the aging of phosphonylated AChE, or a result of their interaction with the PCP receptor?

Pretreatment with the anticonvulsant MK-801 has been reported to protect test animals against GD-induced seizures and convulsions and to increase their survival rate.[29] MK-801 is a potent N-methyl-D-aspartate (NMDA) receptor antagonist[30] that acts through occupation of the PCP site in the NMDA receptor channel, resulting in a noncompetitive steric blockade of the open channel.[31] That MK-801 is a potent and specific ligand for the PCP receptor has been demonstrated by its ability to inhibit the binding of [$^3$H]TCP,[32] its alteration of regional brain energy metabolism in a manner virtually indistinguishable from that of PCP,[33] and its inducement of PCP-like behavioral effects in pigeons, rats, and rhesus monkeys.[34]

Because PCP and some analogs exhibit anticonvulsant effects,[35] the mechanistic question becomes: Does the protection against GD poisoning provided by pretreatment

with 1-[(1-arylcycloalkyl)methyl]amines arise through interactions with AChE or from NMDA/PCP receptor-mediated anticonvulsant activity? If the ability of 1-[(1-aryl-cycloalkyl)methyl]amines' ability to protect against GD is mediated by the PCP receptor, it is unlikely that effective pretreatment compounds free of PCP-like behavioral effects can be found. If, however, their protective effects are mediated through inhibition of AChE activity or by any mechanism unrelated to the NMDA/PCP receptor complex, it should be possible to selectively enhance prophylactic efficacy against GD while concurrently eliminating PCP-like behavioral effects.

As expected, the 1-(2-arylcycloalkyl)amines and dialkylaminoalkyl 1-phenylcyclo-alkane-1-carboxylates were completely inactive in the PCP assay. Some 1-[(1-arylcyclo-alkyl)methyl]amines do exhibit binding to the PCP receptor but with affinities lower than those of PCP. More important, there appears to be no correlation between the PCP receptor affinity and the pretreatment efficacy of the 1-[(1-arylcycloalkyl)methyl]amines.

Affinity for the PCP receptor was determined by the candidate compound's ability to displace [$^3$H]TCP from the PCP receptor in guinea pig brain membranes.* $IC_{50}$s, the concentration required to displace 50% of the specific [$^3$H]TCP binding, were calculated for all compounds tested. $IC_{50}$ data for all 1-[(1-arylcycloalkyl)methyl]amines tested are listed in Appendix D.

A number of 1-[(1-arylcycloalkyl)methyl]amines exhibit an affinity for the PCP receptor and also passed the initial IM pretreatment efficacy screen. For example, the 1-[(1-arylcycloalkyl)methyl]amine binding to the PCP receptor with the highest affinity, PRE-031 ($IC_{50}$ = 433 nM), also passed the initial IM pretreatment efficacy screen (Table 9). As a comparison, the $IC_{50}$ of PRE-031 is almost twice that of PCP ($IC_{50}$ = 230 nM).** Examination of all the binding and survival data, however, leads us to conclude that the two activities are not linked.

$IC_{50}$s similar to that of PRE-031 were determined for PRE-030, -035, and -056 ($IC_{50}$ = 547, 507, and 717 nM, respectively), but all failed the initial IM pretreatment efficacy screen against GD and hence have no potential in this regard. Clearly, therefore, affinity for the PCP receptor alone is insufficient to impart significant pretreatment efficacy against GD. Conversely, PRE-029, -067 and -071 all show significant activity in both the

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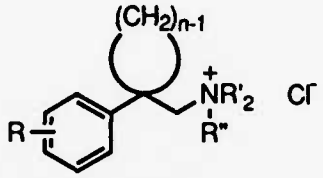
* PCP receptor affinities were determined by Drs. Tsung-Ping Su and Edward J. Cone of the National Institute on Drug Abuse's Addiction Research Center, Baltimore, Maryland.

**The $IC_{50}$ of PCP in this assay was originally estimated to be 100 nM based on the initial binding data, and this value was presented in the USAMRAA Contract DAMD17-88-C-5148 Annual Report and at the USAMRDC 1989 Medical Defense Bioscience Review. A more rigorous calculation incorporating subsequent binding data yielded the current value of 230 nM.

initial IM and oral pretreatment efficacy screens, and all are inactive (i.e., $IC_{50}$ > 10,000 nM) in the PCP receptor assay. Thus it appears that PCP receptor occupation is not a major contributor to the pretreatment efficacy of the 1-[(1-arylcycloalkyl)methyl]amines' against GD. In those compounds that exhibit both properties, however, we cannot rule out some contribution to pretreatment efficacy by PCP receptor occupation.

Table 9*

$IC_{50}$ VALUES AT THE PCP RECEPTOR AND INITIAL IM PRETREATMENT EFFICACY AGAINST 2 x $LD_{50}$ GD OF SELECTED 1-[(1-ARYLCYCLOALKYL)METHYL]AMINES




| SRI Code No. | $NR'_2$ | R | R" | n | $IC_{50}$ (nM) | Survivors 15 min. 1/64 | 15 min. 1/16 | 15 min. 1/4 | 60 min. 1/64 | 60 min. 1/16 | 60 min. 1/4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PCP | - | - | - | - | 230 | Not determined | | | | | |
| PRE-031 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 6 | 433 | 0 | 4 | 5 | 0 | 3 | 5 |
| PRE-030 | Pyrrolidine | 3-$OCH_3$ | H | 6 | 547 | Fail | | | | | |
| PRE-035 | Pyrrolidine | 3-Cl | $CH_3$ | 6 | 507 | Fail[a] | | | | | |
| PRE-056 | $N(CH_3)_2$ | 3-$OCH_3$ | $CH_3$ | 6 | 717 | Fail | | | | | |
| PRE-029 | Pyrrolidine | 3-OH | $CH_3$ | 6 | >10000 | 0 | 0 | 8 | 0 | 0 | 5 |
| PRE-067 | Pyrrolidine | 3-OH | H | 5 | >10000 | 1 | 7 | 8 | 1 | 1 | 6 |
| PRE-071 | Morpholine | 3-$OCH_3$ | $CH_3$ | 5 | >10000 | 3 | 7 | 1 | 0 | 1 | 7 |

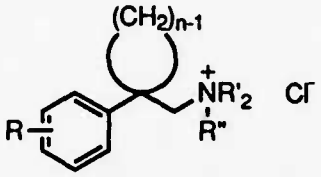
*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. $IC_{50}$s determined against [$^3$H]-TCP.
[a]Evaluated as oral pretreatment; administered at doses equal to 1/16, 1/8, and 1/4 the $LD_{50}$.

We interpret these data to demonstrate that the pretreatment efficacy of the 1-[(1-arylcycloalkyl)methyl]amines is separate from their affinity for the PCP receptor and the corresponding risk of PCP-like behavioral effects. We believe, therefore, that it will be possible to synthesize 1-[(1-arylcycloalkyl)methyl]amines that are effective drugs for pretreatment of GD poisoning and that pose no risk for producing PCP receptor-mediated performance decrements. Actually, the risk of PCP-like behavioral effects is probably minimal even with the 1-[(1-arylcycloalkyl)methyl]amines that do show affinity for the PCP receptor. Without exception, the compounds that were effective against GD and

whose $IC_{50}$s at the PCP receptor were less than five times that of PCP (i.e., $IC_{50}$ < 1250 nM) were quaternary salts (Table 10). As such, their penetration of the CNS and, therefore, access to the PCP receptor should be greatly curtailed.

Table 10*

1-[(1-ARYLCYCLOALKYL)METHYL]AMINES WITH $IC_{50}$ < 1250 nM AT THE PCP RECEPTOR AND PASSING THE INITIAL IM PRETREATMENT EFFICACY SCREEN AGAINST 2 x $LD_{50}$ GD




| SRI Code No. | $NR'_2$ | R | R" | n | $IC_{50}$ (nM) | Survivors 15 min. 1/64 | 15 min. 1/16 | 15 min. 1/4 | 60 min. 1/64 | 60 min. 1/16 | 60 min. 1/4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-031 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 6 | 433 | 0 | 4 | 5 | 0 | 3 | 5 |
| PRE-039 | Piperidine | 3-Cl | $CH_3$ | 6 | 817 | 2 | 3 | 6 | 0 | 1 | 2 |
| PRE-064 | Piperidine | 3-$OCH_3$ | $CH_3$ | 5 | 834 | 2 | 3 | 5 | 1 | 3 | 2 |
| PRE-046[a] | Piperidine | 3-$0CH_3$ | $CH_3$ | 6 | 865 | 1 | 8 | 6 | 1 | 1 | 7 |
| PRE-022[b] | Pyrrolidine | H | $CH_3$ | 6 | 957 | 5 | 6 | 3 | 2 | 3 | 3 |
| PRE-041 | Piperidine | H | $CH_3$ | 5 | 1039 | 0 | 1 | 6 | 1 | 7 | 9 |
| PRE-062 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 5 | 1115 | 1 | 4 | 10 | 0 | 2 | 2 |

*Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), before GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. $IC_{50}$s determined against [$^3$H]-TCP.

[a]Evaluated as oral pretreatment; administered 30 or 120 min before GD challenge.

[b]Evaluated as oral pretreatment; administered 30 or 120 min before GD challenge, at doses equal to 1/16, 1/8 and 1/4 the $LD_{50}$.

# IV CONCLUSIONS

Under the present contract we submitted 84 compounds for evaluation as potential pretreatments for poisoning by the chemical warfare agent GD. By structural family, these compounds included; 45 1-[(1-arylcycloalkyl)methyl]amines, 29 dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates, 6 dialkylaminoalkyl-4,5-dihydro-2(3H)-furanones, and 4 bis-quaternary bis(heteroaryl)alkanes. With the exception of the dialkylaminoalkyl-4,5-dihydro-2(3H)-furanones, which have yet to be evaluated, all structural families provided candidates that looked promising in the MRDC's initial pretreatment efficacy screen against GD in the mouse.

To conform to the MRDC's new priorities for OP pretreatment compound development, as outlined at the 1989 Medical Defense Bioscience Review, only quaternary compounds were submitted during the final three-month period of this contract. The charged nature of these quaternary compounds should greatly curtail their penetration of the CNS and hence reduce their risk of inducing centrally mediated performance decrements.

One important conclusion of this research was that the protective efficacy of the 1-[(1-arylcycloalkyl)methyl]amines is not a function of PCP receptor affinity; these two properties do not appear to be linked. In spite of our findings, the fear that these compounds may produce PCP receptor-mediated behavioral effects will probably prevent further investigation of this family of compounds.

Although we have provided evidence that their protective mechanism does not involve PCP receptor interactions, we still cannot be certain how the 1-[(1-arylcycloalkyl)-methyl]amines provide pretreatment protection against GD. Possible mechanisms include inhibition of AChE phosphonylation or inhibition of aging of GD-inhibited AChE through competitive/noncompetitive inhibition of AChE and blockade of muscarinic or nicotinic cholinergic receptors. Without further in vitro testing, however, we are unable to determine which, if any, of these mechanisms are playing a role in the pretreatment efficacy of the 1-[(1-arylcycloalkyl)methyl]amines.

We identified the dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates as a new family of potential pretreatments to GD poisoning. In addition, they were also inactive in the PCP receptor-binding assay. Structurally related to caramiphen hydrochloride (parpanit), an anticholinergic, several compounds from this family looked extremely

promising in the initial IM pretreatment efficacy screen. The results of the initial oral screens were not so promising, however, perhaps indicating a problem with absorption from the gut or hydrolytic lability. The anticholinergic activity of the dialkylaminoalkyl 1-phenylcycloalkane-1-carboxylates almost certainly contributes to their protective efficacy against GD. However, as in the case of the 1-[(1-arylcycloalkyl)methyl]amines, without in vitro tests we are unable to unambiguously determine their protective mechanism.

Although only four bis-quaternary bis(heteroaryl)alkanes were submitted, three of them looked extremely promising in the initial IM pretreatment efficacy screen against GD. However, as we observed for this series under a previous contract, they were not nearly as effective when administered orally. Again, this disparity may be indicative of a problem with absorption from the gut or hydrolytic lability. In fact, hindered absorption would be even more likely for the doubly charged bis-quaternary bis(heteroaryl)alkanes. As is true for the other compound families, without in vitro testing we are unable to unambiguously identify the protective mechanism of the bis-quaternary bis(heteroaryl)alkanes.

We had proposed that the dialkylaminoalkyl-4,5-dihydro-2(3H)-furanones, lactone-containing ACh analogs, would be superior to acyclic carbamate pretreatment drugs. Because the molecules will acylate the AChE active site serine hydroxyl in a ring-opening reaction, there will be more opportunity for structural modification of the pretreatment molecule to affect its duration of protection. We submitted six compounds from this family, but the results of their initial pretreatment efficacy screens against GD were not received in time for inclusion in this report. We are therefore unable to comment on their potential.

Overall, we are satisfied with the outcome of our work on this contract. We identified potentially valuable leads in each of the families of compounds we investigated. The data we developed that show no correlation between the pretreatment efficacy and PCP receptor affinity of the 1-[(1-arylcycloalkyl)methyl]amines are a valuable discovery in our attempts to understand the mechanisms involved in pretreatment protection against OP poisoning. We are confident that we are moving in a direction that will eventually yield safe and effective pretreatments against the OP chemical warfare agent GD.

# V EXPERIMENTAL DETAILS

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates EM-360 or EM-390 spectrometer; chemical shifts are reported in parts per million (δ) from an internal tetramethylsilane standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (IR) spectra were obtained on a Perkin-Elmer Model 1420 spectrophotometer. Melting points were determined on a Fisher-Johns or Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed by Desert Analytics Organic Microanalysis, Tucson, AZ 85717.

Metallation reactions were conducted in oven-dried apparatus under positive pressure of dry nitrogen or argon. Analytical thin-layer chromatography (TLC) was performed on Analtech Uniplate silica gel GF (scored 10 x 20 cm, 250 μm). Flash column chromatography was performed on silica gel reagent (230-400 mesh) obtained from American Scientific Products.

## 2-Phenylmethylcyclohexanones

**General Procedure.** Cyclohexanone (1 mol) is dissolved in benzene (2 L). Pyrrolidine (1.5 mol) is added and the solution refluxed, with water collecting in a Dean-Stark trap, for 4-6 h. The solvent and excess pyrrolidine are then removed under reduced pressure. The resulting ene-amine is dissolved in dry 1,4-dioxane, and the appropriately substituted benzyl chloride (1.1 mol) added; the solution is refluxed for 6 h. Water (200 mL) is added; the solution is refluxed for an additional 2 h, and the solvents are then removed under reduced pressure. The crude product is extracted into dichloromethane (2 x 500 mL), and the combined organic layers are washed with 5% aqueous HCl (2 x 500 mL), 5% aqueous $Na_2CO_3$ (500 mL), and saturated aqueous NaCl (500 mL). The organic layer is then dried over $MgSO_4$, and the solvents are removed under reduced pressure. The product is then vacuum-distilled.

**2-Phenylmethylcyclohexanone.** The distilled yield was 115 g (61%) as a clear, colorless oil: bp 140-150 °C (1.0 mmHg); $^1H$ NMR ($CDCl_3$) δ 7.27 (s, 5H, ArH), 3.20 (m, 1H, CH), 2.80-1.00 (br m, 10H, cyclic-$CH_2$).

**2-[(3-Methoxyphenyl)methyl]cyclohexanone.** The distilled yield was 137 g (52%) as a clear, colorless oil: bp 150-170 °C (1.0 mmHg); $^1$H NMR ($CDCl_3$) δ 7.75-6.58 (br m, 4H, ArH), 4.89 (s, 3H, $OCH_3$), 3.60-3.05 (br m, 1H, CH), 2.85-1.10 (br m, 10H, $CH_2$).

## 1-[(2-(Phenylmethyl)cycloalkyl]amines

**General Procedure.** The substituted 2-phenylmethylcyclohexanone (214 mmol) and an amine (273 mmol) are dissolved in benzene (650 mL), and the solution is refluxed rapidly for 3 h while water is collected in a Dean-Stark trap; the solvents are removed under reduced pressure. The resulting oil is dissolved in chilled methanol (800 mL); $NaBH_4$ (224 mmol) is added, and the solution is stirred for 16 h. Next, the solution is acidified with 5% aqueous HCl until the pH is less than 2 and the methanol is removed under reduced pressure. The oily residue is poured into 1 N aqueous KOH and extracted with $CH_2Cl_2$ (6 x 250 mL), the combined extracts are dried over $Na_2SO_4$ and the solvents removed under reduced pressure. Vacuum distillation provides the title compounds, typically as viscous oils.

**1-[(2-Phenylmethyl)cyclohexyl]pyrrolidine.** The distilled yield was 28 g (69%) as a viscous, amber-colored oil: bp 160-170 °C (1.0 mmHg); $^1$H NMR ($CDCl_3$) δ 7.28 (s, 5H, ArH), 2.85 (m, 1H, NCH), 2.63 (m, 6H, $CH_2$), 2.25 (m, 1H, CH), 2.15-1-15 (br m, 12H, $CH_2$).

**1-[(2-(3-Methoxyphenyl)methyl])cyclohexyl]pyrrolidine.** The distilled yield was 40.1 g (67%) as a viscous, amber-colored oil: bp 165-170 °C (1.0 mmHg); $^1$H NMR ($CDCl_3$) δ 7.55-7.24 (m, 1H, ArH), 7.15-6.73 (m, 3H, ArH), 3.19 (s, 3H, $OCH_3$), 3.30-1.00 (br m, 20H, CH & $CH_2$).

## Arylcycloalkanecarbonitriles

**General Procedure.** Sodium hydride (60% dispersion in mineral oil; 2.2 mol) is washed several times with hexane and suspended in THF (2.75 L), which is then brought to reflux under Ar(g). A mixture of dibromoalkane (1.05 mol) and a substituted benzyl cyanide (1.0 mol) is added dropwise to the refluxing THF solution over 5 h. Stirring is continued at reflux for 16 h. Excess hydride is then decomposed by the cautious addition of water, and the THF solution is decanted and evaporated to yield a cloudy, brown, amorphous solid. The solid is dissolved in hexanes or dichloromethane (800 mL), washed with water (3 x 1 L), dried over $Na_2SO_4$, and clarified by being passed through a bed of

diatomaceous earth (Celite); the solvents are then removed at reduced pressure. The resulting oil is vacuum-distilled to provide the desired product.

**1-Phenylcyclopentanecarbonitrile.** The distilled yield was 88.64 g (52%) as a clear, colorless oil: bp 90-100 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 7.44 (m, 5H, ArH), 2.66-1.86 (m, 8H, cyclic-$CH_2$).

**1-(3-Methoxyphenyl)cyclopentanecarbonitrile.** The distilled yield was 168 g (83%) as a clear, colorless oil: bp 124-128 °C (0.50 mmHg); $^1$H NMR ($CDCl_3$) δ 7.20 (m, 4H, ArH), 3.87 (s, 3H, $OCH_3$), 2.67-2.03 (br m, 8H, cyclic-$CH_2$).

**1-Phenylcyclohexanecarbonitrile.** The distilled yield was 160 g (80%) as a clear, colorless oil: bp 98-105 °C (0.40 mmHg); $^1$H NMR ($CDCl_3$) δ 7.5 (m, 5H, ArH), 1.9 (br m, 10H, cyclic-$CH_2$).

**1-(3-Methoxyphenyl)cyclohexanecarbonitrile.** The distilled yield was 63.0 g (88%) as a clear, viscous, light yellow oil: bp 110-120 °C (0.07 mmHg); $^1$H NMR ($CDCl_3$) δ 6.99 (m, 4H, ArH), 3.84 (s, 3H, $OCH_3$), 1.78 (m, 10H, cyclic-$CH_2$).

**1-(4-Methylphenyl)cyclohexanecarbonitrile.** The distilled yield was 100.5 g (73%) as a clear, colorless oil: bp 185-120 °C (0.40 mmHg); $^1$H NMR ($CDCl_3$) δ 7.32 (m, 4H, ArH), 2.36 (s, 3H, $CH_3$), 2.33-1.22 (br m, 10H, cyclic-$CH_2$).

**1-(3,4-Dimethoxyphenyl)cyclohexanecarbonitrile.** The distilled yield was 100.5 g (73%) as an oil that crystallized upon cooling: bp 156-160 °C (0.48 mmHg); mp 68-69 °C; $^1$H NMR ($CDCl_3$) δ 6.98 (m, 3H, ArH), 3.94 (d, 6H, $OCH_3$), 2.31-1.61 (br m, 10H, cyclic-$CH_2$).

**1-(2-Thienyl)cyclohexanecarbonitrile.** The distilled yield was 61.0 g (79%) as a clear, colorless oil: bp 105-110 °C (0.10 mmHg); $^1$H NMR ($CDCl_3$) δ 7.08 (m, 3H, ArH), 2.70-2.15 (br m, 10H, cyclic-$CH_2$).

**1-(1-Naphthyl)cyclohexanecarbonitrile.** The distilled yield was 109.8 g (73%) as a colorless liquid that solidified upon standing: bp 190-200 °C (0.7 mmHg); $^1$H NMR ($CDCl_3$) δ 8.80-8.26 (br m, 1H, ArH), 8.05-7.05 (br m, 6H, ArH), 2.80-2.34 (br m, 2H, cyclic-$CH_2$), 2.16-1.60 (br m, 8H, cyclic-$CH_2$).

**2-Ethyl-2-phenylbutanitrile.** The distilled yield was 51.7 g (70%) as a clear, colorless oil: bp 84-85 °C (0.50 mmHg); $^1$H NMR ($CDCl_3$) δ 7.35 (s, 5H, ArH), 2.01 (q, 4H, $CH_2$), 0.93 (t, 6H, $CH_3$).

## Arylcycloalkylcarbaldehydes

**General Procedure.** The arylcycloalkanecarbonitrile (161 mmol) is dissolved in hexane (500 mL), and DiBAL-H (195 mmol, 1.5 M in toluene) is added rapidly dropwise. The reaction is then heated ($T_{Bath}$ = 61 °C) for 16 h. After the mixture has cooled, water (40 mL) and saturated aqueous $NH_4Cl$ (218 mL) are added, and the solution is stirred vigorously for 1-2 h. A 5% aqueous sulfuric acid solution (500 mL) is then added and the solution stirred vigorously overnight. The organic layer is separated and the aqueous layer extracted with dichloromethane (5 x 500 mL). The combined organic layers are dried over $Na_2SO_4$ and the solvents removed under reduced pressure. Vacuum distillation of the resultant oil provides the desired product.

**1-Formyl-1-phenylcyclopropane.** The distilled yield was 30.5 g (54%) as a clear, colorless oil: bp 105-110 °C (0.20 mmHg); $^1H$ NMR ($CDCl_3$) δ 9.26 (s, 1H, CHO), 7.29 (s, 5H, ArH), 1.52 (t, 2H, cyclic-$CH_2$), 1.40 (t, 2H, cyclic-$CH_2$).

**1-Formyl-1-phenylcyclopentane.** The distilled yield was 51.56 g (81%) as a clear, colorless oil: bp 72-86 °C (0.35 mmHg); $^1H$ NMR ($CDCl_3$) δ 9.51 (s, 1H, CHO), 7.33 (m, 5H, ArH), 1.69-1.53 (m, 8H, cyclic-$CH_2$).

**1-Formyl-1-(3-methoxyphenyl)cyclopentane.** The distilled yield was 130 g (76%) as a pale yellow oil: bp 118-122 °C (0.27 mmHg); $^1H$ NMR ($CDCl_3$) δ 9.52 (s, 1H, CHO), 7.36 (m, 1H, ArH), 6.91 (m, 3H, ArH), 3.86 (s, 3H, $OCH_3$), 2.67-1.55 (br m, 8H, cyclic-$CH_2$).

**1-Formyl-1-phenylcyclohexane.** The distilled yield was 26.6 g (87%) as a clear, colorless oil: bp 95-97 °C (0.45 mmHg); $^1H$ NMR ($CDCl_3$) δ 9.5 (s, 1H, CHO), 7.4 (m, 5H, ArH), 1.2-2.5 (m, 10H, cyclic-$CH_2$).

**1-Formyl-1-(3-methoxyphenyl)cyclohexane.** The distilled yield was 62.9 g (70%) as a clear, colorless oil: bp 132-135 °C (0.30 mmHg); $^1H$ NMR ($CDCl_3$) δ 9.48 (s, 1H, CHO), 7.01 (m, 4H, ArH), 3.80 (s, 3H, $OCH_3$), 2.54-1.29 (m, 10H, cyclic-$CH_2$).

