# ACTIONS OF SOME TOXIC SUBSTANCES (PSYCHOTOMIMETICS) ON THE CENTRAL NERVOUS SYSTEM

A. BEBBINGTON B.Sc. Ph.D.

R. W. BRIMBLECOMBE M.Sc. Ph.D.

*Ministry of Defence*
*Chemical Defence Experimental Establishment*
*Porton Down, Wiltshire*



Behavioural changes can result from the administration of a wide range of chemical substances. Brimblecombe (1968), in a brief review, found reports of mental changes occurring after the administration of a variety of medicinal substances and exposure to many industrially important compounds. These effects occurred usually in hypersensitive individuals or after gross over-dosage. However, there is another large group of chemical substances, the psychotropic drugs, which regularly and specifically modify behaviour. Broadly speaking, these drugs can be classified as either psychotherapeutic or psychotomimetic. The former category includes those substances which are used to alleviate major or minor psychological disorders, while the latter group, variously called hallucinogenic, psychodysleptic, psychodelic, and so on, contains drugs that produce changes in mood, perception and behaviour superficially akin to those observed in the naturally occurring psychoses. It is probably these latter substances only which should most properly be considered in a discussion of toxic substances and behaviour.

Attempts to discover relationships between the chemical structure and the psychotomimetic activity of drugs are made difficult by the absence of precise tests for this activity in man and laboratory animals. The human response to a psychotomimetic drug is essentially a subjective one and, although objective tests of psychomotor performance can be applied, they are not adequate substitutes for subjective descriptions of the drug-induced syndromes. Such descriptions are not, however, quantitative and are of little use in formulating structure–activity relationships.

Laboratory animals may not be capable of experiencing many of the effects induced in man by these drugs and, in any case, detection of such ill-defined phenomena is well-nigh impossible. In consequence, investigators have sought to correlate relatively easily measurable changes induced by the drugs with their psychotomimetic activity and have used potencies in producing these changes as measures of such activity.

It is considered by many workers that psychotomimetic drugs interfere with the normal processes of chemical synaptic transmission in the central nervous system (CNS). Although these processes are not understood in detail, there is evidence to suggest that acetylcholine, 5-hydroxytryptamine (serotonin) and catecholamines may function as central neurotransmitters. In the remainder of this paper we will discuss psychotomimetic drugs which may modify the actions of these substances in the CNS. The drugs are probably best divided into sympathomimetic psychotomimetics, including lysergic acid diethylamide (LSD 25), substituted tryptamines and mescaline, and the anticholinergic psychotomimetics.

## 1. Sympathomimetic Psychotomimetics

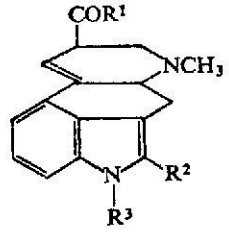
### *a. Lysergic Acid Diethylamide (Lysergide; LSD 25)*

Much work has been carried out with LSD 25 in recent years. Its structural resemblance to the indole derivative, serotonin (see fig. 1), and its activity in antagonizing the actions of this compound on certain isolated tissues have suggested to some workers that LSD 25 interferes directly with the action of serotonin at specific sites within the brain.

It is now apparent that the actions of the drug cannot be explained in such simple terms, for other more potent antagonists of serotonin like 2-bromo-LSD (BOL 148; $R^2 = Br$) have no psychotomimetic activity. After administration of LSD 25, brain-serotonin levels were raised, whereas the concentration of noradrenaline fell by a similar amount (Freedman, 1961), and thus it seems likely that shifts in the equilibrium of amines at central sites are of importance (Freedman & Aghajanian, 1966). Further studies along these lines will be necessary.

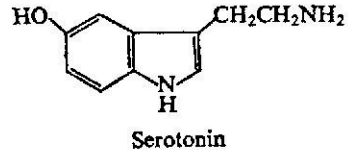
It has been recognized for some time that small doses of LSD 25 produce a rise in body-temperature in a number of species of animals. Horita & Dille (1955) reported that rabbits were the most susceptible species, a finding subsequently confirmed by many other workers. Rothlin, Cerletti, Konzett, Schalch & Taeschler (1956) postulated that a centrally induced "sympathicotonia", of which the elevated body-temperature was only one manifestation, might play an important role in producing the psychotomimetic effects of LSD 25. If this were the case, then a distinct possibility arose of using this hyperthermic response for predicting psychotomimetic potency in LSD 25-like compounds. Hofmann, in 1960, compared the psychotomimetic activities in man of 18 derivatives of lysergic acid with their hyperthermic activities in rabbits. There was a general parallelism between these two activities of the drugs

**FIG. 1.**




LSD 25: $R^1 = N(C_2H_5)_2$, $R^2, R^3 = H$

BOL 148: $R^1 = N(C_2H_5)_2$, $R^2 = Br$, $R^3 = H$



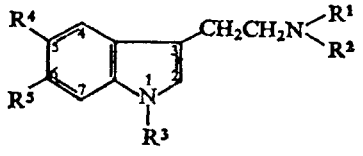

Serotonin

but, in contrast, their in-vitro antiserotonin activities did not parallel their psychotomimetic potencies.

Psychotomimetic activity was retained when the diethylamino group of LSD 25 at $R^1$ was replaced by other amines, but it was always reduced. There was almost complete loss of activity when the double bond in the D ring was saturated. Compounds with substituents at $R^2$ (e.g. BOL 148; $R^2 = Br$) were also inactive. Substitution at $R^3$, as in 1-acetyllysergic acid diethylamide, did not reduce activity. None of these compounds was more active than LSD 25 and it appears that the structural requirements for high activity are rather precise.

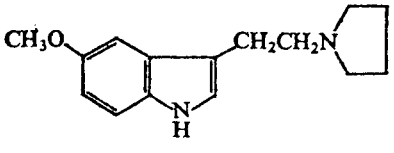
*b. Substituted Tryptamines*

Although tryptamine itself has not been reported as having psychotomimetic activity, alkyl substitution at the side-chain nitrogen atom produces a series of compounds active in man at about