**1-Formyl-1-(4-methylphenyl)cyclohexane.** The distilled yield was 159 g (87%) as a clear, yellow-colored oil: bp 120-148 °C (2.75 mmHg); $^1H$ NMR ($CDCl_3$) δ 9.49 (s, 1H, CHO), 7.25 (m, 4H, ArH), 2.34 (s, 3H, $CH_3$), 2.36-1.14 (br m, 10H, cyclic-$CH_2$).

**1-Formyl-1-(3,4-dimethoxyphenyl)cyclohexane.** The distilled yield was 73.7 g (77%) as a pale yellow oil: bp 142 °C (0.30 mmHg); $^1$H NMR ($CDCl_3$) δ 9.47 (s, 1H, CHO), 6.94 (m, 3H, ArH), 3.93 (s, 6H, $OCH_3$), 2.49-1.27 (br m, 10H, cyclic-$CH_2$).

**1-Formyl-1-(2-thienyl)cyclohexane.** The distilled yield was 40.2 g (65%) as a clear, colorless oil: bp 120-125 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 9.29 (s, 1H, CHO), 7.40-6.60 (br m, 3H, ArH), 3.49-2.84 (br m, 2H, cyclic-$CH_2$), 2.84-2.05 (br m, 8H, cyclic-$CH_2$).

**1-Formyl-1-(1-naphthyl)cyclohexane.** The crude aldehyde was recrystallized from hexanes/toluene. The recrystallized yield was 67.2 g (43%) as a white powder: mp 80-82 °C; $^1$H NMR ($CDCl_3$) δ 9.58 (s, 1H, CHO), 8.25-7.02 (m, 7H, ArH), 2.95-1.00 (br m, 10H, cyclic-$CH_2$).

**2-Ethyl-2-phenylbutanal.** The distilled yield was 43.8 g (83%) as a pale yellow oil: bp 84 °C (1.45 mmHg); $^1$H NMR ($CDCl_3$) δ 9.53 (s, 1H, CHO), 7.28 (m, 5H, ArH), 2.00 (q, 4H, $CH_2$), 1.75 (t, 6H, $CH_3$).

## 1-[(1-Arylcycloalkyl)methyl]amines

**General Procedure.** The arylcycloalkylcarbaldehyde (1.0 equiv.) and an amine (2 equiv.) are mixed together, and 98% formic acid (3 equiv.) is added cautiously, causing a great rise in temperature. The resulting solution is heated ($T_{Bath}$ = 155 °C) under Ar(g) for 1-5 days. After the mixture cools, it is poured into 1 N aqueous KOH (~ 4 mL per mmol of aldehyde), then extracted with dichloromethane (x 5). The combined organic layers are dried over $Na_2SO_4$ and the solvents removed under reduced pressure. The resultant oil is vacuum-distilled to provide the desired amine.

**1-[(1-Phenylcyclopropyl)methyl]pyrrolidine.** The distilled yield was 20.9 g (61%) as a clear, colorless liquid: bp 115-120 °C (0.7 mmHg); $^1$H NMR ($CDCl_3$) δ 7.35 (m, 5H, ArH), 3.69 (s, 2H, $CH_2$), 3.50 (m, 4H, cyclic-$CH_2$), 2.69 (m, 4H, cyclic-$CH_2$), 0.80 (m, 4H, cyclopropyl-H).

**1-[(1-Phenylcyclopropyl)methyl]piperidine.** The distilled yield was 24.8 g (75%) as a clear, colorless oil: bp 115-120 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 7.20 (m, 5H, ArH), 2.52 (s, 2H, $CH_2$), 2.40 (m, 4H, cyclic-$CH_2$), 1.42 (m, 6H, cyclic-$CH_2$), 0.80 (m, 4H, cyclic-$CH_2$).

**4-[(1-Phenylcyclopropyl)methyl]morpholine.** The distilled yield was 24.1 g (65%) as a clear, colorless liquid: bp 112-118 °C (0.7 mmHg); $^1$NMR ($CDCl_3$) δ 7.23 (m, 5H, ArH), 3.59 (m, 4H, cyclic-$CH_2$), 2.51 (s, 2H, $CH_2$), 2.40 (m, 4H, cyclic-$CH_2$), 0.75 (m, 4H, cyclopropyl-H).

**N-[(1-Phenylcyclopropyl)methyl]diethylamine.** The distilled yield was 22.9 g (73%) as a clear, colorless liquid: bp 100-105 °C (0.7 mmHg); $^1$NMR ($CDCl_3$) δ 7.30 (m, 5H, Ar-H), 2.65 (s, 2H, $CH_2$), 2.50 (q, 4H, $CH_2$), 0.85 (m, 10H, $CH_3$ & cyclopropyl-H).

**1-[(1-Phenylcyclopentyl)methyl)pyrrolidine.** The distilled yield was 35.7 g (90%) as a clear, colorless oil: bp 93-100 °C (0.17 mmHg); $^1$NMR ($CDCl_3$) δ 7.33 (m, 5H, ArH), 2.64 (s, 2H, $CH_2$), 2.32-1.40 (m, 16H, cyclic-$CH_2$).

**N-[(1-Phenylcyclopentyl)methyl)diethylamine.** The distilled yield was 29 g (85%) as a colorless liquid: bp 105-115 °C (1.0 mm Hg); $^1$H NMR ($CDCl_3$) δ 7.29 (m, 5H, ArH), 2.47 (s, 2H, $NCH_2$), 2.21 (q, 4H, $NCH_2$); 2.10-1.40 (br m, 8H, cyclic-$CH_2$), 0.80 (t, 6H, $CH_3$).

**1-[(1-(3-Methoxyphenyl)cyclopentyl)methyl]pyrrolidine.** The distilled yield was 35.48 g (87%) as a colorless, viscous oil: bp 125-127 °C (0.40 mmHg); $^1$H NMR ($CDCl_3$) δ 7.02 (br m, 4H, ArH), 3.84 (s, 3H, $OCH_3$), 2.68 (s, 2H, $CH_2$), 2.23, 1.73 (br m, 16H, cyclic-$CH_2$).

**1-[(1-(3-Methoxyphenyl)cyclopentyl)methyl]piperidine.** The distilled yield was 30.7 g (72%) as a pale yellow oil: bp 131-133 °C (0.50 mmHg); $^1$H NMR ($CDCl_3$) δ 7.00 (br m, 4H, ArH), 3.86 (s, 3H, $OCH_3$), 2.37 (s, 2H, $CH_2$), 2.18-1.35 (m, 18H, cyclic-$CH_2$).

**4-[(1-(3-Methoxyphenyl)cyclopentyl)methyl]morpholine.** The distilled yield was 35.3 g (87%) as a colorless oil: bp 154-156 °C (0.80 mmHg); $^1$H NMR ($CDCl_3$) δ 7.01 (br m, 4H, ArH), 3.88 (s, 3H, $OCH_3$), 3.58 (m, 4H, $OCH_2$), 2.44 (s, 2H, $CH_2$), 2.18-1.76 (br m, 12H, cyclic-$CH_2$).

**N-[(1-(3-Methoxyphenyl)cyclopentyl)methyl]dimethylamine.** The distilled yield was 27.51 g (67%) as a colorless oil: bp 112-114 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 7.02 (m, 4H, ArH), 3.84 (s, 3H, $OCH_3$), 2.46 (s, 2H, $CH_2$), 2.00 (s, 6H, $CH_3$), 2.05-1.68 (br m, 8H, cyclic-$CH_2$).

**1-[(1-Phenylcyclohexyl)methyl]pyrrolidine.** The distilled yield was 5.2 g (79%) as a clear, viscous oil: bp 111-116 °C (0.22 mmHg). On standing, the oil solidified

to a white, greasy solid: mp 43-45 °C; $^1$H NMR ($CDCl_3$) δ 7.45 (m, 5H, ArH), 2.60 (s, 2H, $CH_2$), 2.40-1.30 (m, 18H, cyclic-$CH_2$).

**1-[(1-Phenylcyclohexyl)methyl]piperidine.** The distilled yield was 15.5 g (60%) as a clear, viscous oil: bp 110-116 °C (0.35 mmHg); $^1$H NMR ($CDCl_3$) δ 7.42 (m, 5H, ArH), 2.22 (s, 2H, $CH_2$), 2.09 (m, 4H, cyclic-$CH_2$), 1.70-1.21 (m, 16H, cyclic-$CH_2$).

**N-[(1-Phenylcyclohexyl)methyl]diethylamine.** The distilled yield was 17.7 g (67%) as a clear, viscous oil: bp 96-98 °C (0.38 mmHg); $^1$H NMR ($CDCl_3$) δ 7.41 (m, 5H, ArH), 2.36 (s, 2H, $CH_2$), 2.24 (q, 4H, $CH_2$), 1.70-1.15 (m, 10H, cyclic-$CH_2$), 0.8[illegible] (t, 6H, $CH_3$).

**4-[(1-(3-Methoxyphenyl)cyclohexyl)methyl]morpholine.** The distilled yield was 52.0 g (77%) as a clear, colorless oil: bp 102-120 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 7.05 (m, 4H, ArH), 3.85 (s, 3H, $OCH_3$), 2.32 (s, 2H, $CH_2$), 3.56 (m, 4H, $OCH_2$), 2.14 (m, 4H, cyclic-$CH_2$), 1.48 (m, 10H, cyclic-$CH_2$).

**N-[(1-(3-Methoxyphenyl)cyclohexyl)methyl]dimethylamine.** The distilled yield was 45.4 g (86%) as a clear, colorless oil: bp 115-130 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 7.06 (m, 4H, ArH), 3.87 (s, 3H, )$CH_3$), 2.37 (s, 2H, $CH_2$), 2.00 (s, 6H, $CH_3$), 1.49 (br m, 10H, cyclic-$CH_2$).

**1-[(1-(4-Methylphenyl)cyclohexyl)methyl]piperidine.** The distilled yield was 25.0 g (75%) as a clear, colorless oil: bp 105-120 °C (0.30 mmHg); $^1$H NMR ($CDCl_3$) δ 7.29 (m, 4H, ArH), 2.34 (s, 3H, $CH_3$), 2.22 (s, 2H, $CH_2$), 2.14 (br m, 4H, cyclic-$CH_2$),1.43 (br m, 16H, cyclic-$CH_2$).

**1-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]pyrrolidine.** The recrystallized yield was 31.28 g (70%) as off-white needles: mp 75.5-77 °C; $^1$H NMR ($CDCl_3$) δ 6.82 (m, 3H, ArH), 3.88 (d, 6H, $OCH_3$), 2.52 (s, 2H, $CH_2$), 2.35-1.92, 1.90-1.28 (br m, 18H, cyclic-$CH_2$).

**1-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]piperidine.** The distilled yield was 25.2 g (55%) as a pale yellow oil: bp 159-165 °C (0.40 mmHg); $^1$H NMR ($CDCl_3$) δ 6.98 (m, 3H, ArH), 3.96 (d, 6H, $OCH_3$), 2.23 (s, 2H, $CH_2$), 2.13 (br m, 4H, cyclic-$CH_2$), 1.45 (br m, 16H, cyclic-$CH_2$).

**4-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]morpholine.** The recrystallized yield was 20.41 g (51%) as off-white cubic crystals: mp 83-84 °C (0.40

mmHg); $^1$H NMR ($CDCl_3$) δ 6.98 (m, 3H, ArH), 3.93 (d, 6H, $OCH_3$), 3.57 (m, 4H, $OCH_2$), 2.33 (s, 2H, $CH_2$), 2.14 (m, 4H, cyclic-$CH_2$), 1.49 (br m, 10H, cyclic-$CH_2$).

**N-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]dimethylamine.** The distilled yield was 24.84 g (69%) as a pale yellow oil: bp 150-151 °C (1.00 mmHg); $^1$H NMR ($CDCl_3$) δ 6.91 (m, 3H, ArH), 3.91 (s, 6H, $OCH_3$), 2.33 (s, 2H, $CH_2$), 2.00 (s, 6H, $NCH_3$), 2.22-1.25 (m, 10H, cyclic-$CH_2$).

**1-[(1-(2-Thienyl)cyclohexyl)methyl]pyrrolidine.** The distilled yield was 21.0 g (77%) as a clear, colorless oil: bp 126-130 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 7.25-6.74 (m, 3H, ArH), 2.56 (s, 2H, $CH_2$), 2.50-2.10 (br m, 4H, cyclic-$CH_2$), 2.10-1.05 (br m, 14H, cyclic-$CH_2$).

**1-[(1-(2-Thienyl)cyclohexyl)methyl]piperidine.** The distilled yield was 19.1 g (66%) as a clear, colorless oil: bp 120-125 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 7.32-6.60 (br m, 3H, ArH), 2.26 (s, 2H, $CH_2$), 2.13 (m, 6H, cyclic-$CH_2$), 1.90-1.01 (br m, 14H, cyclic-$CH_2$).

**4-[(1-(2-Thienyl)cyclohexyl)methyl]morpholine.** The distilled yield was 9.0 g (55%) as a clear, colorless oil: bp 120-130 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 7.30-6.55 (m, 3H, ArH), 3.53 (m, 4H, $OCH_2$), 2.31 (s, 2H, $CH_2$), 2.26 (m, 4H, cyclic-$CH_2$), 1.85-1.00 (br m, 10H, cyclic-$CH_2$).

**N-[(1-(2-Thienyl)cyclohexyl)methyl]diethylamine.** The distilled yield was 18.2 g (72%) as a clear, colorless oil: bp 110-125 °C (0.20 mmHg); $^1$H NMR ($CDCl_3$) δ 7.30-6.62 (br m, 3H, ArH), 2.60-1.05 (br m, 16H, $CH_2$ & cyclic-$CH_2$), 0.84 (t, 6H, $CH_3$).

**1-[(2-Ethyl-2-phenyl)butyl]pyrrolidine.** The distilled yield was 21.43 g (83%) as a clear, colorless oil: bp 118-119 °C (1.50 mmHg); $^1$H NMR ($CDCl_3$) δ 7.26 (m, 5H, ArH), 2.71 (s, 2H, $CH_2$), 2.22 (m, 4H, cyclic-$CH_2$), 1.81 (q, 4H, $CH_2$), 1.60 (m, 4H, cyclic-$CH_2$), 0.70 (t, 6H, $CH_3$).

**1-[(2-Ethyl-2-phenyl)butyl]piperidine.** The distilled yield was 9.05 g (27%) as a clear, colorless oil: bp 125 °C (1.25 mmHg); $^1$H NMR ($CDCl_3$) δ 7.28 (m, 5H, ArH), 2.43 (s, 2H, $CH_2$), 2.12 (m, 4H, cyclic-$CH_2$), 1.80 (q, 4H, $CH_2$), 1.32 (br m, 6H, cyclic-$CH_2$), 0.71 (t, 6H, $CH_3$).

**4-[(2-Ethyl-2-phenyl)butyl]morpholine.** The distilled yield was 10.8 g (51%) as a colorless oil: bp 115-125 °C (0.8 mmHg); $^1$H NMR ($CDCl_3$) δ 7.31 (m, 5H,

ArH), 3.53 (m, 4H, cyclic-$OCH_2$), 2.12 (m, 4H, cyclic-$CH_2$), 1.82 (q, 4H, $CH_2$), 0.73 (t, 6H, $CH_3$).

## 1-[(1-(Hydroxyphenyl)cycloalkyl)methyl]amines

**General Procedure.** The 1-[(1-(methoxyphenyl)cycloalkyl)methyl]amine is dissolved in $CH_2Cl_2$ (7 mL/mmol) and the solution cooled in an ice bath. $BBr_3$ (1.0 M in $CH_2Cl_2$) is transferred under Ar(g) to an addition funnel and added slowly dropwise. The reaction mixture is stirred at room temperature (RT) overnight. The solution is carefully neutralized with excess MeOH, and 1 N aqueous NaOH is added until the aqueous layer is basic (pH $\geq$ 8). The $CH_2Cl_2$ is separated and the aqueous solution extracted with $CH_2Cl_2$ until no product remains. The combined extracts are dried over $Na_2SO_4$ and the solvents removed under vacuum. The resulting solid residue is dissolved in ethyl acetate, chromatographed on flash silica, and recrystallized from $CH_2Cl_2$/hexane to provide the desired hydroxyphenyl compound as a crystalline solid.

**1-[(1-(3-Hydroxyphenyl)cyclopentyl)methyl]pyrrolidine.** The recrystallized yield was 7.40 g (41%) as an off-white crystalline solid: mp 142-144 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 8.08 (br s, 1H, OH), 7.38-6.62 (m, 4H, ArH), 2.88 (s, 2H, $CH_2$), 2.41 (m, 4H, cyclic-$CH_2$), 2.01-1.53 (m, 12H, cyclic-$CH_2$).

**N-[(1-(3-Hydroxyphenyl)cyclohexyl)methyl]dimethylamine.** The recrystallized yield was 14.7 g (63%) as an off-white, powdery solid: mp 118-120 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 7.61 (br s, 1H, OH), 7.05 (m, [redacted], ArH), 2.58 (s, 2H, $CH_2$), 2.09 (s, 6H, $CH_3$), 1.85-1.30 (br m, 10H, cyclic-$CH_2$).

## 1-[(1-(4-Nitrophenyl)cycloalkyl)methyl]amines

**General Procedure.** Nitric acid (90%) is cooled in a low-temperature bath, and the 1-[(1-phenylcycloalkyl)methyl]amine (62 mmol) is added over a 1-h period while the reaction temperature is maintained at -20 °C. After the addition, the reaction mixture is allowed to warm to 0 °C and stirred for an additional hour before being poured into ice $H_2O$ (500 mL). The amine salt is then extracted into $CHCl_3$ (3 x 100 mL), washed with aqueous NaCl, and neutralized by stirring with 1 N aqueous NaOH (200 mL). The organic layer is washed again with aqueous NaCl and dried over $MgSO_4$, and the solvents are removed under reduced pressure. The resulting yellow oil is purified by forming the HCl salt, which is isolated and recrystallized and then freeing the amine by treatment with aqueous NaOH.

**1-[(1-(4-Nitrophenyl)cyclopentyl)methyl]pyrrolidine.** The crude yield was 28.2 g (91%) as a yellow crystalline solid: mp 80-82 °C; $^1$H NMR ($CDCl_3$) δ 8.20 (d, 2H, ArH), 7.52 (d, 2H, ArH), 2.69 (s, 2H, $CH_2$), 2.50-1.39 (br m, 16H, cyclic-$CH_2$).

**N-[(1-(4-Nitrophenyl)cyclopentyl)methyl]diethylamine.** The crude yield was 20.2 g (67%) as a viscous oil: $^1$H NMR ($CDCl_3$) δ 8.15 (d, 2H, ArH), 7.46 (d, 2H, ArH), 2.51 (s, 2H, $CH_2$), 2.21 (q, 4H, $CH_2$), 2.00-1.45 (br m, 8H, cyclic-$CH_2$), 0.78 (t, 6H, $CH_3$).

**1-[(1-(4-Nitrophenyl)cyclohexyl)methyl]pyrrolidine.** The crude yield was 17.4 g (97%) as a yellow crystalline solid: mp 84-90 °C; $^1$H NMR ($CDCl_3$) δ 8.24 (d, 2H, ArH), 7.60 (d, 2H, ArH), 2.64 (s, 2H, $CH_2$), 2.26 (m, 6H, cyclic-$CH_2$), 2.00-1.05 (br m, 12H, cyclic-$CH_2$).

**1-[(1-(4-Nitrophenyl)cyclohexyl)methyl]piperidine.** The isolated yield was 28.5 g (93%) as a yellow solid, which was used without further purification: mp 64-69 °C; $^1$H NMR ($CDCl_3$) δ 8.15 (d, 2H, ArH), 7.52 (d, 2H, ArH), 2.28 (s, 2H, $CH_2$), 2.22-1.86 (br m, 6H, cyclic-$CH_2$), 1.85-1.02 (br m, 14H, cyclic-$CH_2$).

**N-[(1-(4-Nitrophenyl)cyclohexyl)methyl]diethylamine.** The isolated yield was 20.1 g (66%) as a yellow oil, which was used without further purification: $^1$H NMR ($CDCl_3$) δ 8.22 (m, 2H, ArH), 7.56 (m, 2H, ArH), 2.41 (s, 2H, $CH_2$), 2.28 (q, 4H, $CH_2$), 2.00-1.05 (br m, 10H, cyclic-$CH_2$), 0.78 (t, 6H, $CH_3$).

## 1-[(1-(1-Naphthyl)cycloalkyl)methyl]amine Hydrochlorides

**General Procedure.** The carboxaldehyde (1.0 equiv) and an amine (2.0 equiv) are mixed together, and 98% formic acid (3 equiv) is added cautiously, causing a great rise in temperature. The resulting solution is heated ($T_{Bath}$ = 155 °C) under Ar(g) for 3 weeks. After the mixture cools, it is poured into 1 N aqueous KOH (~ 4 mL per mmol of aldehyde) and extracted with dichloromethane (x 5). The combined organic layers are combined and dried over $MgSO_4$ and the solvents removed under reduced pressure. The resultant oil is heated to 120 °C under vacuum to remove starting materials and residual formamides. The residue is dissolved in ethyl acetate, and HCl(g) is bubbled through the solution to precipitate the HCl salt. The salt is then recrystallized twice from EtOH/EtOAc to give the pure product.

**1-[(1-(1-Naphthyl)cyclohexyl)methyl]pyrrolidine Hydrochloride (PRE-142).** The recrystallized yield was 15.3 g (20%) as a white crystalline solid: mp 230-235 °C; $^1$H NMR ($CDCl_3$) δ 10.90 (br s, 1H, NH), 8.26 (m, 1H, ArH), 7.76 (m, 3H, ArH), 7.46 (m, 3H, ArH), 4.41-0.80 (br m, 20H, $CH_2$ & cyclic-$CH_2$).

**N-[(1-(1-Naphthyl)cyclohexyl)methyl]diethylamine Hydrochloride (PRE-143).** The recrystallized yield was 4.8 g (16%) as a white crystalline solid: mp 164-165 °C; $^1$H NMR ($CDCl_3$) δ 10.49 (br s, 1H, NH), 8.31 (m, 1H, ArH), 7.88 (m, 3H, ArH), 7.50 (m, 3H, ArH), 4.31-0.45 (br m, 22H, $CH_2$, $CH_3$, & cyclic-$CH_2$).

**1-[(1-(1-Napthyl)cyclohexyl)methyl]piperidine Hydrochloride Hemi(ethyl acetate) Solvate (PRE-144).** The recrystallized yield was 7.7 g (22%) as a white crystalline solid: mp 115-118 °C: $^1$H NMR ($CDCl_3$) δ 10.73 (br s, 1H, NH), 8.35 (m, 1H, ArH), 7.84 (m, 3H, ArH), 7.50 (m, 3H, ArH), 4.11 (q, 1H, $CH_3CO_2C\underline{H}_2CH_3$), 3.90-3.30 (br m, 2H, $NCH_2$), 3.30-2.54 (br m, 4H, cyclic-$NCH_2$), 2.54-0.70 (br m, 16H, cyclic-$CH_2$), 2.02 (s, 1.5H, $C\underline{H}_3CO_2CH_2CH_3$), 1.22 (t, 1.5H, $CH_3CO_2CH_2C\underline{H}_3$).

## 1-Phenylcyclohexane-1-carboxylic Acid

1-Phenylcyclohexanecarbonitrile (48 g, 259 mmol) is added to a mixture of 2-hydroxyethyl ether (240 mL) and 40% aqueous KOH (300 mL), forming a heterogeneous solution. The resulting mixture is heated to reflux ($T_{Bath}$ = 150 °C) for 16 h. After cooling for 1 h, the now homogeneous solution is poured into $H_2O$ (2 L) and extracted with $Et_2O$ (x 4). The aqueous layer is acidified to pH 1 by addition of concentrated aqueous HCl and extracted with EtOAc (x 4). The combined EtOAc extracts are dried over $Na_2SO_4$ and the solvents removed under vacuum. Flash chromatography on silica gel and eluting with $CH_2Cl_2$, followed by recrystallization from EtOAc/hexane, provides 42.03 g (81%) of the desired acid as a yellowish-white, powdery solid: mp 121-123 °C; $^1$H NMR ($CDCl_3$) δ 10.97 (br s, 1H, $CO_2H$), 7.27 (m, 5H, ArH), 2.40 (br m, 2H, cyclic-$CH_2$), 1.59 (br m, 8H, cyclic-$CH_2$).

## Dialkylaminoalkyl 1-Phenylcycloalkane-1-carboxylate Hydrochlorides

**General Procedure.** A 1-phenylcycloalkane-1-carboxylic acid is dissolved in $SOCl_2$ (2.5 equiv.) and heated at reflux ($T_{Bath}$ = 70 °C) for 16 h. Excess $SOCl_2$ is removed under aspirator vacuum, and the resulting golden-yellow oil is flushed with Ar(g)

for 1 h. The crude semicrystalline oil is dissolved in $CH_2Cl_2$ (5 mL/g acid) containing $Et_3N$ (1.1 equiv), and the dialkylaminoethanol (1.04 equiv) is added slowly to avoid a sudden exotherm. Typically, a precipitate begins forming in the solution within 5-10 min. After the solution is stirred for 16 h at RT, it is diluted with $CH_2Cl_2$ (30 mL/g acid) and washed with 0.5 M aqueous KOH (x 1); the solvents are removed under reduced pressure. The resulting orange oil is flash-chromatographed on silica gel eluted with EtOAc. The running band is collected, freed of solvent, dissolved in $Et_2O$, and converted to the hydrochloride salt by bubbling HCl(g) through the solution. The precipitate is then collected and recrystallized from ethanol/ethyl acetate.

**2-Dimethylaminoethyl 1-Phenylcyclohexane-1-carboxylate Hydrochloride (PRE-078).** The recrystallized yield was 15.24 g (50%) as a white, powdery solid: mp 178-179.5 °C; $^1H$ NMR ($CDCl_3$) δ 7.32 (s, 5H, ArH), 4.60 (m, 2H, $OCH_2$), 3.15 (br m, 2H, $CH_2N$), 2.42 (m, 6H & 2H, $CH_3$ & cyclic-$CH_2$), 2.10-1.20 (br m, 8H, cyclic-$CH_2$).

**2-(1-Pyrrolidino)ethyl 1-Phenylcyclohexane-1-carboxylate Hydrochloride (PRE-079).** The recrystallized yield was 16.04 g (48%) as a tan flocculent crystalline solid: mp 166-167.5 °C; $^1H$ NMR ($CDCl_3$) δ 7.31 (s, 5H, ArH), 4.60 (m, 2H, $OCH_2$), 3.67-2.98 (br m, 4H, $CH_2N$ & cyclic-$CH_2$), 2.71-1.20 (br m, 16H, cyclic-$CH_2$).

**2-(1-Piperidino)ethyl 1-Phenylcyclohexane-1-carboxylate Hydrochloride (PRE-082).** The recrystallized yield was 5.30 g (40%) as a white crystalline solid: mp 200-202 °C; $^1H$ NMR ($CDCl_3$) δ 12.13 (s, 1H, NH), 7.36 (m, 5H, ArH), 4.61 (m, 2H, $OCH_2$), 3.09 (m, 4H, $CH_2$ & cyclic-$CH_2$), 2.80-0.80 (br m, 18H, cyclic-$CH_2$).

**2-Diethylaminoethyl 1-Phenylcyclohexane-1-carboxylate Hydrochloride (PRE-083).** The recrystallized yield was 5.40 g (41%) as a white crystalline solid: mp 160-162 °C; $^1H$ NMR ($CDCl_3$) δ 12.28 (s, 1H, NH), 7.32 (m, 5H, ArH), 4.58 (t, 2H, $OCH_2$), 3.18 (q, 2H, $CH_2$), 2.78 (m, 4H, $CH_2$), 2.78-1.33 (br m, 10H, cyclic-$CH_2$), 1.18 (t, 6H, $CH_3$).

**2-(4-Morpholino)ethyl 1-Phenylcyclohexane-1-carboxylate Hydrochloride (PRE-084).** The recrystallized yield was 9.30 g (30%) as a white crystalline solid: mp 184-186 °C; $^1H$ NMR ($CDCl_3$) δ 12.93 (s, 1H, NH), 7.37 (m, 5H, ArH), 4.69 (m, 2H, $OCH_2$), 3.92 (m, 4H, cyclic-$OCH_2$), 3.10 (m, 4H, $CH_2$ & cyclic-$CH_2$), 2.38 (m, 4H, cyclic-$CH_2$), 1.70 (t, 8H, cyclic-$CH_2$).

**2-(2-Pyridino)ethyl 1-Phenylcyclohexane-1-carboxylate Hydrochloride (PRE-085).** The recrystallized yield was 5.20 g (53%) as a white crystalline solid: mp 135-137 °C; $^1$H NMR ($CDCl_3$) δ 8.67 (d, 1H, ArH), 7.99 (m, 2H, ArH), 7.32 (s, 5H, ArH), 6.92 (t, 1H, ArH), 4.60 (t, 2H, $OCH_2$), 3.51 (t, 2H, $CH_2$), 2.30 (m, 2H, cyclic-$CH_2$), 1.90-0.95 (br m, 8H, cyclic-$CH_2$).

**2-(1-Piperidino)ethyl 1-Phenylcyclopentane-1-carboxylate Hydrochloride (PRE-134).** The recrystallized yield was 19.1 g (43%) as a white crystalline solid: mp 167-168 °C; $^1$H NMR ($CDCl_3$) δ 12.22 (br s, 1H, NH), 7.29 (s, 5H, ArH), 4.51 (t, 2H, $OCH_2$), 3.06 (m, 4H, cyclic-$CH_2$), 2.57 (m, 2H, $CH_2$), 2.35-1.30 (br m, 14H, cyclic-$CH_2$).

**2-(2-Pyridino)ethyl 1-Phenylcyclopentane-1-carboxylate Hydrochloride (PRE-135).** The recrystallized yield was 20.2 g (46%) as a white crystalline solid: mp 143-145 °C; $^1$H NMR ($CDCl_3$) δ 8.59 (m, 1H, ArH), 7.74 (m, 2H, ArH), 7.23 (s, 5H, ArH), 6.82 (m, 1H, ArH), 4.51 (t, 2H, $CH_2$), 3.46 (t, 2H, $CH_2$), 2.56 (m, 2H, $CH_2$), 2.20-1.46 (br m, 6H, cyclic-$CH_2$).

**2-(4-Morpholino)ethyl 1-Phenylcyclopentane-1-carboxylate Hydrochloride (PRE-136).** The recrystallized yield was 11.2 g (51%) as a white crystalline solid: mp 165-167 °C; $^1$H NMR ($CDCl_3$) δ 13.00 (br m, 1H, NH), 7.29 (s, 5H, ArH), 4.55 (m, 2H, $OCH_2$), 3.89 (m, 4H, cyclic-$OCH_2$), 3.08 (m, 4H, cyclic-$CH_2$), 2.85-1.40 (br m, 10H, $CH_2$ & cyclic-$CH_2$).

**2-(1-Pyrrolidino)ethyl 1-Phenylcyclopropane-1-carboxylate Hydrochloride (PRE-145).** The recrystallized yield was 14.9 g (42%) as a white, crystalline solid: mp 110-112 °C; $^1$H NMR ($CDCl_3$) δ 12.87 (br s, 1H, NH), 7.36 (m, 5H, ArH), 4.56 (m, 2H, $OCH_2$), 3.65-3.02 (br m, 4H, $CH_2$ & cyclic-$CH_2$), 2.70-1.74 (br m, 6H, cyclic-$CH_2$), 1.61 (m, 2H, cyclopropyl-$CH_2$), 1.29 (m, 2H, cyclopropyl-$CH_2$).

**2-(Dimethylamino)ethyl 1-Phenylcyclopropane-1-carboxylate Hydrochloride (PRE-146).** The recrystallized yield was 20.7 g (62%) as a white crystalline solid: mp 132-133 °C; $^1$H NMR ($CDCl_3$) δ 12.38 (br s, 1H, NH), 7.35 (m, 5H, ArH), 4.55 (m, 2H, $OCH_2$), 3.26 (m, 2H, $CH_2$), 2.58 (d, 6H, $CH_3$), 1.62 (m, 2H, cyclopropyl-$CH_2$), 1.28 (m, 2H, cyclopropyl-$CH_2$).

**2-(Diethylamino)ethyl 1-Phenylcylopropane-1-carboxylate Hydrochloride (PRE-147).** The recrystallized yield was 18.4 g (51%) as a white

crystalline solid: mp 126-128 °C; $^1$H NMR ($CDCl_3$) δ 12.38 (br s, 1H, NH), 7.38 (m, 5H, ArH), 4.59 (m, 2H, $OCH_2$), 3.21 (m, 2H, $CH_2$), 2.90 (m, 4H, $CH_2$), 1.65 (m, 2H, cyclopropyl-$CH_2$), 1.30 (m, 2H, cyclopropyl-$CH_2$), 1.20 (t, 6H, $CH_3$).

**2-(2-Pyridino)ethyl 1-Phenylcyclopropane-1-carboxylate Hydrochloride (PRE-148).** The recrystallized yield was 9.9 g (54%) as a white crystalline solid: mp 106-108 °C; $^1$H NMR ($CDCl_3$) δ 8.70 (d, 1H, PyrH), 8.30-7.66 (m, 2H, PyrH), 7.33 (s, 5H, ArH), 7.11 (d, 1H, PyrH), 4.50 (t, 2H, $OCH_2$), 3.49 (t, 2H, $CH_2$), 1.56 (m, 2H, cyclopropyl-$CH_2$), 1.20 (m, 2H, cyclopropyl-$CH_2$).

**2-(4-Morpholino)ethyl 1-Phenylcyclopropane-1-carboxylate Hydrochloride (PRE-149).** The recrystallized yield was 10.0 g (53%) as a white crystalline solid: mp 158-160 °C; $^1$H NMR ($CDCl_3$) δ 12.94 (br s, 1H, NH), 7.39 (m, 5H, ArH), 4.60 (m, 2H, $OCH_2$), 4.30-3.54 (br m, 4H, cyclic-$OCH_2$), 3.41-2.92 (br m, 4H, $NCH_2$ & cyclic-$NCH_2$), 2.86-2.30 (br m, 2H, cyclic-$NCH_2$), 1.60 (m, 2H, cyclopropyl-$CH_2$), 1.28 (m, 2H, cyclopropyl-$CH_2$).

**3-(Dimethylamino)propyl 1-Phenylcyclopropane-1-carboxylate Hydrochloride (PRE-150).** The recrystallized yield was 18.2 g (53%) as a white crystalline solid: mp 141-142 °C; $^1$H NMR ($CDCl_3$) δ 12.09 (br s, 1H, NH), 7.35 (m, 5H, ArH), 4.12 (t, 2H, $OCH_2$), 2.86 (m, 2H, $NCH_2$), 2.71 (d, 6H, $NCH_3$), 2.14 (m, 2H, $CH_2$), 1.59 (m, 2H, cyclopropyl-$CH_2$), 1.21 (m, 2H, cyclopropyl-$CH_2$).

## 3-Formyl-4,5-dihydro-2(3H)-furanone, Sodium Salt.

Sodium hydride (60% dispersion in mineral oil; 1.05 mol) is washed with hexanes, suspended in $Et_2O$ (1 L), and stirred under Ar(g). Immediately after the addition of ethanol (5 mL), a mixture of γ-butyrolactone and ethyl formate (1 mol each) is added by drops at a rate that maintains a gentle reflux. The mixture is then stirred at RT overnight. The solid salt is collected by filtration and washed with anhydrous $Et_2O$. The product is dried under vacuum and used as is in the subsequent reactions. The crude yield was 134 g (98%) of an off-white powder: mp 200-205 °C (dec.); $^1$H NMR (DMSO-$d_6$/$D_2O$) δ 8.55 (m, 1H, $CHO^-$), 4.09 (t, 2H, cyclic-$OCH_2$), 2.62 (t, 2H, cyclic-$CH_2$).

## 3-Dialkylaminomethyl-4,5-dihydro-2(3H)-furanones

**General Procedure.** 3-Formyl-4,5-dihydro-2(3H)-furanone, sodium salt (200 mmol), and the appropriate dialkylamine hydrochloride (400 mmol) are added to dimethoxyethane (400 mL) containing 3Å molecular sieves (25 g). Sodium cyanoboro-

hydride (200 mmol) is added, and the mixture is stirred overnight under Ar(g). The mixture is then filtered through Celite to remove the solids. The solids are washed with methanol (200 mL), and the combined filtrates are acidified with concentrated aqueous HCl (CAUTION: cyanide vapors). The mixture is then stirred overnight under a steady stream of Ar(g). The solvents are removed under vacuum, and the oily residue is taken up in water (100 mL) and washed with ethyl acetate (200 mL). The aqueous layer is made alkaline by saturating with $Na_2CO_3$ and then extracted with chloroform (4 x 200 mL). The chloroform layers are combined and dried with $MgSO_4$, and the solvents are removed under reduced pressure. The product is twice vacuum-distilled.

**3-(1-Pyrrolidino)methyl-4,5-dihydro-2(3H)-furanone.** The distilled yield was 19.4 g (57%) as a clear, colorless oil: bp 115-120 °C (0.8 mmHg); $^1$H NMR ($CDCl_3$) δ 4.31 (m, 2H, cyclic-$OCH_2$), 3.10-1.98 (br m, 9H, $NCH_2$, cyclic-$NCH_2$, cyclic-$CH_2$, & cyclic-CH), 1.95-1.51 (br m, 4H, cyclic-$CH_2$).

**3-(Dimethylamino)methyl-4,5-dihydro-2(3H)-furanone.** The distilled yield was 8.0 g (26%) as a clear, colorless oil: bp 85-87 °C (0.6 mmHg); $^1$H NMR ($CDCl_3$) δ 4.39 (m, 2H, cyclic-$OCH_2$), 3.25-2.00 (br m, 5H, $NCH_2$, cyclic-$CH_2$, & cyclic-CH), 2.30 (s, 6H, $CH_3$).

## 3-Dialkylaminoethyl-4,5-dihydro-2(3H)-furanones

**General Procedure.** Sodium hydride (60% dispersion in mineral oil; 0.4 mol) is washed with hexanes and suspended in THF (700 mL). Immediately following the addition of ethanol (1 mL), 3-acetyl-4,5-dihydro-2(3H)-furanone (0.4 mol) is added dropwise over 1 h. A solution of 2-dialkylaminoethyl chloride (0.4 mol, freshly prepared from the hydrochloride salt) is then added, and the mixture is refluxed overnight under Ar(g). After the addition of a small amount of ethanol to quench any residual NaH, the THF is removed under reduced pressure and the residue is taken up in anhydrous ethanol (250 mL). An additional 200 mL of ethanol, containing sodium (0.4 mol), is then added and the solution overnight. The solvent is removed and the mixture dissolved in $H_2O$ (150 mL) and acidified to pH 1 with aqueous HCl. The solution is then stirred at RT for 2 h. The nonbasic components are removed by extraction with ether (2 x 100 mL). The aqueous phase is made alkaline by saturation with $Na_2CO_3$ and extraction with chloroform (10 x 100 mL). The chloroform layers are combined and dried over $MgSO_4$ and the solvents removed under reduced pressure. The resulting oil is distilled twice to yield the pure product.

**3-[2-(1-Pyrrolidino)ethyl]-4,5-dihydro-2(3H)-furanone.** The distilled yield was 19.4 g (34%) as a clear, colorless oil: bp 125-130 °C (0.9 mmHg); $^1$H NMR ($CDCl_3$) δ 4.38 (m, 2H, cyclic-$OCH_2$), 3.10-1.50 (br m, 15H, $CH_2$, cyclic-$CH_2$, & cyclic-CH).

**3-[2-(1-Piperidino)ethyl-4,5-dihydro-2(3H)-furanone.** The distilled yield was 6 g (15%) as a clear, colorless oil: bp 130-135 °C (0.8 mmHg); $^1$H NMR ($CDCl_3$) δ 4.31 (m, 2H, cyclic-$OCH_2$), 2.72-1.90 (br m, 9H, $NCH_2$, cyclic-$NCH_2$, cyclic-$CH_2$, & cyclic-CH), 1.85-1.10 (br m, 8H, $CH_2$ & cyclic-$CH_2$).

**3-(2-Diethylamino)ethyl-4,5-dihydro-2(3H)-furanone.** The distilled yield was 26 g (35%) as a clear, colorless oil: bp 115-120 °C (0.7 mmHg); $^1$H NMR ($CDCl_3$) δ 4.32 (m, 2H, cyclic-$OCH_2$), 3.22-1.30 (br m, 5H, $CH_2$, cyclic-$CH_2$, & cyclic-CH), 2.80-2.30 (m, 6H $NCH_2$), 1.40 (t, 6H, $CH_3$).

## Hydrochloride Salts

**General Procedure.** The parent amine is dissolved in $Et_2O$ and HCl(g) is bubbled rapidly through the stirred solution. The resultant precipitate is filtered, washed with $Et_2O$, dried under vacuum, and recrystallized from EtOH/EtOAc.

**1-[(1-(3-Methoxyphenyl)cyclopentyl)methyl]piperidine Hydrochloride (PRE-063).** The recrystallized yield was 5.39 g (68%) as a powdery white solid: mp 175-176 °C; $^1$H NMR ($CDCl_3$) δ 7.38-6.82 (m, 4H, ArH), 3.90 (s, 3H, $OCH_3$), 3.32 (d, 2H, $CH_2$), 3.51-3.15 (br m, 2H, cyclic-$CH_2$), 2.55-1.48 (br m, 16H, cyclic-$CH_2$).

**4-[(1-(3-Methoxyphenyl)cyclopentyl)methyl]morpholine Hydrochloride (PRE-065).** The recrystallized yield was 6.74 g (73%) as a white, fluffy solid: mp 165-166 °C; $^1$H NMR ($CDCl_3$) δ 7.53-6.79 (m, 4H, ArH), 4.69-4.16 (m, 4H, cyclic-$OCH_2$), 3.92 (s, 3H, $OCH_3$), 3.42 (d, 2H, $CH_2$), 3.91-2.64 (m, 6H, cyclic-$CH_2$), 2.38-1.63 (m, 6H, cyclic-$CH_2$).

**N-[(1-(3-Methoxyphenyl)cyclopentyl)methyl]dimethylamine Hydrochloride (PRE-066).** The recrystallized yield was 7.31 g (79%) as a white, powdery solid: mp 185-186 °C; $^1$H NMR ($CDCl_3$) δ 7.53-6.78 (m, 4H, ArH), 3.91 (s, 3H, $OCH_3$), 3.40 (br s, 2H, $CH_2$), 2.58 (br s, 6H, $NCH_3$), 2.58-1.62 (br m, 8H, cyclic-$CH_2$).

**1-[(1-(3-Hydroxyphenyl)cyclopentyl)methyl]pyrrolidine Hydrochloride (PRE-067).** The recrystallized yield was 7.01 g (82%) as a white, crystalline solid: mp 144-145 °C; $^1$H NMR ($CDCl_3/CD_3OD$) δ 7.43-6.81 (m, 4H, ArH), 3.57 (s, 2H, $CH_2$), 3.65-2.70 (br m, 4H, cyclic-$CH_2$), 2.20-1.76 (m, 12H, cyclic-$CH_2$).

**1-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]piperidine Hydrochloride (PRE-068).** The recrystallized yield was 5.72 g (72%) as a white crystalline solid: mp 198-200 °C; $^1$H NMR ($CDCl_3$) δ 7.32-6.88 (m, 3H, ArH), 4.02 (d, 6H, $OCH_3$), 3.09 (br d, 4H, $CH_2$ & cyclic-$CH_2$), 2.95-1.25 (br m, 18H, cyclic-$CH_2$).

**1-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]pyrrolidine Hydrochloride (PRE-072).** The recrystallized yield was 9.28 g (83%) as fine white crystals: mp 229-230 °C; $^1$H NMR ($CDCl_3$/DMSO-$d_6$) δ 7.06 (m, 3H, ArH), 3.87 (d, 6H, $OCH_3$), 3.37-2.98 (m, 4H, $CH_2$ & cyclic-$CH_2$), 2.77-1.38 (m, 16H, cyclic-$CH_2$).

**N-[(1-(3-Hydroxyphenyl)cyclohexyl)methyl]dimethylamine Hydrochloride (PRE-073).** The recrystallized yield was 6.93 g (91%) as white cubic crystals: mp 172-173 °C; $^1$H NMR ($CDCl_3$/DMSO-$d_6$) δ 9.50 (s, 1H, ArOH), 6.92 (m, 4H, ArH), 3.35 (m, 2H, $CH_2$), 2.47 (d, 6H, $CH_3$), 2.20-1.25 (m, 10H, cyclic-$CH_2$).

**4-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]morpholine Hydrochloride (PRE-074).** The recrystallized yield was 9.15 g (77%) as a white, powdery solid: mp 223-224 °C; $^1$H NMR ($CDCl_3$) δ 7.05 (m, 3H, ArH), 4.75-3.47 (m, 4H, $OCH_2$), 3.96 (2 x s, 6H, $OCH_3$), 3.13 (br d, 2H, $CH_2$), 3.00-2.34 (m, 6H, cyclic-$CH_2$), 1.53 (br m, 8H, cyclic-$CH_2$).

**N-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]dimethylamine Hydrochloride (PRE-075).** The recrystallized yield was 9.11 g (76%) as a white, chunky solid: mp 199-200 °C; $^1$H NMR ($CDCl_3$) δ 7.02 (m, 3H, ArH), 3.97 (d, 6H, $OCH_3$), 3.13 (d, 2H, $CH_2$), 2.84-2.29 (br m, 2H, cyclic-$CH_2$), 2.48 (d, 6H, $NCH_3$), 1.53 (br m, 8H, cyclic-$CH_2$).

**1-[(2-Ethyl-2-phenyl)butyl]pyrrolidine Hydrochloride (PRE-076).** The recrystallized yield was 8.90 g (77%) as fine, white needles: mp 174-175 °C; $^1$H NMR ($CDCl_3$) δ 7.36 (m, 5H, ArH), 3.65-3.20 (br m, 2H, cyclic-$CH_2$), 3.32 (d, 2H, $CH_2$), 2.19 (br m, 10H, $CH_2$ & cyclic-$CH_2$), 0.83 (t, 6H, $CH_3$).

**1-[(2-Ethyl-2-phenyl)butyl]piperidine Hydrochloride (PRE-077).** The recrystallized yield was 9.60 g (93%) as fine white needles: mp 160-161 °C; $^1$H NMR ($CDCl_3$) δ 7.34 (m, 5H, ArH), 3.36-2.90 (br m, 2H, cyclic-$CH_2$), 3.23 (d, 2H, $CH_2$),

2.57-1.80 (m, 8H, $CH_2$ & cyclic-$CH_2$), 1.74-1.34 (m, 4H, cyclic-$CH_2$), 0.82 (t, 6H, $CH_3$).

**1-[(1-(2-Thienyl)cyclohexyl)methyl]piperidine Hydrochloride (PRE-088).** The recrystallized yield was 9.1 g (27%) as a white crystalline solid: mp 210-213 °C; $^1H$ NMR ($CDCl_3$) δ 10.85 (br s, 1H, NH), 7.40 (d, 1H, ArH), 7.27 (d, 1H, ArH), 6.98 (m, 1H, ArH), 3.30 (m, 2H, cyclic-$CH_2$), 3.10 (d, 2H, $CH_2$), 2.70-1.10 (br m, 18H, cyclic-$CH_2$).

**1-[(1-(2-Thienyl)cyclohexyl)methyl]pyrrolidine Hydrochloride (PRE-091).** The recrystallized yield was 9.1 g (89%) as a white crystalline solid: mp 193-195 °C; $^1H$ NMR ($CDCl_3$) δ 11.20 (br s, 1H, NH), 7.28 (m, 2H, ArH), 7.01 (m, 1H, ArH), 3.49 (m, 2H, cyclic-$CH_2$), 3.22 (d, 2H, $CH_2$), 2.74-1.18 (br m, 16H, cyclic-$CH_2$).

**N-[(1-(2-Thienyl)cyclohexyl)methyl]diethylamine Hydrochloride (PRE-092).** The recrystallized yield was 5.9 g (21%) as a white crystalline solid: mp 177-179 °C; $^1H$ NMR ($CDCl_3$) δ 10.52 (br s, 1H, NH), 7.54 (d, 1H, ArH), 7.27 (d, 1H, ArH), 7.02 (m, 1H, ArH), 3.03 (d, 2H, $CH_2$), 2.81 (m, 4H, $CH_2$), 2.65 (m, 2H, cyclic-$CH_2$), 2.00-1.48 (br m, 8H, $CH_2$), 1.31 (t, 6H, $CH_3$).

**4-[(1-(2-Thienyl)cyclohexyl)methyl]morpholine Hydrochloride (PRE-093).** The recrystallized yield was 3.9 g (22%) as a white crystalline solid: mp 220-235 °C (d); $^1H$ NMR ($CDCl_3$) δ 12.05 (br s, 1H, NH), 7.33 (m, 2H, ArH), 7.08 (m, 1H, ArH), 4.48 (m, 2H, cyclic-$CH_2$), 3.70 (m, 2H, cyclic-$CH_2$), 3.18 (d, 2H, $CH_2$), 3.00 (m, 2H, cyclic-$CH_2$), 2.90-2.30 (br m, 4H, cyclic-$CH_2$), 2.10-1.00 (br m, 8H, cyclic-$CH_2$).

**1-[(1-(4-Nitrophenyl)cyclohexyl)methyl]piperidine Hydrochloride (PRE-094).** The recrystallized yield was 8.5 g (76%) as a white crystalline solid: mp 228-230 °C; $^1H$ NMR ($CDCl_3$) δ 11.60-10.75 (br s, 1H, NH), 8.10 (m, 4H, ArH), 3.28 (d, 2H, $CH_2$), 3.55-2.90 (br m, 2H, cyclic-$CH_2$), 2.88-0.90 (br m, 18H, cyclic-$CH_2$).

**N-[(1-(4-Nitrophenyl)cyclohexyl)methyl]diethylamine Hydrochloride (PRE-095).** The recrystallized yield was 10.5 g (47%) as a white crystalline solid: mp 186-187 °C; $^1H$ NMR ($CDCl_3$) δ 11.12-10.48 (br s, 1H, NH), 8.14 (m, 4H, ArH), 3.15 (d, 2H, $CH_2$), 2.90 (m, 4H, $CH_2$), 2.71 (m, 2H, cyclic-$CH_2$), 2.22-1.05 (br m, 8H, cyclic-$CH_2$), 1.29 (t, 6H, $CH_3$).

**1-[(1-Phenylcyclopropyl)methyl]piperidine Hydrochloride (PRE-096).** The recrystallized yield was 6.4 g (60%) as a white crystalline solid: mp 181-183

°C; $^1$H NMR ($CDCl_3$) δ 12.00-11.08 (br m, 1H, NH), 7.41 (m, 5H, ArH), 3.44 (d, 2H, $CH_2$), 3.29 (m, 2H, cyclic-$CH_2$), 2.94-1.43 (br m, 8H, cyclic-$CH_2$), 1.28 (m, 4H, cyclic-$CH_2$).

**N-[(1-Phenylcyclopropyl)methyl]diethylamine Hydrochloride (PRE-097).** The recrystallized yield was 6.0 g (66%) as a white crystalline solid: mp 127-129 °C; $^1$H NMR ($CDCl_3$) δ 11.50 (br s, 1H, NH), 7.48 (m, 5H, ArH), 3.40 (d, 2H, $CH_2$), 3.01 (m, 4H, $CH_2$), 1.21 (m, 10H, $CH_3$ & cyclopropyl-$CH_2$).

**4-[(1-Phenylcyclopropyl)methyl]morpholine Hydrochloride (PRE-098).** The recrystallized yield was 5.6 g (44%) as a white crystalline solid: mp 175-177 °C; $^1$H NMR ($CDCl_3$) δ 12.20 (br m, 1H, NH), 7.41 (m, 5H, ArH), 4.60-3.63 (m, 4H, cyclic-0$CH_2$), 3.54 (d, 2H, $CH_2$), 3.37-2.40 (br m, 4H, cyclic-N$CH_2$), 1.30 (m, 4H, cyclopropyl-$CH_2$).

**1-[(1-(4-Nitrophenyl)cyclohexyl)methyl]pyrrolidine Hydrochloride Hemihydrate (PRE-129).** The recrystallized yield was 4.7 g (60%) as a white crystalline solid: mp 230-233 °C d; $^1$H NMR ($CDCl_3$) δ 11.60 (br s, 1H, NH), 8.30 (d, 2H, ArH), 7.80 (d, 2H, ArH), 3.40 (m, 2H, cyclic-$CH_2$), 3.27 (d, 2H, $CH_2$), 2.90-1.00 (br, m, 16H, cyclic-$CH_2$).

**1-[(1-(4-Nitrophenyl)cyclopentyl)methyl]pyrrolidine Hydrochloride (PRE-137).** The recrystallized yield was 8.1 g (72%) as a white crystalline solid: mp 222-226 °C (dec); $^1$H NMR ($CDCl_3$) δ 11.58 (br s, 1H, NH), 8.21 (d, 2H, ArH), 7.72 (d, 2H, ArH), 3.46 (m, 4H, $CH_2$ & cyclic-$CH_2$), 2.90-1.50 (br m, 14H, cyclic-$CH_2$).

**N-[(1-(4-Nitrophenyl)cyclopentyl)methyl]diethylamine Hydrochloride (PRE-139).** The recrystallized yield was 7.0 g (77%) as a white crystalline solid: mp 156-158 °C; $^1$H NMR ($CDCl_3$) δ 10.94 (br s, 1H, NH), 8.27 (d, 2H, ArH), 7.85 (d, 2H, ArH), 3.40 (d, 2H, $CH_2$), 2.92 (m, 4H, $CH_2$), 2.35 (m, 4H, cyclic-$CH_2$), 1.85 (m, 4H, cyclic-$CH_2$), 1.30 (t, 6H, $CH_3$).

**4-[(2-Ethyl-2-phenyl)butyl]morpholine Hydrochloride (PRE-140).** The recrystallized yield was 7.0 g (63%) as a white crystalline solid: mp 186-188 °C; $^1$H NMR ($CDCl_3$) δ 11.82 (br s, 1H, NH), 7.41 (m, 5H, ArH), 4.41 (m, 2H, cyclic-$OCH_2$), 3.59 (m, 2H, cyclic-$OCH_2$), 3.27 (d, 2H, $CH_2$), 3.10-2.40 (br m, 4H, cyclic-$CH_2$), 2.06 (m, 4H, $CH_2$), 0.82 (t, 6H, $CH_3$).

**3-(Dimethylaminomethyl)-4,5-dihydro-2(3H)-furanone Hydrochloride (PRE-151).** The recrystallized yield was 5.9 g (58%) as a white

crystalline solid: mp 196-197 °C; $^1$H NMR (DMSO-$d_6$/$D_2O$) δ 4.31 (m, 2H, cyclic-$OCH_2$), 3.69-3.18 (m, 3H, $NCH_2$ & cyclic-CH), 2.87 (s, 6H, $NCH_3$), 2.19 (m, 2H, cyclic-$CH_2$).

**3-[2-(1-Piperidino)ethyl]-4,5-dihydro-2(3H)-furanone Hydrochloride (PRE-152).** The recrystallized yield was 5.2 g (74%) as a white crystalline solid: mp 202-203 °C; $^1$H NMR ($CDCl_3$/–DMSO-$d_6$) δ 4.27 (m, 2H, cyclic-$OCH_2$), 3.72-1.26 (br m, 17H, $CH_2$, cyclic-$CH_2$, & cyclic-CH).

**3-[2-(1-Pyrrolidino)ethyl]-4,5-dihydro-2(3H)-furanone Hydrochloride (PRE-153).** The recrystallized yield was 5.1 g (61%) as a white crystalline solid: mp 140-142 °C; $^1$H NMR ($CDCl_3$/DMSO-$d_6$) δ 12.14 (br s, 1H, NH), 4.32 (m, 2H, $OCH_2$), 3.76 (m, 2H, $NCH_2$), 3.36 (m, 2H, $NCH_2$), 2.99 (m, 2H, $NCH_2$), 2.83-2.42 (br m, 1H, cyclic-CH), 2.42-1.86 (br m, 8H, $CH_2$ & cyclic-$CH_2$).

**3-(2-Diethylaminoethyl)-4,5-dihydro-2(3H)-furanone Hydrochloride (PRE-154).** The recrystallized yield was 11.5 g (96%) as a white crystalline solid: mp 116-118 °C; $^1$H NMR ($CDCl_3$) δ 11.80 (s, 1H, NH), 4.35 (m, 2H, $OCH_2$), 3.70-3.01 (br m, 6H, $NCH_2$), 3.01-1.70 (br m, 5H, $CH_2$, cyclic-$CH_2$, & cyclic-CH), 1.41 (t, 6H, $CH_3$).

**3-[(1-Pyrrolidino)methyl]-4,5-dihydro-2(3H)-furanone Hydrochloride (PRE-155).** The recrystallized yield was 8.6 g (89%) as a white crystalline solid: mp 190-191°C; $^1$H NMR ($D_2O$) δ 4.42 (m, 2H, cyclic-$OCH_2$), 4.02-2.95 (br m, 7H, $NCH_2$, cyclic-$NCH_2$, & cyclic-CH), 2.88-2.40 (m, 2H, cyclic-$CH_2$), 2.37-1.55 (br m, 4H, cyclic-$CH_2$).

**1-[(1-Phenylcyclopropyl)methyl]pyrrolidine Hydrochloride (PRE-156).** The recrystallized yield was 5.1 g (54%) as a white crystalline solid: mp 162-164 °C; $^1$H NMR ($CDCl_3$) δ 11.81 (br s, 1H, NH), 7.36 (m, 5H, ArH), 3.50 (m, 2H, cyclic-$NCH_2$), 3.42 (d, 2H, $NCH_2$), 2.68 (m, 2H, cyclic-$NCH_2$), 1.99 (m, 4H, cyclic-$CH_2$), 1.21 (m, 4H, cyclopropyl-$CH_2$).

## Methochloride Salts

**General Procedure.** The parent amine is dissolved in $Et_2O$/MeCN (2/1), and methyl iodide (5 equiv) is added. The flask is flushed with Ar(g) and sealed, and the solution is stirred in the dark at RT for 2-10 days. Once TLC indicates that the reaction is complete, the solvents are removed at reduced pressure. The resultant solid is suspended

in $Et_2O$, filtered, washed with $Et_2O$, and dried under vacuum to provide the crude methoiodide salt. This salt is dissolved in deionized water and passed through an excess of chloride exchange resin (Amberlite IRA-400, styrene-DVB). Removal of the water at reduced pressure provides the crude methochloride salt, which is recrystallized from EtOH/EtOAc.

**1-[(1-(3-Methoxyphenyl)cyclopentyl)methyl]piperidine Methochloride (PRE-064).** The recrystallized yield was 6.87 g (72%) as a white, powdery solid: mp 233-234 °C (dec); $^1H$ NMR ($CDCl_3$) δ 7.60-6.85 (m, 4H, ArH), 4.33 (s, 2H, $CH_2$), 3.93 (s, 3H, $OCH_3$), 3.52 (br m, 4H, cyclic-$CH_2$), 3.09 (s, 3H, $CH_3$), 2.54-1.45 (br m, 14H, cyclic-$CH_2$).

**1-[(1-(4-Methylphenyl)cyclohexyl)methyl]piperidine Methochloride Ethanolate (PRE-069).** The recrystallized yield was 5.08 g (43%) as a white, fluffy solid: mp 211 °C (dec; bubbles at 161 °C); $^1H$ NMR ($CDCl_3$) δ 7.27 (br q, 4H, ArH), 3.90 (s, 2H, $CH_2$), 3.74 (q, 2H, EtOH), 3.43 (br m, 4H, $NCH_2$), 2.97 (s, 3H, $NCH_3$), 2.32 (s, 3H, $ArCH_3$), 2.78, 1.98-1.37 (m, 16H, cyclic-$CH_2$), 1.23 (t, 3H, EtOH).

**4-[(1-(3-Methoxyphenyl)cyclohexyl)methyl]morpholine Methochloride (PRE-070).** The recrystallized yield was 5.38 g (37%) as a white, fluffy solid: mp 258-262 °C (dec); $^1H$ NMR ($CDCl_3$) δ 7.13 (br m, 4H, ArH), 4.06-3.71 (br m, 9H, $CH_3$, $CH_2$, & cyclic-$CH_2$), 3.52-3.00 (br m, 4H, cyclic-$CH_2$), 3.05 (s, 3H, $NCH_3$), 2.72-1.08 (br m, 10H, cyclic-$CH_2$).

**4-[(1-(3-Methoxyphenyl)cyclopentyl)methyl]morpholine Methochloride (PRE-071).** The recrystallized yield was 7.70 g (80%) as white, powdery crystals: mp 225-226 °C (dec); $^1H$ NMR ($CDCl_3$) δ 7.17 (m, 4H, ArH), 4.50 (s, 2H, cyclic-$CH_2$), 3.84 (s, 7H, $OCH_3$ & cyclic-$CH_2$), 3.50 (br m, 4H, $CH_2$ & cyclic-$CH_2$), 3.38 (s, 3H, $NCH_3$), 2.72-1.33 (br m, 8H, cyclic-$CH_2$).

**1-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]pyrrolidine Methochloride Ethanolate (PRE-080).** The recrystallized yield was 8.53 g (73%) as a white, powdery solid: mp 223-224 °C (dec); $^1H$ NMR ($CDCl_3$) δ 7.03 (m, 3H, ArH), 4.10 (m, 2H, cyclic-$CH_2$), 4.01, 3.95 (2 x s, 6H, $OCH_3$), 3.73 (q, 2H, EtOH), 3.48 (br m, 4H, $CH_2$ & cyclic-$CH_2$), 2.87 (br s, 3H, $CH_3$), 2.44, 2.07, 1.51 (3 x m, 14H, cyclic-$CH_2$), 1.22 (t, 3H, EtOH).

**1-[(1-(3,4-Dimethoxyphenyl)cyclohexyl)methyl]piperidine Methochloride Hemihydrate (PRE-081).** The recrystallized yield was 7.39 g (64%) as an off-white, powdery solid: mp 224-225 °C (dec); $^1H$ NMR ($CDCl_3$) δ 6.98 (m, 3H,

ArH), 4.02 (m, 2H, cyclic-$CH_2$), 4.03, 3.97 (2 x s, 6H, $OCH_3$), 3.44 (br m, 4H, $CH_2$ & cyclic-$CH_2$), 2.94 (br s, 3H, $NCH_3$), 3.02-2.32 (m, 4H, cyclic-$CH_2$), 1.98-1.40 (br m, 12H, cyclic-$CH_2$).

**2-Dimethylaminoethyl 1-Phenylcyclohexane-1-carboxylate Methochloride Hemihydrate (PRE-086).** The recrystallized yield was 10.22 g (79%) as a white crystalline solid: mp 162-163.5 °C (anneals at 145 °C); $^1$H NMR ($CDCl_3$) δ 7.33 (s, 5H, ArH), 4.52 (br m, 2H, $CH_2$), 3.90 (br m, 2H, $CH_2$), 3.25 (s, 1H, $H_2O$), 3.12 (s, 9H, $CH_3$), 2.69-1.28 (br m, 10H, cyclic-$CH_2$).

**2-(1-Pyrrolidino)ethyl 1-Phenylcyclohexane-1-carboxylate Methochloride (PRE-087).** The recrystallized yield was 10.91 g (71%) as a white crystalline solid: mp 173-174.5 °C; $^1$H NMR ($CDCl_3$) δ 7.34 (s, 5H, ArH), 4.53 (m, 2H, $CH_2$), 4.08 (m, 2H, $CH_2$), 3.48 (m, 4H, cyclic-$CH_2$), 3.00 (s, 3H, $CH_3$), 2.61-1.35 (br m, 14H, cyclic-$CH_2$).

**2-(1-Piperidino)ethyl 1-Phenylcyclohexane-1-carboxylate Methochloride (PRE-089).** The recrystallized yield was 7.7 g (83%) as a white crystalline solid: mp 174-176 °C; $^1$H NMR ($CDCl_3$) δ 7.34 (s, 5H, ArH), 4.50 (m, 2H, $CH_2$), 4.00 (m, 2H, $CH_2$), 3.36 (m, 4H, cyclic-$CH_2$), 3.09 (s, 3H, $CH_3$), 2.60-2.20 (br m, 2H, cyclic-$CH_2$), 2.10-0.90 (br m, 14H, cyclic-$CH_2$).

**2-(Diethylamino)ethyl 1-Phenylcyclohexane-1-carboxylate Methochloride (PRE-090).** The recrystallized yield was 8.3 g (59%) as a white crystalline solid: mp 131-133 °C; $^1$H NMR ($CDCl_3$) δ 7.33 (s, 5H, ArH), 4.50 (t, 2H, $CH_2$), 3.85 (t, 2H, $CH_2$), 3.28 (q, 4H, $CH_2$), 3.02 (s, 3H, $CH_3$), 2.60-2.10 (br m, 2H, cyclic-$CH_2$), 2.00-1.32 (br m, 8H, cyclic-$CH_2$), 1.15 (t, 6H, $CH_3$).

**N-[(1-Phenylcyclopropyl)methyl]diethylamine Methochloride (PRE-099).** The recrystallized yield was 7.4 g (42%) as a white crystalline solid: mp 168-170 °C; $^1$H NMR ($CDCl_3$) δ 7.46 (m, 5H, ArH), 4.11 (s, 2H, $CH_2$), 4.50 (q, 4H, $CH_2$), 3.19 (s, 3H, $CH_3$), 1.70-0.95 (m, 10H, $CH_3$ & cyclopropyl-$CH_2$).

**1-[(1-(2-Thienyl)cyclohexyl)methyl]pyrrolidine Methochloride Hemihydrate (PRE-127).** The recrystallized yield was 6.9 g (46%) as a white crystalline solid: mp 115-117 °C; $^1$H NMR ($CDCl_3$) δ 7.32 (m, 1H, ArH), 7.11 (m, 2H, ArH), 3.99 (s, 2H, $CH_2$), 3.90-3.25 (br m, 4H, cyclic-$CH_2$), 3.00 (s, 3H, $CH_3$), 2.80 (s, 1H, $H_2O$), 2.50-1.00 (br m, 14H, cyclic-$CH_2$).

**1-[(1-Phenylcyclopropyl)methyl]pyrrolidine Methochloride (PRE-128).** The recrystallized yield was 4.4 g (30%) as a white crystalline solid: mp 227-230 °C d; $^1$H NMR ($CDCl_3$) δ 7.38 (m, 5H, ArH), 4.21 (s, 2H, $CH_2$), 3.50 (m, 4H, cyclic-$CH_2$), 3.26 (s, 3H, $CH_3$), 2.11 (m, 4H, cyclic-$CH_2$), 1.38 (t, 2H, cyclopropyl-$CH_2$), 1.14 (t, 2H, cyclopropyl-$CH_2$).

**1-[1-(4-Nitrophenyl)cyclohexylmethyl]pyrrolidine Methochloride Monohydrate (PRE-130).** The recrystallized yield was 4.4 g (34%) as a white crystalline solid: mp 222-226 °C d; $^1$H NMR ($CDCl_3$) δ 8.30 (d, 2H, ArH), 7.95 (d, 2H, ArH), 4.36 (s, 2H, $CH_2$), 4.00-3.25 (br m, 4H, cyclic-$CH_2$), 2.86 (s, 3H, $CH_3$), 2.70-1.00 (br m, 14H, cyclic-$CH_2$).

**1-[(1-(2-Thienyl)cyclohexyl)methyl]piperidine Methochloride Hemiethanolate (PRE-131).** The recrystallized yield was 3.4 g (14%) as a white crystalline solid: mp 156-158 °C; $^1$H NMR ($CDCl_3$) δ 7.34 (m, 1H, ArH), 7.11 (m, 2H, ArH), 3.90 (s, 2H, $CH_2$), 3.47 (m, 4H, cyclic-$CH_2$), 3.12 (s, 3H, $CH_3$), 2.55-1.00 (br m, 16H, cyclic-$CH_2$).

**1-[(1-(4-Nitrophenyl)cyclohexyl)methyl]piperidine Methochloride Monohydrate (PRE-132).** The recrystallized yield was 7.7 g (39%) as a white crystalline solid mp 184-186 °C; $^1$H NMR ($CDCl_3$) δ 8.27 (d, 2H, ArH), 7.94 (d, 2H, ArH), 4.06 (s, 2H, $CH_2$), 3.35 (m, 4H, cyclic-$CH_2$), 3.23 (s, 3H, $CH_3$), 2.86 (s, 2H, $H_2O$), 2.70-2.20 (br m, 2H, cyclic-$CH_2$), 2.15-1.00 (br m, 14H, cyclic-$CH_2$).

**1-[(1-Phenylcyclopropyl)methyl]piperidine Methochloride Hemiethanolate (PRE-133).** The recrystallized yield was 8.2 g (39%) as a white crystalline solid: mp 228-232 °C d; $^1$H NMR ($CDCl_3$/DMSO-$d_6$) δ 7.40 (m, 5H, ArH), 5.50, q, 1H, $CH_3C\underline{H}_2OH$), 4.23 (t, 1/2 H, $CH_3CH_2O\underline{H}$), 3.92 (s, 2H, $CH_2$), 3.24 (m, 4H, cyclic-$CH_2$), 2.99 (s, 3H, $CH_3$), 1.90-1.40 (br m, 6H, cyclic-$CH_2$), 1.14 (m, 4H & 1.5H, cyclopropyl-$CH_2$ & $C\underline{H}_3CH_2OH$).

**1-[(1-(4-Nitrophenyl)cyclopentyl)methyl]pyrrolidine Methochloride (PRE-138).** The recrystallized yield was 7.7 g (45%) as a white crystalline solid: mp 208-212 °C (dec); $^1$H NMR (DMSO-$d_6$) δ 8.21 (d, 2H, ArH), 7.97 (d, 2H, ArH), 4.23 (s, 2H, $CH_2$), 3.49 (s, 2H, $H_2O$), 3.31 (m, 4H, cyclic-$CH_2$), 2.72 (s, 3H, $CH_3$), 2.35 (m, 2H, cyclic-$CH_2$), 2.25-1.15 (br m, 10H, cyclic-$CH_2$).

**2-(1-Piperidino)ethyl 1-Phenylcyclopentane-1-carboxylate Methochloride (PRE-141).** The recrystallized yield was 9.4 g (57%) as a white

crystalline solid: mp 176-178 °C; $^1$H NMR ($CDCl_3$) δ 7.27 (s, 5H, ArH), 4.48 (m, 2H, $CH_2$), 4.02 (m, 2H, $CH_2$), 3.38 (m, 4H, cyclic-$CH_2$), 3.10 (s, 3H, $CH_3$), 2.80-2.35 (br m, 2H cyclic $CH_2$), 2.25-1.40 (br m, 12H, cyclic-$CH_2$).

**N-[(1-(4-Nitrophenyl)cyclopentyl)methyl]diethylamine Methochloride 3/4 Hydrate (PRE-157).** The recrystallized yield was 9.1 g (65%) as a white crystalline solid: mp 182-192 °C (dec.); $^1$H NMR ($CDCl_3$/DMSO-$d_6$) δ 8.24 (d, 2H, ArH), 7.98 (d, 2H, ArH), 4.24 (s, 2H, $NCH_2$), 3.35 (s, 1.5H, $H_2O$), 3.31 (q, 4H, $NCH_2$), 2.98 (s, 3H, $NCH_3$), 2.68-1.00 (br m, 8H, cyclic-$CH_2$), 1.28 (t, 6H, $CH_3$).

**1-[(2-Ethyl-2-phenyl)butyl]piperidine Methochloride (PRE-158).** The recrystallized yield was 4.0 g (27%) as a white crystalline solid: mp 194-196 °C (dec.); $^1$H NMR ($CDCl_3$) δ 7.42 (m, 5H, ArH), 4.06 (s, 2H, $NCH_2$), 3.49 (m, 4H, cyclic-$NCH_2$), 2.99 (s, 3H, $NCH_3$), 2.01 (q, 4H, $CH_2$), 1.71 (m, 6H, cyclic-$CH_2$), 0.89 (t, 6H, $CH_3$).

**2-Dimethylaminoethyl 1-Phenylcyclopropane-1-carboxylate Methochloride (PRE-159).** The recrystallized yield was 8.8 g (62%) as a white crystalline solid: mp 162-164 °C; $^1$H NMR ($CDCl_3$) δ 7.32 (s, 5H, ArH), 4.50 (m, 2H, $OCH_2$), 4.00 (m, 2H, $NCH_2$), 3.22 (s, 9H, $CH_3$), 1.62 (m, 2H, cyclopropyl-$CH_2$), 1.31 (m, 2H, cyclopropyl-$CH_2$).

**3-Dimethylaminopropyl 1-Phenylcyclopropane-1-carboxylate Methochloride Hemihydrate (PRE-160).** The recrystallized yield was 6.6 g (50%) as a white crystalline solid: mp 131-133 °C; $^1$H NMR ($CDCl_3$) δ 7.29 (m, 5H, ArH), 4.09 (t, 2H, $OCH_2$), 3.50-2.95 (m, 2H, $NCH_2$), 3.22 (s, 9H, $CH_3$), 2.00 (m, 2H, $CH_2$), 1.59 (m, 2H, cyclopropyl-$CH_2$), 1.23 (m, 2H, cyclopropyl-$CH_2$).

**2-Dimethylaminoethyl 1-Phenylcyclopentane-1-carboxylate Methochloride (PRE-161).** The recrystallized yield was 7.2 g (45%) as a white crystalline solid: mp 182-184 °C; $^1$H NMR ($CDCl_3$) δ 7.28 (s, 5H, ArH), 4.43 (m, 2H, $OCH_2$), 3.41 (m, 2H, $NCH_2$), 3.13 (s, 9H, $CH_3$), 2.55 (m, 2H, cyclic-$CH_2$), 2.18-1.46 (br m, 6H, cyclic-$CH_2$).

**2-Diethylaminoethyl 1-Phenylcyclopentane-1-carboxylate Methochloride (PRE-162).** The recrystallized yield was 12.3 g (78%) as a white, crystalline solid: mp 102-104 °C; $^1$H NMR ($CDCl_3$) δ 7.29 (s, 5H, ArH), 4.46 (m, 2H, $OCH_2$), 3.84 (m, 2H, $NCH_2$), 3.31 (q, 4H, $NCH_2$), 3.02 (s, 3H, $NCH_3$), 2.75-2.30 (br m, 2H, cyclic-$CH_2$), 2.20-1.51 (br m, 6H, cyclic-$CH_2$), 1.18 (t, CH, $CH_3$).

**3-[2-(1-Piperidino)ethyl]-4,5-dihydro-2(3H)-furanone Methochloride (PRE-163).** The recrystallized yield was 6.8 g (36%) as a white crystalline solid: mp 160-162 °C; $^1$H NMR ($CDCl_3$) δ 4.60-3.45 (br m, 8H, cyclic-$OCH_2$, $NCH_2$, & cyclic-$NCH_2$), 3.35 (s, 3H, $NCH_3$), 3.03-1.50 (br m, 11H, $CH_2$, cyclic-$CH_2$, & cyclic-CH).

**3-Dimethylaminopropyl 1-Phenylcyclopentane-1-carboxylate Methochloride 1/4 Hydrate (PRE-164).** The recrystallized yield was 9.9 g (62%) as a white crystalline solid: mp 155-156 °C; $^1$H NMR ($CDCl_3$) δ 7.31 (m, 5H, ArH), 4.17 (t, 2H, $OCH_2$), 3.17 (s, 9H, $NCH_3$), 3.30-2.88 (m, 2H, $NCH_2$), 2.77-2.47 (br m, 2H, cyclic-$CH_2$), 2.18-1.50 (br m, 8H, $CH_2$ & cyclic-$CH_2$).

**N-(2-Ethyl-2-phenylbutyl)diethylamine Methochloride (PRE-165).** The recrystallized yield was 3.4 g (23%) as a white crystalline solid: mp 173-174 °C; $^1$H NMR ($CDCl_3$) δ 7.38 (m, 5H, ArH), 3.89 (s, 2H, $NCH_2$), 3.38 (q, 4H, $NCH_2$), 2.90 (s, 3H, $NCH_3$), 1.99 (q, 4H, $CH_2$), 1.24 (t, 6H, $CH_3$), 0.84 (t, 6H, $CH_3$).

**2-(1-Pyrrolidino)ethyl 1-Phenylcyclopropane-1-carboxylate Methochloride (PRE-166).** The recrystallized yield was 3.9 g (41%) as a white crystalline solid: mp 149-152 °C; $^1$H NMR ($CDCl_3$) δ 7.28 (m, 5H, ArH), 4.43 (m, 2H, $OCH_2$), 4.01 (m, 2H, $NCH_2$), 3.45 (m, 4H, cyclic-$NCH_2$), 3.06 (s, 3H, $NCH_3$), 2.00 (m, 4H, cyclic-$CH_2$), 1.61 (m, 2H, cyclopropyl-$CH_2$), 1.28 (m, 2H, cyclopropyl-$CH_2$).

**2-(1-Pyrrolidino)ethyl 1-Phenylcyclopentane-1-carboxylate Methochloride Hemihydrate (PRE-167).** The recrystallized yield was 10.9 g (80%) as a white crystalline solid: mp 149-152 °C; $^1$H NMR ($CDCl_3$) δ 7.29 (m, 5H, ArH), 4.44 (m, 2H, $OCH_2$), 4.00 (m, 2H, $NCH_2$), 3.43 (m, 4H, cyclic-$NCH_2$), 2.99 (s, 3H, $NCH_3$), 3.16-2.85 (m, 2H, cyclic-$CH_2$), 2.26-1.45 (br m, 10H, cyclic-$CH_2$).

**2-Diisopropylaminoethyl 1-Phenylcyclopentane-1-carboxylate Methochloride 1/4 Hydrate (PRE-168).** The recrystallized yield was 8.4 g (66%) as a white crystalline solid: mp 147-148 °C; $^1$H NMR ($CDCl_3$) δ 7.27 (s, 5H, ArH), 4.45 (m, 2H, $OCH_2$), 3.82 (m, 4H, $NCH_2$ & NCH), 2.78 (s, 3H, $NCH_3$), 2.72-2.30 (br m, 2H, cyclic-$CH_2$), 2.25-1.55 (br m, 6H, cyclic-$CH_2$), 1.30 (d, 12H, $CH_3$).

**3-Diethylaminopropyl 1-Phenylcyclopentane-1-carboxylate Methochloride Hemihydrate (PRE-169).** The recrystallized yield was 8.6 g (76%) as a white crystalline solid: mp 190-195 °C; $^1$H NMR ($CDCl_3$) δ 7.30 (m, 5H, ArH), 4.18 (t, 2H, $OCH_2$), 3.41 (q, 4H, $NCH_2$), 3.20-2.85 (m, 2H, $NCH_2$), 3.07 (s, 3H, $NCH_3$),

2.77-2.38 (m, 2H, cyclic-$CH_2$), 2.25-1.45 (br m, 8H, $CH_2$ & cyclic-$CH_2$), 1.15 (t, 6H, $CH_3$).

**1-[(2-Phenylmethyl)cyclohexyl]pyrrolidine Methochloride (PRE-201).** The recrystallized yield was 7.3 g (41%) as a white crystalline solid: mp 218-220 °C d; $^1H$ NMR ($CDCl_3$) δ 7.17 (s, 5H, ArH), 4.60-3.50 (br m, 5H, CH & cyclic-$CH_2$), 3.22 (s, 3H, $CH_3$), 2.84 (s, 2H, $CH_2$), 2.58-1.10 (br m, 13H, CH & cyclic-$CH_2$).

**1-[(2-[(3-Methoxyphenyl)methyl)cyclohexyl]pyrrolidine Methochloride (PRE-208).** The recrystallized yield was 10.0 g (47%) as a white crystalline solid: mp 200-202 °C; $^1H$ NMR ($CDCl_3$) δ 7.17 (m, 1H, ArH), 6.73 (m, 3H, ArH), 4.42-4.03 (br m, 1H, cyclic-NCH), 4.03-3.45 (br m, 4H, cyclic $NCH_2$), 3.80 (s, 3H, $OCH_3$), 3.23 (s, 3H, $NCH_3$), 3.10-2.52 (br m, 3H, $CH_2$ & cyclic-CH), 2.50-1.10 (br m, 12H, cyclic-$CH_2$).

## Bis(heteroaryl)alkanes

**1,4-Bis(4-pyridyl)butane.** A solution of 4-vinylpyridine (123 g, 1.2 mol) in t-butanol (110 g, 1.5 mol), is added to lithium metal (16.8 g, 2.4 mol) in THF (1 L) over 2 h. An ice bath is used to maintain the reaction temperature between 20° and 25 °C during the addition. The mixture is stirred at RT overnight. The THF is removed under reduced pressure, and the residue is dissolved in water (200 mL). The aqueous solution is extracted with $Et_2O$ (3 x 200 mL), the combined extracts dried over $MgSO_4$, and the solvents removed under reduced pressure. Vacuum distillation provides the product as a light amber colored-oil that crystallizes on standing: bp 155-160 C (0.5 mmHg); mp 117-119 °C; $^1H$ NMR ($CDCl_3$) δ 8.55 (m, 4H, ArH), 7.13 (m, 4H, ArH), 3.66 (m, 4H, $CH_2$), 2.68 (m, 4H, $CH_2$).

**Bis(imidazolyl)methane.** Imidazole (190 g, 2.8 mol) is dissolved in a mixture of dichloromethane (3 L) and 50% aqueous NaOH (1600 g) containing tetrabutyl-ammonium hydrogensulfate (38.5 g, 0.14 mol) as a phase transfer catalyst. The mixture is refluxed for 6 h, then cooled and allowed to stand overnight. Solids form upon cooling and are collected by filtration. The solvent layers are separated, and the aqueous layer is extracted with ethyl acetate. The combined organic layers are dried over $MgSO_4$ and the solvents removed to yield additional solid. The solids are combined and recrystallized from EtOH/EtOAc to yield a product that is still contaminated with a water-soluble impurity. The solids are taken up in a mixture of water and ethyl acetate (300 mL each) and the layers separated. The aqueous layer is extracted with more ethyl acetate (2 x 300 mL). The

organic layers are combined and dried over $MgSO_4$ and the solvents removed to give 60 g (29%) of the desired product as a white powder: mp 168-170 °C; $^1H$ NMR ($CDCl_3$) δ 7.78 (s, 2H, ArH), 7.15 (s, 2H, ArH), 7.05 (s, 2H, ArH), 6.18 (s, 2H, ArH).

**1,6-Bis(imidazolyl)hexane.** Imidazole (100 g, 1.47 mol) is dissolved in a mixture of $Et_2O$ (500 mL) and 50% aqueous NaOH (400 mL) containing tetrabutylammonium hydrogensulfate (19 g) as a phase transfer catalyst. 1,6-Dibromohexane (170.8 g, 0.70 mol) is then added dropwise with vigorous stirring, at a rate that maintains a gentle reflux. The reaction is then heated at reflux for an additional 4 h, then cooled overnight. The organic layers are separated and washed with water (3 x 200 mL) and salt brine (200 mL). The solvent is then removed and the product vacuum-distilled to yield 110 g (64%) as a colorless oil, which solidifies slowly on standing: bp 210-220 °C (0.1 mm Hg); $^1H$ NMR ($CDCl_3$) δ 7.62 (s, 2H, ArH), 7.13 (s, 2H, ArH), 6.93 (s, 2H, ArH), 3.91 (t, 4H, $CH_2$), 2.20-1.40 (br m, 4H, $CH_2$), 1.40-0.80 (br m, 4H, $CH_2$).

## Bis-Quaternary Bis(heteroaryl)alkanes

**General Procedure.** To a stirred solution of the bis(imidazolyl)alkane (28 mmol) in dry N,N-dimethylformamide (DMF; 50 mL) is added the chloromethylalkylether (63 mmol). The resulting mixture is stirred overnight at RT. The solid is collected and recrystallized from EtOH/$Et_2O$.

**1,4-Bis[4-(1-Phenylmethoxymethyl)pyridinium]butane Dichloride (PRE-123).** The recrystallized yield was 11.1 g (45%) as a white crystalline solid: mp 180-183 °C; $^1H$ NMR (DMSO-$d_6$/$D_2O$) δ 9.05 (d, 4H, ArH), 8.05 (d, 4H, ArH), 7.34 (s, 10H, ArH), 6.02 (s, 4H, $CH_2$), 4.76 (s, 4H, $CH_2$), 3.01 (br m, 4H, $CH_2$), 1.88 (br m, 4H, $CH_2$).

**Bis[1-(3-Phenylmethoxymethyl)imidazolium]methane Dichloride (PRE-124).** The recrystallized yield was 12.6 g (50%) as a white crystalline solid: mp 202-204 °C; $^1H$ NMR (DMSO-$d_6$/$D_2O$) δ 7.92 (m, 4H, ArH), 7.38 (s, 10H, ArH), 6.75 (s, 2H, $CH_2$), 5.80 (s, 4H, $CH_2$), 4.77 (s, 4H, $CH_2$).

**1,2-Bis[4-(1-Phenylmethoxymethyl)pyridinium]ethane Dichloride Hemihydrate (PRE-125).** The recrystallized yield was 10.6 g (37%) as a white crystalline solid: mp 140-142 °C; $^1H$ NMR (DMSO-$d_6$/$D_2O$) δ 9.94 (d, 4H, ArH), 8.05 (d, 4H, ArH), 7.37 (s, 10H, ArH), 8.02 (s, 4H, $CH_2$), 4.80 (s, 4H, $CH_2$), 3.44 (s, 4H, $CH_2$).

**1,6-Bis[1-(3-Phenylmethoxymethyl)imidazolium]hexane Dichloride (PRE-126).** The recrystallized yield was 8.2 g (40%) as a white, crystalline solid: mp 106-110 °C; $^1$H NMR (DMSO-$d_6$) δ 9.51 (m, 2H, ArH), 7.89 (m, 4H, ArH), 7.38 (br s, 10H, ArH), 5.81 (br s, 4H, $CH_2$), 4.71 (s, 4H, $ArCH_2$), 4.27 (t, 4H, $NCH_2$), 2.15-1.55 (br m, 4H, $CH_2$), 1.55-0.92 (br m, 4H, $CH_2$).

## Initial Pretreatment Efficacy Against GD (In Vivo)

The subject compounds were administered to mice either IM, 15 or 60 min before GD challenge, or orally, 30 or 120 minutes before GD challenge. Typical doses evaluated were 1/4, 1/16, and 1/64 the predetermined $LD_{50}$. As a negative reference pretreatment cell, saline was administered instead of the test compound. As a positive control for survival, pyridostigmine (0.10 mg/kg) was administered to a separate group of animals.

All pretreatment groups received atropine sulfate (11.2 mg/kg) and pralidoxime chloride (2-PAM, 25 mg/kg) intramuscularly exactly 10 seconds after GD challenge using a total dose volume of 0.5 mL/kg body weight. All animals were allocated to pretreatment cells in a randomized block design. The 24-hour survival rate of animals pretreated with each dose of the test compound was compared with that observed in the negative reference pretreatment cell. Differences in the survival rates were compared using Fisher's exact test ($p < 0.05$, $n = 10$). In this test, a survival rate difference of at least four is required to identify improved efficacy of the candidate over that observed with the reference pretreatment. In these experiments, survival of animals given either the negative reference pretreatment or the positive control pretreatment were within the 95% tolerance limits of the respective historical mean survival values (data not shown).

## PCP Receptor Binding Affinity (In Vitro)

Brains from male Hartley guinea pigs weighing 300-450 g were used in the study. Whole brain (including cerebellum) was dissected from guinea pig after carbon dioxide asphyxia. The brain was homogenized in 10 volumes (v/wet weight) of ice-cold 5 nM Tris-HCl (pH 7.4) using a polytron at a setting of 4 for 20 sec. The homogenates were diluted to double the volume with the same Tris buffer and centrifuged thereafter for 20 min at 20,000 x g at 4 °C. The pellets were then resuspended in ice-cold $H_2O$ (20 volumes) and allowed to stand at 4 °C for 10 min. The suspension was centrifuged at 20,000 x g at 4 °C for 30 min. The resulting pellets were finally suspended in 100 volumes (v/original wet tissue weight) of 5 nM Tris-HCl (pH 7.4). The homogenates were then homogenizer

(three strokes) with a glass-glass Dounce homogenized (Wheaton 40 mL, pestle B) before use. The homogenates were prepared fresh every day for each experiment.

In the binding assay for PCP receptors, 50 μL of [$^3$H]TCP (40 nM) was incubated with 2 mL of the brain homogenates with and without different concentrations of candidate compounds. In the meantime, a set of test tubes containing 0.1 mM (final concentration) nonradioactive PCP accompanied each assay to define the amount of "specific binding" (i.e., displaceable) of [$^3$H]TCP to PCP receptors. After incubation at 22 °C for 1 h, the radioactivity bound to homogenates was separated from the free by filtering the homogenates through a GF/C filter (double layer) using a Brandel cell harvester (48-channel) under reduced pressure. The trapped homogenates were then washed three times with 5 mL of ice-cold 5 mM Tris-HCl (pH 7.4) to remove extra unbound radioactivity. Before assay, the filters were presoaked in 0.5% polyethyleneimine to eliminate [$^3$H]TCP binding to the filter. The filters were then placed in liquid scintillation vials containing 5 mL of scintillation fluid. The radioactivity was measured with a liquid scintillation counter (Packard TriCarb). [$^3$H]TCP binding to PCP receptors (i.e., "specific binding") constituted about 90% of the total binding. Inhibitory potency of each compound was expressed as $IC_{50}$ (concentration needed to inhibit 50% of the specific [$^3$H]TCP binding to PCP receptors). $IC_{50}$s were calculated from dose-response curves plotted in a log-logit fashion, with the logit being

$$\log\left(\frac{\%\text{Inhibition}}{100 - \%\text{Inhibition}}\right)$$

The slope for each plot is taken as the Hill coefficient. Typically, a plot of at least four doses covering a 20%-80% inhibition range is constructed. In a straight competitive inhibition in which a drug is competing with a radioactive ligand for only a single population of binding sites, the Hill coefficient should be close to 1.0. Deviation from 1.0 suggests two possibilities: (1) more than one binding site is being examined or (2) the drug is not a competitive inhibitor to the receptor. Further experiments are then needed to confirm which is which.

Strictly speaking, the affinity of a drug for a receptor site should be measured by directly examining the binding of that drug (e.g., in the form of a radioactive compound) to receptors. However, the affinity can also be derived indirectly from the potency of that drug that inhibits the binding of another drug to the same receptor. Assuming a competitive inhibition, the Chang and Prusoff equation converts $IC_{50}$ into $K_i$:

$$K_i = \frac{IC_{50}}{1 + \left(\frac{[Drug]}{K_d}\right)}$$

where [Drug] is the concentration of labeled drug in the assay and $K_d$ is the affinity of the labeled drug for the receptor. $K_d$ of [$^3$H]TCP binding to the PCP receptor is 10 nM.

The experiments were performed in quadruplicate for each drug dose. At least three dose-response curves were obtained for each drug and $IC_{50}$s calculated (usually by McPherson's EBDA program). $K_i$s can thus be obtained.

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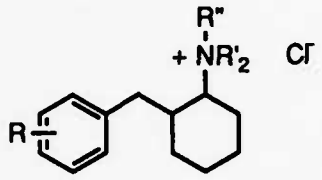
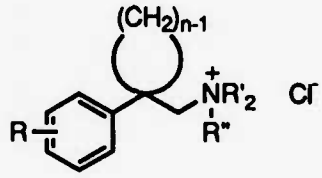
Appendix A

# COMPOUNDS SUBMITTED FOR IN VIVO EVALUATION

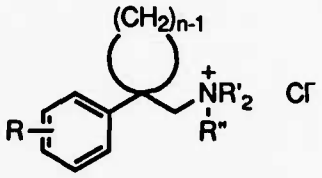


| SRI Code No. | WRAIR Code No. | R | $NR'_2$ | R" | Amount (g) |
|---|---|---|---|---|---|
| PRE-201[a] | BL57164 | H | Pyrrolidine | $CH_3$ | 5.00 |
| PRE-208[a] | BM00544 | 3-$OCH_3$ | Pyrrolidine | $CH_3$ | 5.00 |

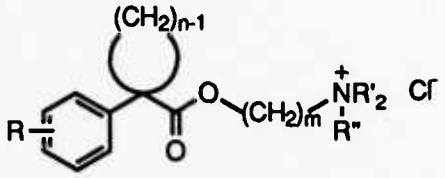
a. Resubmission.



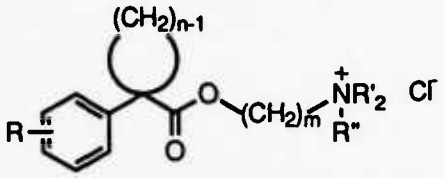
| SRI Code No. | WRAIR Code No. | R | n | $NR'_2$ | R" | Amount (g) |
|---|---|---|---|---|---|---|
| PRE-063 | BL50398 | 3-$OCH_3$ | 5 | Piperidine | H | 4.00 |
| PRE-064 | BL50405 | 3-$OCH_3$ | 5 | Piperidine | $CH_3$ | 4.00 |
| PRE-065 | BL50414 | 3-$OCH_3$ | 5 | Morpholine | H | 5.00 |
| PRE-066 | BL50423 | 3-$OCH_3$ | 5 | $N(CH_3)_2$ | H | 5.00 |
| PRE-067 | BL51117 | 3-OH | 5 | Pyrrolidine | H | 5.00 |
| PRE-068 | BL51126 | 3,4-$(OCH_3)_2$ | 6 | Piperidine | H | 4.00 |
| PRE-069 | BL51395 | 4-$CH_3$ | 6 | Piperidine | $CH_3$ | 3.50 |
| PRE-070 | BL51402 | 3-$OCH_3$ | 6 | Morpholine | $CH_3$ | 3.50 |
| PRE-071 | BL52365 | 3-$OCH_3$ | 5 | Morpholine | $CH_3$ | 5.00 |
| PRE-072 | BL52374 | 3,4-$(OCH_3)_2$ | 6 | Pyrrolidine | H | 7.00 |
| PRE-073 | BL52383 | 3-OH | 6 | $N(CH_3)_2$ | H | 4.40 |
| PRE-074 | BL52605 | 3,4-$(OCH_3)_2$ | 6 | Morpholine | H | 7.00 |
| PRE-075 | BL52614 | 3,4-$(OCH_3)_2$ | 6 | $N(CH_3)_2$ | H | 7.00 |



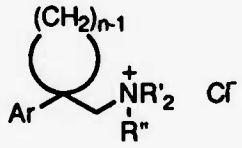

| SRI Code No. | WRAIR Code No. | R | n | NR'2 | R" | Amount (g) |
|---|---|---|---|---|---|---|
| PRE-076 | BL52623 | H | $(CH_2CH_3)_2$ | Pyrrolidine | H | 6.50 |
| PRE-077 | BL52632 | H | $(CH_2CH_3)_2$ | Piperidine | H | 7.00 |
| PRE-080 | BL53264 | 3,4-$(OCH_3)_2$ | 6 | Pyrrolidine | $CH_3$ | 7.00 |
| PRE-081 | BL53273 | 3,4-$(OCH_3)_2$ | 6 | Piperidine | $CH_3$ | 6.00 |
| PRE-094 | BL56014 | 4-$NO_2$ | 6 | Piperidine | H | 5.00 |
| PRE-095 | BL56032 | 4-$NO_2$ | 6 | $NEt_2$ | H | 5.00 |
| PRE-096 | BL56023 | H | 3 | Piperidine | H | 5.00 |
| PRE-097 | BL56578 | H | 3 | $NEt_2$ | H | 5.00 |
| PRE-098 | BL56587 | H | 3 | Morpholine | H | 4.00 |
| PRE-099 | BL56596 | H | 3 | $NEt_2$ | $CH_3$ | 5.00 |
| PRE-128 | BL57100 | H | 3 | Pyrrolidine | $CH_3$ | 3.00 |
| PRE-129 | BL57119 | 4-$NO_2$ | 6 | Pyrrolidine | H | 3.00 |
| PRE-130 | BL57128 | 4-$NO_2$ | 6 | Pyrrolidine | $CH_3$ | 3.00 |
| PRE-132 | BL57146 | 4-$NO_2$ | 6 | Piperidine | $CH_3$ | 5.00 |
| PRE-133 | BL527155 | H | 3 | Piperidine | $CH_3$ | 5.00 |
| PRE-137 | BL58536 | 4-$NO_2$ | 5 | Pyrrolidine | H | 5.00 |
| PRE-138 | BL58643 | 4-$NO_2$ | 5 | Pyrrolidine | $CH_3$ | 5.00 |
| PRE-139 | BL58652 | 4-$NO_2$ | 5 | $NEt_2$ | H | 5.00 |
| PRE-140 | BL58661 | H | $(CH_2CH_3)_2$ | Morpholine | H | 5.00 |
| PRE-156 | BM00517 | H | 3 | Pyrrolidine | H | 4.00 |
| PRE-157 | BM00526 | 4-$NO_2$ | 5 | $NEt_2$ | $CH_3$ | 5.00 |
| PRE-158 | BM00535 | H | $(CH_2CH_3)_2$ | Piperidine | $CH_3$ | 3.00 |
| PRE-165 | BM02379 | H | $(CH_2CH_3)_2$ | $NEt_2$ | $CH_3$ | 3.00 |



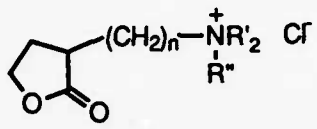

| SRI Code No. | WRAIR Code No. | n | m | $NR'_2$ | R" | Amount (g) |
|---|---|---|---|---|---|---|
| PRE-078 | BL52712 | 6 | 2 | $N(CH_3)_2$ | H | 7.00 |
| PRE-079 | BL52721 | 6 | 2 | Pyrrolidine | H | 7.00 |
| PRE-082 | BL53960 | 6 | 2 | Piperidine | H | 4.10 |
| PRE-083 | BL53979 | 6 | 2 | $NEt_2$ | H | 4.10 |
| PRE-084 | BL53988 | 6 | 2 | Morpholine | H | 8.00 |
| PRE-085 | BL53997 | 6 | 2 | 2-Pyridyl | H | 4.10 |
| PRE-086 | BL54903 | 6 | 2 | $N(CH_3)_2$ | $CH_3$ | 7.50 |
| PRE-087 | BL54912 | 6 | 2 | Pyrrolidine | $CH_3$ | 7.50 |
| PRE-089 | BL55320 | 6 | 2 | Piperidine | $CH_3$ | 6.00 |
| PRE-090 | BL55339 | 6 | 2 | $NEt_2$ | $CH_3$ | 6.00 |
| PRE-134 | BL58509 | 5 | 2 | Piperidine | H | 5.00 |
| PRE-135 | BL58518 | 5 | 2 | 2-Pyridyl | H | 5.00 |
| PRE-136 | BL58527 | 5 | 2 | Morpholine | H | 5.00 |
| PRE-141 | BL58670 | 5 | 2 | Piperidine | $CH_3$ | 5.00 |
| PRE-145 | BL59319 | 3 | 2 | Pyrrolidine | H | 5.00 |
| PRE-146 | BL59328 | 3 | 2 | $N(CH_3)_2$ | H | 5.00 |
| PRE-147 | BL59471 | 3 | 2 | $NEt_2$ | H | 5.00 |
| PRE-148 | BL59480 | 3 | 2 | 2-Pyridyl | H | 5.00 |
| PRE-149 | BL59499 | 3 | 2 | Morpholine | H | 5.00 |
| PRE-150 | BL59506 | 3 | 3 | $N(CH_3)_2$ | H | 5.00 |
| PRE-159 | BM01998 | 3 | 2 | $N(CH_3)_2$ | $CH_3$ | 5.00 |
| PRE-160 | BM02324 | 3 | 3 | $N(CH_3)_2$ | $CH_3$ | 5.00 |
| PRE-161 | BM02333 | 5 | 2 | $N(CH_3)_2$ | $CH_3$ | 5.00 |



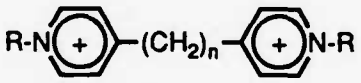
| SRI Code No. | WRAIR Code No. | n | m | $NR'_2$ | R" | Amount (g) |
|---|---|---|---|---|---|---|
| PRE-162 | BM02342 | 5 | 2 | $NEt_2$ | $CH_3$ | 5.00 |
| PRE-164 | BM02360 | 5 | 3 | $N(CH_3)_2$ | $CH_3$ | 5.00 |
| PRE-166 | BM02388 | 3 | 2 | Pyrrolidine | $CH_3$ | 3.00 |
| PRE-167 | BM02379 | 5 | 2 | Pyrrolidine | $CH_3$ | 5.00 |
| PRE-168 | BM02404 | 5 | 2 | $N(i\text{-}Pr)_2$ | $CH_3$ | 5.00 |
| PRE-169 | BM02413 | 5 | 3 | NEt2 | $CH_3$ | 5.00 |



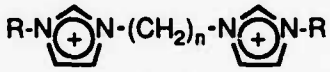
| SRI Code No. | WRAIR Code No. | Ar | $NR'_2$ | n | R" | Amount (g) |
|---|---|---|---|---|---|---|
| PRE-088 | BL55311 | 2-Thienyl | Piperidine | 6 | H | 7.00 |
| PRE-091 | BL55464 | 2-Thienyl | Pyrrolidine | 6 | H | 7.00 |
| PRE-092 | BL55473 | 2-Thienyl | $NEt_2$ | 6 | H | 5.00 |
| PRE-093 | BL55482 | 2-Thienyl | Morpholine | 6 | H | 3.40 |
| PRE-127 | BL57093 | 2-Thienyl | Pyrrolidine | 6 | $CH_3$ | 5.00 |
| PRE-131 | BL57137 | 2-Thienyl | Piperidine | 6 | $CH_3$ | 3.00 |
| PRE-142 | BL59293 | 1-Naphthyl | Pyrrolidine | 6 | H | 5.00 |
| PRE-143 | BL59300 | 1-Naphthyl | $NEt_2$ | 6 | H | 3.00 |
| PRE-144 | BM00508 | 1-Naphthyl | Piperidine | 6 | H | 5.00 |



| SRI Code No. | WRAIR Code No. | n | $NR'_2$ | R" | Amount (g) |
|---|---|---|---|---|---|
| PRE-151 | BL59677 | 1 | $N(CH_3)_2$ | H | 4.00 |
| PRE-152 | BL59686 | 2 | Piperidine | H | 4.00 |
| PRE-153 | BL59695 | 2 | Pyrrolidine | H | 4.00 |
| PRE-154 | BL59702 | 2 | $NEt_2$ | H | 5.00 |
| PRE-155 | BL59711 | 1 | Pyrrolidine | H | 5.00 |
| PRE-163 | BM02351 | 2 | Piperidine | $CH_3$ | 5.00 |



2Cl⁻



2Cl⁻

| SRI Code No. | WRAIR Code No. | Amine | n | R | Amount (g) |
|---|---|---|---|---|---|
| PRE-123 | BL54001 | Pyridine | 4 | $CH_2OCH_2Ph$ | 8.00 |
| PRE-124 | BL54010 | Imidazole | 1 | $CH_2OCH_2Ph$ | 8.00 |
| PRE-125 | BL54029 | Pyridine | 2 | $CH_2OCH_2Ph$ | 8.00 |
| PRE-126 | BL56041 | Imidazole | 6 | $CH_2OCH_2Ph$ | 5.00 |

## Appendix B

## PHYSICAL DATA OF SUBMITTED COMPOUNDS

| SRI Code No. | WRAIR No. | mp (°C) | Solubility (mol/L) | Log P | | CHN Analysis Calculated | Found |
|---|---|---|---|---|---|---|---|
| PRE-063 | BL50398 | 175-176 | >0.79 | >3.40 | C | 69.77 | 69.97 |
| | | | | | H | 9.11 | 9.20 |
| | | | | | N | 4.52 | 4.49 |
| | | | | | Cl | 11.44 | 11.46 |
| PRE-064 | BL50405 | 232-234 d | >0.61 | -1.43 | C | 70.46 | 70.50 |
| | | | | | H | 9.34 | 9.56 |
| | | | | | N | 4.32 | 4.33 |
| | | | | | Cl | 10.94 | 10.75 |
| PRE-065 | BL50414 | 165-166 | 0.62 | 2.60 | C | 65.48 | 65.71 |
| | | | | | H | 8.40 | 8.60 |
| | | | | | N | 4.49 | 4.47 |
| | | | | | Cl | 11.37 | 10.97 |
| PRE-066 | BL50423 | 185-186 | >0.99 | 1.66 | C | 66.77 | 66.70 |
| | | | | | H | 8.97 | 9.06 |
| | | | | | N | 5.19 | 5.18 |
| | | | | | Cl | 13.14 | 13.16 |
| PRE-067 | BL51117 | 144-145 | >1.02 | 0.78 | C | 68.19 | 68.46 |
| | | | | | H | 8.58 | 8.45 |
| | | | | | N | 4.97 | 4.84 |
| | | | | | Cl | 12.58 | 12.39 |
| PRE-068 | BL51126 | 198-200 | >0.80 | 2.55 | C | 67.87 | 68.13 |
| | | | | | H | 9.11 | 9.38 |
| | | | | | N | 3.96 | 3.97 |
| | | | | | Cl | 10.02 | 9.90 |
| PRE-069 | BL51395 | 211 d[a] | >0.57 | -0.96 | C | 71.80 | 71.55 |
| | | | | | H | 10.41 | 10.49 |
| | | | | | N | 3.81 | 3.42 |
| | | | | | Cl | 9.63 | 9.24 |
| PRE-070 | BL51402 | 258-262 d | >0.69 | -1.73 | C | 67.14 | 67.43 |
| | | | | | H | 8.90 | 9.10 |
| | | | | | N | 4.12 | 4.37 |
| | | | | | Cl | 10.43 | 10.14 |
| PRE-071 | BL52365 | 225-226 | >1.01 | -2.05 | C | 66.34 | 66.29 |
| | | | | | H | 8.66 | 8.68 |
| | | | | | N | 4.30 | 4.38 |
| | | | | | Cl | 10.88 | 10.90 |
| PRE-072 | BL52374 | 229-230 | >0.86 | 1.33 | C | 67.14 | 67.30 |
| | | | | | H | 8.90 | 9.00 |
| | | | | | N | 4.12 | 4.09 |
| | | | | | Cl | 10.43 | 10.34 |

| SRI Code No. | WRAIR No. | mp (°C) | Solubility (mol/L) | Log P | | CHN Analysis Calculated | Found |
|---|---|---|---|---|---|---|---|
| PRE-073 | BL52383 | 172-173 | >0.99 | 1.39 | C | 66.77 | 66.86 |
| | | | | | H | 8.97 | 9.14 |
| | | | | | N | 5.19 | 5.16 |
| | | | | | Cl | 13.14 | 12.88 |
| PRE-074 | BL52605 | 223-224 | >0.60 | 3.45 | C | 64.12 | 64.14 |
| | | | | | H | 8.50 | 8.64 |
| | | | | | N | 3.94 | 4.04 |
| | | | | | Cl | 9.96 | 9.67 |
| PRE-075 | BL52614 | 199-200 | >0.93 | 1.37 | C | 65.06 | 64.94 |
| | | | | | H | 8.99 | 9.15 |
| | | | | | N | 4.46 | 4.36 |
| | | | | | Cl | 11.30 | 11.02 |
| PRE-076 | BL52623 | 174-175 | >0.74 | 1.98 | C | 71.75 | 71.90 |
| | | | | | H | 9.78 | 9.86 |
| | | | | | N | 5.23 | 5.26 |
| | | | | | Cl | 13.24 | 13.33 |
| PRE-077 | BL52632 | 160-161 | >1.10 | 3.30 | C | 72.44 | 72.52 |
| | | | | | H | 10.01 | 10.19 |
| | | | | | N | 4.97 | 5.00 |
| | | | | | Cl | 12.58 | 12.42 |
| PRE-078 | BL52712 | 178-179.5 | 0.34 | 2.40 | C | 65.48 | 65.56 |
| | | | | | H | 8.40 | 8.45 |
| | | | | | N | 4.49 | 4.57 |
| | | | | | Cl | 11.37 | 11.42 |
| PRE-079 | BL52721 | 166-167.5 | 0.64 | 2.68[b] | C | 67.54 | 67.66 |
| | | | | | H | 8.35 | 8.43 |
| | | | | | N | 4.15 | 4.15 |
| | | | | | Cl | 10.49 | 10.26 |
| PRE-080 | BL53264 | 223-224 d | >0.63 | -1.73 | C | 66.06 | 66.31 |
| | | | | | H | 9.58 | 9.29 |
| | | | | | N | 3.50 | 3.74 |
| | | | | | Cl | 8.86 | 9.01 |
| PRE-081 | BL53273 | 224-225 d | >0.59 | -1.52 | C | 66.91 | 66.99 |
| | | | | | H | 9.36 | 9.34 |
| | | | | | N | 3.72 | 3.63 |
| | | | | | Cl | 9.40 | 9.13 |
| PRE-082 | BL53960 | 200-202 | 0.02 | >2.60 | C | 68.26 | 68.32 |
| | | | | | H | 8.59 | 8.70 |
| | | | | | N | 3.98 | 3.92 |
| | | | | | Cl | 10.07 | 9.98 |
| PRE-083 | BL53979 | 160-162 | 0.04 | [c] | C | 67.14 | 67.13 |
| | | | | | H | 8.89 | 9.17 |
| | | | | | N | 4.12 | 3.95 |
| | | | | | Cl | 10.43 | 10.26 |

| SRI Code No. | WRAIR No. | mp (°C) | Solubility (mol/L) | Log P | | CHN Analysis Calculated | Found |
|---|---|---|---|---|---|---|---|
| PRE-084 | BL53988 | 184-186 | 0.05 | [c] | C | 64.49 | 64.39 |
| | | | | | H | 7.97 | 8.18 |
| | | | | | N | 3.96 | 3.95 |
| | | | | | Cl | 10.02 | 10.01 |
| PRE-085 | BL53997 | 135-137 | 0.08 | [d] | C | 69.45 | 69.59 |
| | | | | | H | 6.99 | 7.12 |
| | | | | | N | 4.05 | 4.05 |
| | | | | | Cl | 10.25 | 10.14 |
| PRE-086 | BL54903 | 162-163.5[e] | >0.73 | -1.32 | C | 64.56 | 64.40 |
| | | | | | H | 8.73 | 8.90 |
| | | | | | N | 4.18 | 4.08 |
| | | | | | Cl | 10.59 | 10.31 |
| PRE-087 | BL54912 | 173-174.5 | >0.83 | -1.21 | C | 68.26 | 68.12 |
| | | | | | H | 8.59 | 8.80 |
| | | | | | N | 3.98 | 3.97 |
| | | | | | Cl | 10.07 | 9.88 |
| PRE-088 | BL55311 | 210-213 | >0.74 | >2.73 | C | 64.01 | 64.17 |
| | | | | | H | 8.74 | 8.88 |
| | | | | | N | 4.67 | 4.63 |
| | | | | | Cl | 11.82 | 11.62 |
| PRE-089 | BL55320 | 174-176 | >0.55 | -0.99 | C | 68.92 | 69.01 |
| | | | | | H | 8.82 | 8.93 |
| | | | | | N | 3.83 | 3.83 |
| | | | | | Cl | 9.69 | 9.51 |
| PRE-090 | BL55339 | 131-133 | >0.65 | -1.33 | C | 67.87 | 67.70 |
| | | | | | H | 9.14 | 9.33 |
| | | | | | N | 3.96 | 3.92 |
| | | | | | Cl | 10.02 | 9.83 |
| PRE-091 | BL55464 | 193-195 | >0.65 | 2.29 | C | 62.91 | 63.21 |
| | | | | | H | 8.45 | 8.61 |
| | | | | | N | 4.89 | 4.89 |
| | | | | | Cl | 12.25 | 12.25 |
| PRE-092 | BL55473 | 177-179 | >0.67 | 2.24 | C | 62.58 | 62.76 |
| | | | | | H | 9.10 | 9.25 |
| | | | | | N | 4.80 | 4.81 |
| | | | | | Cl | 12.34 | 12.11 |
| PRE-093 | BL55482 | 220-235 d | >0.75 | >2.63 | C | 59.68 | 59.81 |
| | | | | | H | 8.01 | 8.13 |
| | | | | | N | 4.64 | 4.69 |
| | | | | | Cl | 11.74 | 11.49 |
| PRE-094 | BL56014 | 228-230 | 0.12 | 2.56 | C | 63.74 | 63.79 |
| | | | | | H | 8.03 | 7.98 |
| | | | | | N | 8.26 | 8.21 |
| | | | | | Cl | 10.46 | 10.24 |

| SRI Code No. | WRAIR No. | mp (°C) | Solubility (mol/L) | Log P | | CHN Analysis Calculated | Found |
|---|---|---|---|---|---|---|---|
| PRE-095 | BL56032 | 186-187 | >0.99 | 2.47 | C | 62.47 | 62.47 |
| | | | | | H | 8.33 | 8.48 |
| | | | | | N | 8.57 | 8.51 |
| | | | | | Cl | 10.84 | 10.91 |
| PRE-096 | BL56023 | 181-183 | >1.03 | 1.05 | C | 71.55 | 71.71 |
| | | | | | H | 8.81 | 9.02 |
| | | | | | N | 5.56 | 5.53 |
| | | | | | Cl | 14.03 | 13.81 |
| PRE-097 | BL56578 | 127-129 | >1.03 | 0.50 | C | 70.12 | 70.18 |
| | | | | | H | 9.25 | 9.32 |
| | | | | | N | 5.84 | 5.66 |
| | | | | | Cl | 14.78 | 14.84 |
| PRE-098 | BL56587 | 175-177 | >0.99 | 1.99 | C | 66.26 | 66.27 |
| | | | | | H | 7.94 | 7.98 |
| | | | | | N | 5.52 | 5.41 |
| | | | | | Cl | 13.97 | 13.74 |
| PRE-099 | BL56596 | 168-170 | >1.18 | -2.08 | C | 70.98 | 71.13 |
| | | | | | H | 9.53 | 9.76 |
| | | | | | N | 5.52 | 5.44 |
| | | | | | Cl | 13.97 | 13.85 |
| PRE-123 | BL54001 | 180-183 d | >0.56 | -2.45 | C | 68.57 | 68.56 |
| | | | | | H | 6.52 | 6.49 |
| | | | | | N | 5.33 | 5.42 |
| PRE-124 | BL54010 | 202-204 | >0.36 | >-1.74 | C | 59.87 | 59.79 |
| | | | | | H | 5.68 | 5.55 |
| | | | | | N | 12.14 | 12.12 |
| PRE-125 | BL54029 | 140-142 | >0.33 | >-1.75 | C | 66.40 | 66.01 |
| | | | | | H | 6.17 | 5.99 |
| | | | | | N | 5.53 | 5.56 |
| PRE-126 | BL56041 | 106-110 | >0.81 | -2.68 | C | 63.27 | 62.97 |
| | | | | | H | 6.83 | 6.88 |
| | | | | | N | 10.54 | 10.48 |
| | | | | | Cl | 13.34 | 13.22 |
| PRE-127 | BL57093 | 115-117 | >1.01 | -1.58 | C | 62.21 | 62.21 |
| | | | | | H | 8.81 | 8.95 |
| | | | | | N | 4.53 | 4.50 |
| | | | | | Cl | 11.47 | 11.42 |
| | | | | | S | 10.38 | 10.36 |
| PRE-128 | BL57100 | 227-230 d | >1.36 | -2.44 | C | 71.54 | 71.45 |
| | | | | | H | 8.80 | 8.71 |
| | | | | | N | 5.56 | 5.37 |
| | | | | | Cl | 14.07 | 13.90 |

| SRI Code No. | WRAIR No. | mp (°C) | Solubility (mol/L) | Log P | | CHN Analysis Calculated | Found |
|---|---|---|---|---|---|---|---|
| PRE-129 | BL57119 | 230-233 d | 0.20 | 2.84 | C | 61.16 | 61.31 |
| | | | | | H | 7.85 | 7.59 |
| | | | | | N | 8.38 | 8.41 |
| | | | | | Cl | 10.62 | 10.57 |
| PRE-130 | BL57128 | 222-226 d | >1.01 | -1.62 | C | 60.58 | 60.80 |
| | | | | | H | 8.19 | 8.07 |
| | | | | | N | 7.85 | 7.76 |
| | | | | | Cl | 9.93 | 10.07 |
| PRE-131 | BL57137 | 156-158 | >1.03 | -1.31[b] | C | 64.16 | 64.11 |
| | | | | | H | 9.27 | 9.34 |
| | | | | | N | 4.15 | 4.20 |
| | | | | | Cl | 10.52 | 10.69 |
| | | | | | S | 9.51 | 9.74 |
| PRE-132 | BL57146 | 184-186 | 0.04 | -1.40 | C | 61.52 | 61.64 |
| | | | | | H | 8.42 | 8.53 |
| | | | | | N | 7.55 | 7.53 |
| | | | | | Cl | 9.55 | 9.14 |
| PRE-133 | B57155 | 228-232 d | >1.01 | -1.93 | C | 70.69 | 70.43 |
| | | | | | H | 9.42 | 9.51 |
| | | | | | N | 4.85 | 5.09 |
| | | | | | Cl | 12.27 | 12.03 |
| PRE-134 | BL58509 | 167-168 | >0.96 | ≥ 2.50 | C | 67.54 | 67.56 |
| | | | | | H | 8.35 | 8.56 |
| | | | | | N | 4.14 | 4.10 |
| | | | | | Cl | 10.59 | 10.61 |
| PRE-135 | BL58518 | 143-145 | >1.20 | ≥ 3.00 | C | 68.77 | 68.74 |
| | | | | | H | 6.68 | 6.73 |
| | | | | | N | 4.22 | 4.20 |
| | | | | | Cl | 10.68 | 10.94 |
| PRE-136 | BL58527 | 165-167 | >0.94 | ≥ 3.00 | C | 63.61 | 63.63 |
| | | | | | H | 7.71 | 7.76 |
| | | | | | N | 4.12 | 4.05 |
| | | | | | Cl | 10.43 | 10.54 |
| PRE-137 | BL58536 | 222-226 d | >1.16 | ≥ 1.95 | C | 61.83 | 61.92 |
| | | | | | H | 7.46 | 7.61 |
| | | | | | N | 9.01 | 9.01 |
| | | | | | Cl | 11.41 | 11.38 |
| PRE-138 | BL58643 | 208-212 d | >1.16 | -1.74 | C | 59.55 | 59.57 |
| | | | | | H | 7.93 | 8.24 |
| | | | | | N | 8.17 | 8.14 |
| | | | | | Cl | 10.34 | 10.23 |
| PRE-139 | BL58652 | 156-158 | >1.31 | 2.22 | C | 61.43 | 61.56 |
| | | | | | H | 8.06 | 8.22 |
| | | | | | N | 8.95 | 8.89 |
| | | | | | Cl | 11.33 | 11.49 |

| SRI Code No. | WRAIR No. | mp (°C) | Solubility (mol/L) | Log P | | CHN Analysis Calculated | Found |
|---|---|---|---|---|---|---|---|
| PRE-140 | BL58661 | 186-188 | >1.51 | 1.92 | C | 67.70 | 67.74 |
| | | | | | H | 9.23 | 9.44 |
| | | | | | N | 4.93 | 4.88 |
| | | | | | Cl | 12.49 | 12.30 |
| PRE-141 | BL58670 | 176-178 | >1.09 | -1.21 | C | 68.26 | 68.33 |
| | | | | | H | 8.59 | 8.61 |
| | | | | | N | 3.98 | 3.91 |
| | | | | | Cl | 10.07 | 9.86 |
| PRE-142 | BL59293 | 230-235 | >1.48 | 2.84 | C | 76.45 | 76.40 |
| | | | | | H | 8.55 | 8.62 |
| | | | | | N | 4.24 | 4.35 |
| | | | | | Cl | 10.75 | 10.49 |
| PRE-143 | BL59300 | 164-165 | >1.10 | 1.93 | C | 75.99 | 75.95 |
| | | | | | H | 9.11 | 9.14 |
| | | | | | N | 4.22 | 4.08 |
| | | | | | Cl | 10.68 | 10.49 |
| PRE-144 | BM00508 | 115-118 | >0.86 | 2.18 | C | 74.29 | 73.91 |
| | | | | | H | 8.83 | 8.99 |
| | | | | | N | 3.67 | 3.74 |
| | | | | | Cl | 9.13 | 9.15 |
| PRE-145 | BL59319 | 110-112 | >1.72 | 1.45 | C | 64.97 | 64.91 |
| | | | | | H | 7.50 | 7.52 |
| | | | | | N | 4.74 | 4.78 |
| | | | | | Cl | 11.98 | 11.90 |
| PRE-146 | BL59328 | 132-133 | >1.36 | 1.35 | C | 62.33 | 62.48 |
| | | | | | H | 7.47 | 7.59 |
| | | | | | N | 5.19 | 5.17 |
| | | | | | Cl | 13.14 | 13.33 |
| PRE-147 | BL59471 | 126-128 | >1.61 | 1.49 | C | 64.31 | 64.16 |
| | | | | | H | 8.12 | 8.16 |
| | | | | | N | 4.70 | 4.70 |
| | | | | | Cl | 11.90 | 11.75 |
| PRE-148 | BL59480 | 106-108 | >1.39 | 2.96 | C | 67.21 | 66.96 |
| | | | | | H | 5.97 | 5.86 |
| | | | | | N | 4.61 | 4.41 |
| | | | | | Cl | 11.67 | 11.73 |
| PRE-149 | BL59499 | 158-160 | >1.37 | 1.97 | C | 61.63 | 61.43 |
| | | | | | H | 7.11 | 7.10 |
| | | | | | N | 4.49 | 4.42 |
| | | | | | Cl | 11.37 | 11.07 |
| PRE-150 | BL59506 | 141-142 | >1.46 | 0.93 | C | 63.48 | 63.62 |
| | | | | | H | 7.81 | 7.84 |
| | | | | | N | 4.94 | 5.09 |
| | | | | | Cl | 12.49 | 12.09 |

| SRI Code No. | WRAIR No. | mp (°C) | Solubility (mol/L) | Log P | | CHN Analysis Calculated | Found |
|---|---|---|---|---|---|---|---|
| PRE-151 | BL59677 | 196-197 | >1.87 | d | C | 46.80 | 46.87 |
| | | | | | H | 7.85 | 7.87 |
| | | | | | N | 7.80 | 7.75 |
| | | | | | Cl | 19.73 | 19.75 |
| PRE-152 | BL59686 | 202-203 | >1.39 | d | C | 56.52 | 56.60 |
| | | | | | H | 8.62 | 8.64 |
| | | | | | N | 5.99 | 5.93 |
| | | | | | Cl | 15.17 | 15.12 |
| PRE-153 | BL59695 | 140-142 | >1.68 | d | C | 54.67 | 54.76 |
| | | | | | H | 8.26 | 8.21 |
| | | | | | N | 6.38 | 6.42 |
| | | | | | Cl | 16.14 | 16.17 |
| PRE-154 | BL59702 | 116-118 | >1.61 | d | C | 54.17 | 54.04 |
| | | | | | H | 9.09 | 9.15 |
| | | | | | N | 6.32 | 6.24 |
| | | | | | Cl | 15.99 | 16.00 |
| PRE-155 | BL59711 | 190-191 | >1.89 | d | C | 52.56 | 52.52 |
| | | | | | H | 7.84 | 7.73 |
| | | | | | N | 6.81 | 6.69 |
| | | | | | Cl | 17.24 | 17.17 |
| PRE-156 | BM00517 | 162-164 | >1.42 | 0.45 | C | 70.72 | 70.58 |
| | | | | | H | 8.48 | 8.50 |
| | | | | | N | 5.89 | 5.83 |
| | | | | | Cl | 14.90 | 14.79 |
| PRE-157 | BM00526 | 182-192 d | >1.01 | -1.88 | C | 59.99 | 60.32 |
| | | | | | H | 8.44 | 8.51 |
| | | | | | N | 8.23 | 8.18 |
| | | | | | Cl | 10.41 | 10.49 |
| PRE-158 | BM00535 | 194-196 d | >1.03 | -1.34 | C | 73.07 | 73.00 |
| | | | | | H | 10.22 | 10.41 |
| | | | | | N | 4.73 | 4.66 |
| | | | | | Cl | 11.98 | 11.66 |
| PRE-159 | BM01998 | 162-164 | >1.19 | -2.45 | C | 63.48 | 63.53 |
| | | | | | H | 7.81 | 7.99 |
| | | | | | N | 4.94 | 4.75 |
| | | | | | Cl | 12.49 | 12.16 |
| PRE-160 | BM02324 | 131-133 | >0.93 | -2.37 | C | 62.63 | 62.54 |
| | | | | | H | 8.21 | 8.38 |
| | | | | | N | 4.56 | 4.48 |
| | | | | | Cl | 11.55 | 11.15 |
| PRE-161 | BM02333 | 182-184 | >1.11 | -1.69 | C | 65.48 | 65.72 |
| | | | | | H | 8.40 | 8.61 |
| | | | | | N | 4.49 | 4.47 |
| | | | | | Cl | 11.37 | 11.02 |

| SRI Code No. | WRAIR No. | mp (°C) | Solubility (mol/L) | Log P | | CHN Analysis Calculated | Found |
|---|---|---|---|---|---|---|---|
| PRE-162 | BM02342 | 102-104 | >1.06 | -1.46 | C | 67.14 | 67.05 |
| | | | | | H | 8.90 | 9.14 |
| | | | | | N | 4.12 | 4.11 |
| | | | | | Cl | 10.43 | 10.10 |
| PRE-163 | BM02351 | 160-162 | >1.18 | d | C | 58.17 | 58.51 |
| | | | | | H | 8.95 | 9.14 |
| | | | | | N | 5.65 | 5.58 |
| | | | | | Cl | 14.31 | 13.91 |
| PRE-164 | BM02360 | 155-156 | >1.03 | -1.58 | C | 65.44 | 65.64 |
| | | | | | H | 8.70 | 8.81 |
| | | | | | N | 4.24 | 4.18 |
| | | | | | Cl | 10.73 | 10.40 |
| PRE-165 | BM02379 | 173-174 | >1.03 | -1.54 | C | 71.93 | 71.88 |
| | | | | | H | 10.65 | 10.75 |
| | | | | | N | 4.93 | 4.78 |
| | | | | | Cl | 12.49 | 12.44 |
| PRE-166 | BM02388 | 149-152 | >1.17 | -2.12 | C | 65.90 | 66.17 |
| | | | | | H | 7.81 | 7.90 |
| | | | | | N | 4.52 | 4.44 |
| | | | | | Cl | 11.44 | 11.61 |
| PRE-167 | BM02379 | 135-136 | >1.08 | -1.44 | C | 65.79 | 66.04 |
| | | | | | H | 8.42 | 8.40 |
| | | | | | N | 4.04 | 4.00 |
| | | | | | Cl | 10.22 | 10.18 |
| PRE-168 | BM02404 | 147-148 | >0.86 | -1.19 | C | 67.72 | 67.92 |
| | | | | | H | 9.33 | 9.61 |
| | | | | | N | 3.76 | 3.74 |
| | | | | | Cl | 9.52 | 9.49 |
| PRE-169 | BM02413 | 190-195 | >0.86 | -1.31 | C | 66.18 | 66.20 |
| | | | | | H | 9.17 | 9.57 |
| | | | | | N | 3.66 | 3.81 |
| | | | | | Cl | 9.77 | 9.59 |
| PRE-201[f] | BL57164 | 218-220 d | >0.90 | -1.38 | C | 73.56 | 73.18 |
| | | | | | H | 9.60 | 9.67 |
| | | | | | N | 4.77 | 4.65 |
| | | | | | Cl | 12.06 | 12.23 |
| PRE-208[f] | BM00544 | 200-202 | >1.04 | -1.27 | C | 70.45 | 70.28 |
| | | | | | H | 9.33 | 9.56 |
| | | | | | N | 4.32 | 4.20 |
| | | | | | Cl | 10.94 | 10.60 |

[a]Bubbles appear at 161 °C.

[b]Log P increases with decreasing octanol/buffer ratio.

[c]Unable to determine due to instability.

[d]Unable to determine due to low uv absorbance.

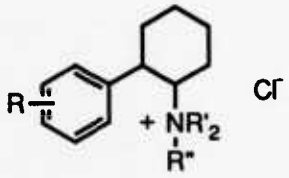
[e]Anneals at 145 °C.

[f]Previously submitted under contract DAMD17-85-C-5148.

# Appendix C

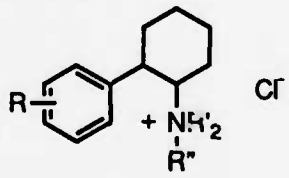
## INITIAL PRETREATMENT EFFICACY TABLES*

### INITIAL IM PRETREATMENT EFFICACY OF 1-(2-ARYLCYCLOHEXYL)AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-016 | Pyrrolidine | 3-OH | H | 0.01 | 0 | 0 | 6 | 0 | 3 | 7 | - |
| PRE-017 | Pyrrolidine | 3-$OCH_3$ | H | 0.13 | 2 | 4 | 9 | 2 | 8 | 9 | - |
| PRE-019 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 0.03 | 0 | 2 | 10 | 1 | 2 | 7 | - |
| PRE-020 | Piperidine | 3-$OCH_3$ | H | 0.38 | 0 | 2 | 4 | 1 | 0 | 2 | - |

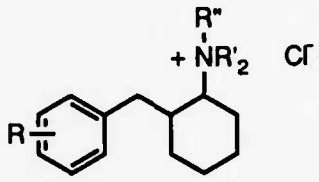
### INITIAL ORAL PRETREATMENT EFFICACY OF 1-(2-ARYLCYCLOHEXYL)AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | Oral $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-016 | Pyrrolidine | 3-OH | H | 0.20 | 1 | 1 | 9 | 1 | 2 | 4 | 0.05 |
| PRE-017 | Pyrrolidine | 3-$OCH_3$ | H | 0.20 | 0 | 5 | 10 | 1 | 2 | 8 | 0.01 |
| PRE-018 | Pyrrolidine | 3-OH | $CH_3$ | 0.20 | - | 2 | 2 | - | 8 | 9 | - |
| PRE-019 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 0.18 | 1 | 4 | 3 | 1 | 4 | 6 | 0.01 |
| PRE-020 | Piperidine | 3-$OCH_3$ | H | 0.99 | - | 0 | 4 | - | 1 | 3 | - |

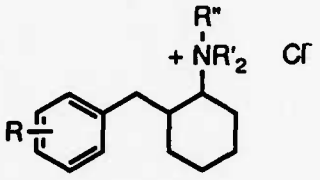
*For all initial pretreatment efficacy tables, Pretreatment compounds are administered either 15 or 60 min (IM), or 30 or 120 min (oral), prior to GD challenge, at doses equal to 1/64, 1/16, or 1/4 their $LD_{50}$. All animals receive atropine and 2-PAM (IM) 10 s after GD challenge. Number of survivors out of 10 is indicated. Compounds shown in boldface were submitted under Contract DAMD17-88-C-8001.

INITIAL IM PRETREATMENT EFFICACY OF
1-[(2-PHENYLMETHYL)CYCLOALKYL)]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE



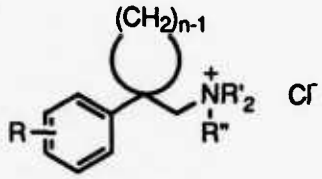

| SRI Code No. | $NR'_2$ | R | R" | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-200 | Pyrrolidine | H | H | >0.11 | 0 | 2 | 5 | 1 | 0 | 4 | - |
| **PRE-201** | **Pyrrolidine** | **H** | **$CH_3$** | **>1.30** | **0** | **4** | **2** | **0** | **1** | **4** | - |
| PRE-202 | Piperidine | H | $CH_3$ | 0.20 | 0 | 2 | 1 | 0 | 0 | 2 | - |
| PRE-203 | Piperidine | H | H | >0.11 | 0 | 2 | 3 | 3 | 0 | 5 | - |
| PRE-204 | Pyrrolidine | 4-$OCH_3$ | H | 0.29 | 0 | 0 | 3 | 0 | 0 | 0 | - |
| PRE-206 | Pyrrolidine | 4-$OCH_3$ | $CH_3$ | 0.20 | 0 | 0 | 1 | 1 | 1 | 1 | - |
| PRE-207 | Pyrrolidine | 3-$OCH_3$ | H | >0.51 | 0 | 3 | 6 | 0 | 1 | 2 | - |
| **PRE-208** | **Pyrrolidine** | **3-$OCH_3$** | **$CH_3$** | **0.32** | **1** | **2** | **6** | **0** | **0** | **1** | - |
| PRE-209 | Pyrrolidine | 4-OH | H | >0.05 | 1 | 0 | 1 | 0 | 0 | 1 | - |
| PRE-211 | Pyrrolidine | 4-OH | $CH_3$ | 0.19 | 1 | 0 | 2 | 0 | 1 | 0 | - |
| PRE-212 | Pyrrolidine | 3-OH | H | >0.03 | 0 | 0 | 4 | 0 | 0 | 4 | - |
| PRE-214 | Morpholine | H | H | >0.03 | 0 | 1 | 1 | 0 | 1 | 0 | - |
| PRE-216 | Pyrrolidine | 4-$CH_3$ | $CH_3$ | 0.27 | 0 | 0 | 4 | 1 | 0 | 4 | - |
| PRE-217 | Morpholine | 3-$OCH_3$ | H | >0.14 | 1 | 0 | 1 | 0 | 0 | 1 | - |

INITIAL ORAL PRETREATMENT EFFICACY OF
1-[(2-PHENYLMETHYL)CYCLOALKYL)]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | Oral $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-200 | Pyrrolidine | H | H | 0.94 | 1 | 1 | 4 | 1 | 2 | 1 | 0.23 |
| **PRE-201** | **Pyrrolidine** | **H** | **$CH_3$** | **3.25** | **0** | **4** | **5** | **0** | **3** | **5** | **0.20** |
| PRE-203 | Piperidine | H | H | >1.02 | 0 | 5 | 0 | 0 | 2 | 0 | 0.21 |
| PRE-207 | Pyrrolidine | 3-$OCH_3$ | H | 1.92 | 1 | 0 | 2 | 2 | 0 | 2 | - |
| **PRE-208** | **Pyrrolidine** | **3-$OCH_3$** | **$CH_3$** | **>3.09** | **0** | **0** | **8** | **1** | **1** | **0** | **0.77** |
| PRE-212 | Pyrrolidine | 3-OH | H | >0.34 | 0 | 0 | 1 | 0 | 0 | 0 | - |

INITIAL IM PRETREATMENT EFFICACY OF
1-[(1-ARYLCYCLOALKYL)METHYL]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | n | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-023 | Piperidine | H | H | 6 | 0.59 | 1 | 2 | 3 | 0 | 1 | 6 | - |
| PRE-028 | Pyrrolidine | 3-OH | H | 6 | >0.68 | 1 | 7 | 7 | 1 | 6 | 8 | - |
| PRE-029 | Pyrrolidine | 3-OH | $CH_3$ | 6 | 0.32 | 0 | 0 | 8 | 0 | 0 | 5 | - |
| PRE-030 | Pyrrolidine | 3-$OCH_3$ | H | 6 | 0.28 | 0 | 0 | 0 | 1 | 2 | 0 | - |
| PRE-031 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 6 | 0.25 | 0 | 4 | 5 | 0 | 3 | 5 | 0.02 |
| PRE-032 | Morpholine | H | $CH_3$ | 6 | 0.28 | 0 | 0 | 0 | 1 | 3 | 2 | - |
| PRE-037 | Pyrrolidine | H | $CH_3$ | 5 | 0.13 | 0 | 0 | 4 | 2 | 2 | 3 | - |
| PRE-039 | Piperidine | 3-Cl | $CH_3$ | 6 | 0.30 | 2 | 3 | 6 | 0 | 1 | 2 | 0.08 |
| PRE-040 | Piperidine | 3-Cl | H | 6 | >0.12 | 2 | 1 | 0 | 0 | 0 | 0 | - |
| PRE-041 | Piperidine | H | $CH_3$ | 5 | 0.26 | 0 | 1 | 6 | 1 | 7 | 9 | 0.02 |
| PRE-043 | $N(CH_3)_2$ | 3-$OCH_3$ | H | 6 | 0.54 | 0 | 1 | 1 | 1 | 2 | 0 | - |
| PRE-045 | Pyrrolidine | 4-$OCH_3$ | H | 6 | 0.16 | 0 | 0 | 2 | 1 | 0 | 2 | - |
| PRE-046 | Piperidine | 3-$OCH_3$ | $CH_3$ | 6 | 0.29 | 2 | 2 | 3 | 0 | 1 | 4 | - |
| PRE-047 | Morpholine | 3-$OCH_3$ | H | 6 | >1.23 | - | - | 1 | - | - | 0 | - |
| PRE-048 | Piperidine | 3-OH | H | 6 | 0.39 | 5 | 2 | 3 | 0 | 1 | 5 | - |
| PRE-049 | Piperidine | 3-$OCH_3$ | H | 6 | 0.81 | 0 | 1 | 2 | 0 | 2 | 3 | - |
| PRE-050 | Piperidine | 4-$OCH_3$ | H | 6 | >1.23 | 0 | 0 | 1 | 0 | 0 | 6 | - |
| PRE-051 | Morpholine | 3-OH | H | 6 | >1.28 | 0 | 0 | 0 | 0 | 0 | 1 | - |
| PRE-053 | Piperidine | 4-$CH_3$ | H | 6 | 1.25 | - | - | 1 | - | - | 0 | - |
| PRE-054 | $N(CH_3)_2$ | 4-$CH_3$ | H | 6 | 0.52 | 0 | 1 | 0 | 0 | 0 | 4 | - |
| PRE-055 | Pyrrolidine | 4-OH | H | 6 | 1.35 | - | - | 1 | - | - | 1 | - |
| PRE-056 | $N(CH_3)_2$ | 3-$OCH_3$ | $CH_3$ | 6 | 0.18 | 0 | 0 | 0 | 2 | 0 | 1 | - |
| PRE-057 | $N(CH_3)_2$ | 4-$CH_3$ | $CH_3$ | 6 | 0.15 | 0 | 1 | 1 | 2 | 1 | 1 | - |
| PRE-060 | Pyrrolidine | 4-OH | $CH_3$ | 6 | 0.41 | 1 | 2 | 3 | 0 | 0 | 4 | - |
| PRE-061 | Pyrrolidine | 3-$OCH_3$ | H | 5 | 0.18 | 3 | 2 | 4 | 0 | 2 | 4 | 0.04 |

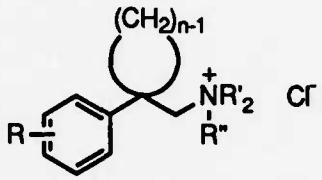
| SRI Code No. | Amine | R | R' | n | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-062 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 5 | 0.17 | 1 | 4 | 10 | 0 | 2 | 2 | 0.01 |
| PRE-063 | Piperidine | 3-$OCH_3$ | H | 5 | 0.32 | 3 | 2 | 3 | 0 | 5 | 0 | 0.02 |
| PRE-065 | Morpholine | 3-$OCH_3$ | H | 5 | >0.61 | 1 | 0 | 1 | 0 | 0 | 0 | - |
| PRE-066 | $N(CH_3)_2$ | 3-$OCH_3$ | H | 5 | 0.37 | 0 | 1 | 0 | 0 | 0 | 0 | - |
| PRE-067 | Pyrrolidine | 3-OH | H | 5 | 0.11 | 1 | 7 | 8 | 1 | 1 | 6 | 0.01 |
| PRE-068 | Piperidine | 3,4-$(OCH_3)_2$ | H | 6 | 0.31 | 0 | 0 | 3 | 0 | 1 | 1 | - |
| PRE-069 | Piperidine | 4-$CH_3$ | $CH_3$ | 6 | 0.16 | 1 | 3 | 8 | 0 | 0 | 1 | 0.04 |
| PRE-070 | Morpholine | 3-$OCH_3$ | $CH_3$ | 6 | 0.71 | 1 | 1 | 1 | 0 | 0 | 1 | - |
| PRE-071 | Morpholine | 3-$OCH_3$ | $CH_3$ | 5 | >1.23 | 3 | 7 | 1 | 0 | 1 | 7 | 0.08 |
| PRE-072 | Pyrrolidine | 3,4-$(OCH_3)_2$ | H | 6 | 0.06 | 1 | 0 | 0 | 1 | 0 | 1 | - |
| PRE-073 | $N(CH_3)_2$ | 3-OH | H | 6 | 1.01 | 4 | 3 | 6 | 0 | 1 | 1 | 0.02 |
| PRE-074 | Morpholine | 3,4-$(OCH_3)_2$ | H | 6 | >0.81 | [0 | 0 | 0 | 0 | 1 | 0][a] | - |
| PRE-075 | $N(CH_3)_2$ | 3,4-$(OCH_3)_2$ | H | 6 | >1.27 | 0 | 0 | 0 | 0 | 0 | 0 | - |
| PRE-080 | Pyrrolidine | 3,4-$(OCH_3)_2$ | $CH_3$ | 6 | 0.56 | 2 | 0 | 0 | 0 | 3 | 1 | - |
| PRE-081 | Piperidine | 3,4-$(OCH_3)_2$ | $CH_3$ | 6 | >1.06 | 3 | 3 | 1 | 2 | 5 | 0 | 0.07 |
| PRE-094 | Piperidine | 4-$NO_2$ | H | 6 | >2.80 | [0 | 0 | 0 | 1 | 2 | 1][b] | - |
| PRE-095 | $NEt_2$ | 4-$NO_2$ | H | 6 | 0.009 | [0 | 0 | 0 | 1 | 0 | 1][c] | - |
| PRE-096 | Piperidine | H | H | 3 | 0.38 | 0 | 1 | 1 | 0 | 0 | 0 | - |
| PRE-097 | $NEt_2$ | H | H | 3 | 0.33 | 0 | 0 | 0 | 0 | 0 | 0 | - |
| PRE-098 | Morpholine | H | H | 3 | >1.58 | 0 | 0 | 0 | 0 | 0 | 0 | - |
| PRE-099 | $NEt_2$ | H | $CH_3$ | 3 | 0.22 | 0 | 1 | 1 | 1 | 2 | 0 | - |
| PRE-128 | Pyrrolidine | H | $CH_3$ | 3 | 0.14 | 2 | 0 | 3 | 1 | 2 | 2 | - |
| PRE-129 | Pyrrolidine | 4-$NO_2$ | H | 6 | 0.39 | 0 | 0 | 1 | 0 | 0 | 0 | - |
| PRE-130 | Pyrrolidine | 4-$NO_2$ | $CH_3$ | 6 | 0.54 | 0 | 0 | 3 | 3 | 2 | 7 | 0.13 |
| PRE-132 | Piperidine | 4-$NO_2$ | $CH_3$ | 6 | >0.77 | 0 | 1 | 0 | 0 | 1 | 0 | - |
| PRE-133 | Piperidine | H | $CH_3$ | 3 | 0.18 | 0 | 3 | 6 | 3 | 2 | 5 | 0.05 |

[a]Doses evaluated were 1/3, 1/12, and 1/48 $LD_{50}$.

[b]Doses evaluated were 1/20, 1/80, and 1/360 $LD_{50}$.

[c]Doses evaluated were 2.16, 8.62, and 34.48 x $LD_{50}$? Probable error on data report.

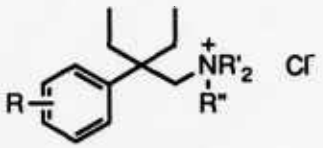
INITIAL ORAL PRETREATMENT EFFICACY OF
1-[(1-ARYLCYCLOALKYL)METHYL]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | n | Oral $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-021 | Pyrrolidine | H | H | 6 | 0.87 | - | 0 | 3 | - | 1 | 2 | - |
| PRE-022 | Pyrrolidine | H | $CH_3$ | 6 | 3.71 | - | 5 | 3 | - | 2 | 3 | - |
| PRE-023 | Piperidine | H | H | 6 | 2.02 | 0 | 0 | 1 | 0 | 1 | 3 | 0.01 |
| PRE-024 | Morpholine | H | H | 6 | 3.72 | - | 0 | 0 | - | 2 | 1 | - |
| PRE-025 | Piperidine | H | $CH_3$ | 6 | 1.65 | - | 0 | 0 | - | 0 | 0 | - |
| PRE-026 | $NEt_2$ | H | H | 6 | 1.11 | - | 4 | 1 | - | 0 | 3 | - |
| PRE-027 | $NEt_2$ | H | $CH_3$ | 6 | 5.37 | - | 1 | 0 | - | 0 | 0 | - |
| PRE-028 | Pyrrolidine | 3-OH | H | 6 | 2.01 | 0 | 3 | 7 | 0 | 2 | 9 | 0.51 |
| PRE-029 | Pyrrolidine | 3-OH | $CH_3$ | 6 | >3.23 | 2 | 3 | 6 | 0 | 4 | 4 | 0.20 |
| PRE-031 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 6 | >3.09 | 0 | 1 | 1 | 0 | 1 | 4 | 0.77 |
| PRE-032 | Morpholine | H | $CH_3$ | 6 | 0.54 | - | 1 | 1 | - | 4 | 7 | - |
| PRE-033 | $N(CH_3)_2$ | H | $CH_3$ | 6 | 3.41 | - | 0 | 0 | - | 0 | 0 | - |
| PRE-034 | $N(CH_3)_2$ | H | H | 6 | 0.93 | - | 0 | 2 | - | 1 | 1 | - |
| PRE-035 | Pyrrolidine | 3-Cl | $CH_3$ | 6 | 1.96 | - | 1 | 0 | - | 1 | 0 | - |
| PRE-036 | Pyrrolidine | 3-Cl | H | 6 | 0.78 | - | 0 | 0 | - | 0 | 0 | - |
| PRE-037 | Pyrrolidine | H | $CH_3$ | 5 | >3.57 | 2 | 3 | 4 | 1 | 6 | 5 | 0.22 |
| PRE-038 | Pyrrolidine | H | H | 5 | 0.75 | - | 0 | 2 | - | 0 | 1 | - |
| PRE-039 | Piperidine | 3-Cl | $CH_3$ | 6 | 2.01 | 2 | 2 | 7 | 1 | 2 | 5 | 0.50 |
| PRE-040 | Piperidine | 3-Cl | H | 6 | 5.09 | - | 0 | 2 | - | 0 | 0 | - |

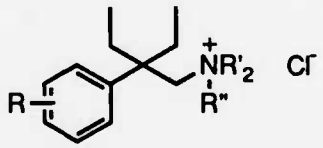
| SRI Code No. | Amine | R | R' | n | Oral $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-042 | Piperidine | H | H | 5 | 2.69 | - | 0 | 0 | - | 1 | 5 | - |
| PRE-046 | Piperidine | 3-$OCH_3$ | $CH_3$ | 6 | 2.96 | 1 | 8 | 6 | 1 | 1 | 7 | 0.18 |
| PRE-054 | $N(CH_3)_2$ | 4-$CH_3$ | H | 6 | 2.22 | 0 | 1 | 1 | 1 | 1 | 0 | - |
| PRE-060 | Pyrrolidine | 4-OH | $CH_3$ | 6 | >3.23 | 0 | 2 | 7 | 0 | 1 | 0 | 0.81 |
| PRE-061 | Pyrrolidine | 3-$OCH_3$ | H | 5 | 0.66 | 0 | 0 | 7 | 0 | 0 | 5 | 0.16 |
| PRE-062 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 5 | >3.23 | 0 | 5 | 5 | 0 | 0 | 2 | 0.20 |
| **PRE-063** | **Piperidine** | **3-$OCH_3$** | **H** | **5** | **1.55** | **0** | **1** | **3** | **1** | **0** | **6** | **0.39** |
| **PRE-064** | **Piperidine** | **3-$OCH_3$** | **$CH_3$** | **5** | **2.51** | **2** | **3** | **5** | **1** | **3** | **2** | **0.63** |
| **PRE-067** | **Pyrrolidine** | **3-OH** | **H** | **5** | **1.01** | **0** | **9** | **8** | **0** | **3** | **9** | **0.06** |
| **PRE-069** | **Piperidine** | **4-$CH_3$** | **$CH_3$** | **6** | **>2.72** | **2** | **2** | **4** | **0** | **1** | **3** | **0.68** |
| **PRE-071** | **Morpholine** | **3-$OCH_3$** | **$CH_3$** | **5** | **>3.07** | **0** | **0** | **4** | **0** | **0** | **6** | **0.77** |
| **PRE-073** | **$N(CH_3)_2$** | **3-OH** | **H** | **6** | **1.51** | **1** | **2** | **2** | **1** | **1** | **5** | **0.38** |
| **PRE-081** | **Piperidine** | **3,4-$(OCH_3)_2$** | **$CH_3$** | **6** | **>2.65** | **0** | **3** | **2** | **0** | **1** | **7** | **0.66** |

INITIAL IM PRETREATMENT EFFICACY OF
α,α-DIALKYLPHENETHYLAMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE



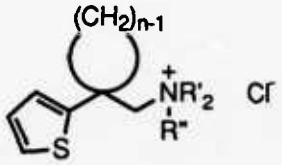

| SRI Code No. | $NR'_2$ | R | R" | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-076** | **Pyrrolidine** | **H** | **H** | **0.55** | **1** | **0** | **0** | **0** | **0** | **2** | **-** |
| **PRE-077** | **Piperidine** | **H** | **H** | **1.75** | **0** | **1** | **0** | **0** | **2** | **6** | **0.35** |

INITIAL ORAL PRETREATMENT EFFICACY OF
α,α-DIALKYLPHENETHYLAMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | Oral $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-077** | **Piperidine** | **H** | **H** | **2.53** | **0** | **4** | **5** | **1** | **3** | **6** | **0.16** |

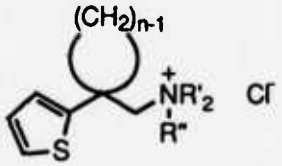
INITIAL IM PRETREATMENT EFFICACY OF
1-[(1-(2-THIENYL)CYCLOALKYL)METHYL]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R" | n | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-088** | **Piperidine** | **H** | **6** | **>1.13** | **[0** | **1** | **6** | **0** | **0** | **3][a]** | **0.33** |
| **PRE-091** | **Pyrrolidine** | **H** | **6** | **0.74** | **0** | **0** | **2** | **0** | **0** | **1** | **-** |
| **PRE-092** | **$NEt_2$** | **H** | **6** | **1.25** | **2** | **6** | **4** | **0** | **0** | **2** | **0.08** |
| **PRE-093** | **Morpholine** | **H** | **6** | **>1.33** | **0** | **0** | **0** | **0** | **0** | **0** | **-** |
| **PRE-127** | **Pyrrolidine** | **$CH_3$** | **6** | **0.20** | **0** | **1** | **4** | **1** | **2** | **4** | **0.05** |
| **PRE-131** | **Piperidine** | **$CH_3$** | **6** | **0.16** | **0** | **0** | **4** | **1** | **0** | **4** | **0.04** |

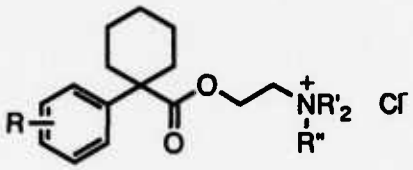
[a]Doses evaluated were 1/3, 1/12, and 1/48 $LD_{50}$.

INITIAL ORAL PRETREATMENT EFFICACY OF
1-[(1-(2-THIENYL)CYCLOALKYL)METHYL]AMINES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R" | n | Oral $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRE-088** | **Piperidine** | **H** | **6** | **3.17** | **0** | **0** | **5** | **1** | **1** | **7** | **0.79** |

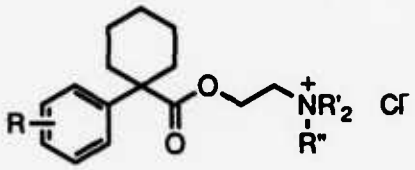
INITIAL IM PRETREATMENT EFFICACY OF
DIALKYLAMINOALKYL 1-PHENYLCYCLOALKANE-1-CARBOXYLATES
AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-078 | $N(CH_3)_2$ | H | H | >0.91 | [2 | 0 | 6 | 0 | 0 | 0][a] | 0.32 |
| PRE-079 | Pyrrolidine | H | H | >1.04 | 0 | 0 | 6 | 0 | 0 | 4 | 0.30 |
| PRE-082 | Piperidine | H | H | >0.16 | [0 | 0 | 1 | 0 | 0 | 1][b] | - |
| PRE-083 | $NEt_2$ | H | H | >0.54 | [0 | 5 | 9 | 1 | 2 | 10][b] | 0.07 |
| PRE-084 | Morpholine | H | H | >0.27 | [0 | 0 | 0 | 0 | 0 | 0][a] | - |
| PRE-085 | 2-Pyridyl | H | H | >1.01 | 0 | 0 | 0 | 2 | 0 | 0 | - |
| PRE-086 | $N(CH_3)_2$ | H | $CH_3$ | 0.65 | 4 | 10 | 10 | 0 | 0 | 5 | 0.01 |
| PRE-087 | Pyrrolidine | H | $CH_3$ | 0.41 | 0 | 3 | 5 | 1 | 1 | 7 | 0.10 |
| PRE-089 | Piperidine | H | $CH_3$ | 0.49 | 0 | 2 | 0 | 2 | 2 | 6 | 0.12 |
| PRE-090 | $NEt_2$ | H | $CH_3$ | 0.57 | 0 | 0 | 1 | 0 | 4 | 6 | 0.04 |

[a]Doses evaluated were 1/3, 1/12, and 1/48 $LD_{50}$.
[b]Doses evaluated were 1/2, 1/8, and 1/32 $LD_{50}$.

INITIAL ORAL PRETREATMENT EFFICACY OF
DIALKYLAMINOALKYL 1-PHENYLCYCLOALKANE-1-CARBOXYLATES
AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | $NR'_2$ | R | R" | IM $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-078 | $N(CH_3)_2$ | H | H | >3.21 | 0 | 1 | 4 | 0 | 0 | 0 | 0.80 |
| PRE-079 | Pyrrolidine | H | H | >2.96 | 0 | 0 | 0 | 1 | 1 | 1 | - |
| PRE-087 | Pyrrolidine | H | $CH_3$ | 2.33 | [ | | | | | ][a] | 0.58 |
| PRE-089 | Piperidine | H | $CH_3$ | 2.46 | 0 | 0 | 0 | 0 | 3 | 0 | - |
| PRE-090 | $NEt_2$ | H | $CH_3$ | >2.83 | 1 | 1 | 4 | 0 | 2 | 4 | 0.71 |

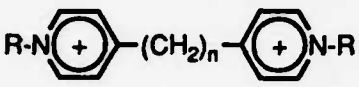
[a]No data sheet received.

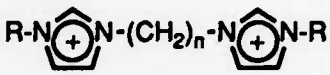
INITIAL IM PRETREATMENT EFFICACY OF
BIS-QUATERNARY BIS(HETEROARYL)ALKANES
AGAINST 2 x $LD_{50}$ GD IN THE MOUSE


| SRI Code No. | Amine | R | n | IM $LD_{50}$ (mmol/kg) | Survivors 15 min 1/64 | 15 min 1/16 | 15 min 1/4 | 60 min 1/64 | 60 min 1/16 | 60 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-102 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 1 | 0.17 | 2 | 2 | 1 | 0 | 1 | 0 | - |
| PRE-105 | Pyridine | $-CH_2OCH(CH_3)C(CH_3)_3$ | 2 | 0.05 | 3 | 6 | 10 | 0 | 0 | 0 | - |
| PRE-107 | Pyridine | $-CH_2O$-cyc-$(C_6H_{11})$ | 2 | 0.05 | 0 | 0 | 0 | 1 | 3 | 8 | - |
| PRE-109 | Pyridine | $-CH_2OCH_2Ph$ | 3 | O.15 | - | 7 | 0 | - | 5 | 4 | - |
| PRE-110 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 4 | 0.09 | - | 7 | 7 | - | 0 | 9 | - |
| PRE-118 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 6 | 0.10 | 5 | 9 | 10 | 2 | 1 | 10 | 0.002 |
| PRE-119 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 8 | 0.13 | 2 | 5 | 8 | 0 | 4 | 9 | 0.008 |
| PRE-120 | Imidazole | $-CH_2O(CH_2)_2C{\equiv}CH$ | 1 | >1.20 | [0 | 2 | 5 | 3 | 1 | 3][a] | 0.24 |
| PRE-121 | Imidazole | $-CH_2O(CH_2)_2C{\equiv}CH$ | 3 | 0.50 | 1 | 2 | 4 | 3 | 3 | 1 | 0.13 |
| **PRE-123** | **Pyridine** | **$-CH_2OCH_2Ph$** | **4** | **0.15** | **6** | **5** | **0** | **6** | **10** | **5** | **0.002** |
| **PRE-124** | **Imidazole** | **$-CH_2OCH_2Ph$** | **1** | **0.15** | **0** | **0** | **0** | **3** | **1** | **0** | **-** |
| **PRE-125** | **Pyridine** | **$-CH_2OCH_2Ph$** | **2** | **0.17** | **1** | **2** | **2** | **1** | **4** | **9** | **0.01** |
| **PRE-126** | **Imidazole** | **$-CH_2OCH_2Ph$** | **6** | **0.14** | **3** | **7** | **9** | **0** | **5** | **8** | **0.01** |

[a]Doses evaluated were 1/80, 1/20, and 1/5 $LD_{50}$.

## INITIAL ORAL PRETREATMENT EFFICACY OF BIS-QUATERNARY BIS(HETEROARYL)ALKANES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE




| SRI Code No. | Amine | R | n | Oral $LD_{50}$ (mmol/kg) | Survivors 30 min 1/64 | 30 min 1/16 | 30 min 1/4 | 120 min 1/64 | 120 min 1/16 | 120 min 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-100 | Imidazole | $-CH_2OCH_3$ | 1 | 12.94 | - | - | 2 | - | - | 1 | - |
| PRE-101 | Imidazole | $-CH_2O(CH_2)_7CH_3$ | 1 | 1.65 | - | 2 | 0 | - | 1 | 0 | - |
| PRE-102 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 1 | 1.83 | - | 1 | 4 | - | 0 | 1 | - |
| PRE-103 | Pyridine | $-CH_2OCH_3$ | 2 | 8.32 | - | 0 | 1 | - | 0 | 0 | - |
| PRE-104 | Imidazole | $-CH_2O$-cyc-$(C_6H_{11})$ | 1 | 3.07 | - | 0 | 1 | - | 0 | 4 | - |
| PRE-105 | Pyridine | $-CH_2OCH(CH_3)C(CH_3)_3$ | 2 | >2.02 | 1 | 0 | 6 | 1 | 1 | 6 | 0.51 |
| PRE-106 | Pyridine | $-CH_2O(CH_2)_7CH_3$ | 2 | 1.01 | - | 2 | 2 | - | 1 | 1 | - |
| PRE-107 | Pyridine | $-CH_2O$-cyc-$(C_6H_{11})$ | 2 | >2.04 | 0 | 0 | 0 | 2 | 1 | 1 | - |
| PRE-109 | Pyridine | $-CH_2OCH_2Ph$ | 3 | 0.85 | - | 0 | 1 | - | 1 | 1 | - |
| PRE-110 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 4 | 1.10 | - | 1 | 5 | - | 0 | 1 | - |
| PRE-111 | Imidazole | $-CH_2O(CH_2)_7CH_3$ | 4 | 2.91 | - | 2 | 0 | - | 0 | 0 | - |
| PRE-117 | Imidazole | $-CH_2O$-cyc-$(C_6H_{11})$ | 3 | 2.95 | - | 1 | 3 | - | 0 | 1 | - |
| PRE-118 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 6 | 1.43 | 3 | 5 | 6 | 0 | 1 | 0 | 0.09 |
| PRE-119 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 8 | >1.74 | 0 | 1 | 0 | 0 | 0 | 0 | - |
| PRE-120 | Imidazole | $-CH_2O(CH_2)_2C{\equiv}CH$ | 1 | >2.37 | 1 | 0 | 2 | 0 | 0 | 2 | - |
| PRE-121 | Imidazole | $-CH_2O(CH_2)_2C{\equiv}CH$ | 3 | >2.37 | 2 | 0 | 1 | 1 | 1 | 1 | - |
| **PRE-123** | **Pyridine** | **$-CH_2OCH_2Ph$** | **4** | **0.59** | **0** | **0** | **2** | **2** | **4** | **5** | **0.04** |
| **PRE-125** | **Pyridine** | **$-CH_2OCH_2Ph$** | **2** | **>1.97** | **0** | **0** | **3** | **0** | **1** | **1** | **-** |

INITIAL IM TREATMENT EFFICACY OF
BIS-QUATERNARY BIS(HETEROARYL)ALKANES AGAINST GA
IN THE MOUSE


| SRI Code No. | Amine | R | n | Oral $LD_{50}$ (mmol/kg) | Survivors w/ Atr. 1/64 | w/ Atr. 1/16 | w/ Atr. 1/4 | w/ Atr./2-PAM 1/64 | w/ Atr./2-PAM 1/16 | w/ Atr./2-PAM 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-102 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 1 | 0.17 | 1 | 1 | 0 | - | - | - | - |
| PRE-109 | Pyridine | $-CH_2OCH_2Ph$ | 3 | 0.15 | 7 | 9 | 3 | 7 | 4 | 0 | - |
| PRE-110 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 4 | 0.09 | 0 | 3 | 0 | 0 | 3 | 1 | - |

[a]Treatment compound administered with atropine or atropine/2-PAM 10 s after GA challenge, at doses equal to the indicated fraction of their $LD_{50}$. Number of survivors out of 10 is indicated.

## INITIAL IM TREATMENT EFFICACY OF BIS-QUATERNARY BIS(HETEROARYL)ALKANES AGAINST 2 x $LD_{50}$ GD IN THE MOUSE


| SRI Code No. | Amine | R | n | Oral $LD_{50}$ (mmol/kg) | Survivors w/ Atr. 1/64 | w/ Atr. 1/16 | w/ Atr. 1/4 | w/ Atr./2-PAM 1/64 | w/ Atr./2-PAM 1/16 | w/ Atr./2-PAM 1/4 | MED (mmol/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE-100 | Imidazole | $-CH_2OCH_3$ | 1 | 7.58 | 0 | 0 | 0 | - | - | - | - |
| PRE-101 | Imidazole | $-CH_2O(CH_2)_7CH_3$ | 1 | 0.26 | 0 | 1 | 0 | - | - | - | - |
| PRE-102 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 1 | 0.17/0.15[b] | [0 | 0 | 0][c] | 1 | 2 | 3 | - |
| PRE-103 | Pyridine | $-CH_2OCH_3$ | 2 | 0.28 | 1 | 0 | 2 | - | - | - | - |
| PRE-104 | Imidazole | $-CH_2O$-cyc-$(C_6H_{11})$ | 1 | 0.32 | 0 | 0 | 0 | - | - | - | - |
| PRE-105 | Pyridine | $-CH_2OCH(CH_3)C(CH_3)_3$ | 2 | 0.07/0.05[b] | 4 | 7 | 1 | [0 | 3 | 6][c] | 0.01 |
| PRE-106 | Pyridine | $-CH_2O(CH_2)_7CH_3$ | 2 | 1.12 | 0 | 0 | 0 | - | - | - | - |
| PRE-107 | Pyridine | $-CH_2O$-cyc-$(C_6H_{11})$ | 2 | 0.04 | 0 | 6 | 4 | 1 | 2 | 4 | - |
| PRE-108 | Imidazole | $-CH_2OCH_3$ | 4 | 0.77 | 0 | 0 | 0 | 1 | 1 | 0 | - |
| PRE-109 | Pyridine | $-CH_2OCH_2Ph$ | 3 | 0.15 | 6 | 5 | 0 | 9 | 6 | 2 | - |
| PRE-110 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 4 | 0.09 | 8 | 7 | 5 | 9 | 5 | 5 | - |
| PRE-111 | Imidazole | $-CH_2O(CH_2)_7CH_3$ | 4 | 1.54 | 0 | 0 | 0 | - | - | - | - |
| PRE-112 | Imidazole | $-CH_2O$-cyc-$(C_6H_{11})$ | 4 | 0.16 | 4 | 1 | 0 | 8 | 5 | 2 | - |
| PRE-113 | Imidazole | $-CH_2OCH_2Ph$ | 4 | 0.16 | 2 | 1 | 1 | 7 | 7 | 0 | - |
| PRE-114 | Imidazole | $-CH_2OCH_2Ph$ | 3 | 0.04/0.17[b] | 0 | 0 | 0 | 2 | 1 | 0 | - |
| PRE-115 | Imidazole | $-CH_2O(CH_2)_7CH_3$ | 3 | 0.03 | 1 | 1 | 0 | - | - | - | - |
| PRE-116 | Imidazole | $-CH_2OCH(CH_3)C(CH_3)_3$ | 3 | 0.15 | 5 | 6 | 4 | 8 | 7 | 3 | - |
| PRE-117 | Imidazole | $-CH_2O$-cyc-$(C_6H_{11})$ | 3 | 0.15 | 2 | 3 | 2 | - | - | - | - |
| PRE-122 | Imidazole | $-C(CH_3)_3$ | 3 | 0.22 | - | - | - | [1 | 1 | 2][c] | - |

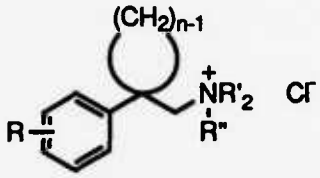
[a]Treatment compound administered with atropine or atropine/2-PAM 10 s after GD challenge, at doses equal to the indicated fraction of their $LD_{50}$. Number of survivors out of 10 is indicated.

[b]Tests performed on different occasions yielded two different $LD_{50}$'s.

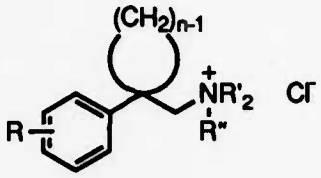
[c]Doses evaluated were 1/64, 1/16, and 1/4 $LD_{50}$.

## APPENDIX D

## $IC_{50}$ VALUES OF THE 1-[(1-ARYLCYCLOALKYL)METHYL]AMINES AT THE PCP RECEPTOR




| SRI Code No. | Amine | R | R' | n | $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| PCP | - | - | - | - | 230 |
| PRE-021 | Pyrrolidine | H | H | 6 | 1,255 |
| PRE-022 | Pyrrolidine | H | $CH_3$ | 6 | 957 |
| PRE-023 | Piperidine | H | H | 6 | 1,814 |
| PRE-024 | Morpholine | H | H | 6 | >25,000 |
| PRE-025 | Piperidine | H | $CH_3$ | 6 | 837 |
| PRE-026 | $NEt_2$ | H | H | 6 | >25,000 |
| PRE-027 | $NEt_2$ | H | $CH_3$ | 6 | >10,000 |
| PRE-028 | Pyrrolidine | 3-OH | H | 6 | 1,309 |
| PRE-029 | Pyrrolidine | 3-OH | $CH_3$ | 6 | >10,000 |
| PRE-030 | Pyrrolidine | 3-$OCH_3$ | H | 6 | 547 |
| PRE-031 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 6 | 433 |
| PRE-032 | Morpholine | H | $CH_3$ | 6 | >10,000 |
| PRE-033 | $N(CH_3)_2$ | H | $CH_3$ | 6 | 2,793 |
| PRE-034 | $N(CH_3)_2$ | H | H | 6 | >25,000 |
| PRE-035 | Pyrrolidine | 3-Cl | $CH_3$ | 6 | 507 |
| PRE-036 | Pyrrolidine | 3-Cl | H | 6 | 859 |
| PRE-037 | Pyrrolidine | H | $CH_3$ | 5 | >10,000 |
| PRE-038 | Pyrrolidine | H | H | 5 | >25,000 |
| PRE-039 | Piperidine | 3-Cl | $CH_3$ | 6 | 817 |
| PRE-040 | Piperidine | 3-Cl | H | 6 | 1,816 |
| PRE-041 | Piperidine | H | $CH_3$ | 5 | 1,039 |
| PRE-042 | Piperidine | H | H | 5 | >25,000 |
| PRE-043 | $N(CH_3)_2$ | 3-$OCH_3$ | H | 6 | >25,000 |
| PRE-045 | Pyrrolidine | 4-$OCH_3$ | H | 6 | >25,000 |
| PRE-046 | Piperidine | 3-$OCH_3$ | $CH_3$ | 6 | 865 |




| SRI Code No. | Amine | R | R' | n | $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| PRE-047 | Morpholine | 3-$OCH_3$ | H | 6 | >25,000 |
| PRE-048 | Piperidine | 3-OH | H | 6 | >25,000 |
| PRE-049 | Piperidine | 3-$OCH_3$ | H | 6 | >25,000 |
| PRE-050 | Piperidine | 4-$OCH_3$ | H | 6 | >25,000 |
| PRE-051 | Morpholine | 3-OH | H | 6 | >25,000 |
| PRE-053 | Piperidine | 4-$CH_3$ | H | 6 | >25,000 |
| PRE-054 | $N(CH_3)_2$ | 4-$CH_3$ | H | 6 | >25,000 |
| PRE-055 | Pyrrolidine | 4-OH | H | 6 | >25,000 |
| PRE-056 | $N(CH_3)_2$ | 3-$OCH_3$ | $CH_3$ | 6 | 717 |
| PRE-057 | $N(CH_3)_2$ | 4-$CH_3$ | $CH_3$ | 6 | >10,000 |
| PRE-058 | Piperidine | 4-$OCH_3$ | $CH_3$ | 6 | >10,000 |
| PRE-059 | $N(CH_3)_2$ | 3-OH | $CH_3$ | 6 | >10,000 |
| PRE-060 | Pyrrolidine | 4-OH | $CH_3$ | 6 | >10,000 |
| PRE-061 | Pyrrolidine | 3-$OCH_3$ | H | 5 | 1,665 |
| PRE-062 | Pyrrolidine | 3-$OCH_3$ | $CH_3$ | 5 | 1,115 |
| PRE-063 | Piperidine | 3-$OCH_3$ | H | 5 | >10,000 |
| PRE-064 | Piperidine | 3-$OCH_3$ | $CH_3$ | 5 | 834 |
| PRE-065 | Piperidine | 3-$OCH_3$ | H | 5 | >10,000 |
| PRE-066 | $N(CH_3)_2$ | 3-$OCH_3$ | H | 5 | 2,613 |
| PRE-067 | Pyrrolidine | 3-OH | H | 5 | >10,000 |
| PRE-068 | Piperidine | 3,4-$(OCH_3)_2$ | H | 6 | >25,000 |
| PRE-069 | Piperidine | 4-$CH_3$ | $CH_3$ | 6 | >10,000 |
| PRE-070 | Morpholine | 3-$OCH_3$ | $CH_3$ | 6 | >10,000 |
| PRE-071 | Morpholine | 3-$OCH_3$ | $CH_3$ | 5 | >10,000 |
| PRE-072 | Pyrrolidine | 3,4-$(OCH_3)_2$ | H | 6 | >25,000 |
| PRE-073 | $N(CH_3)_2$ | 3-OH | H | 6 | >25,000 |
| PRE-074 | Morpholine | 3,4-$(OCH_3)_2$ | H | 6 | >25,000 |
| PRE-075 | $N(CH_3)_2$ | 3,4-$(OCH_3)_2$ | H | 6 | >25,000 |

[a]$IC_{50}$ for the displacement of [$^3$H]TCP from the PCP receptor in guinea pig brain membranes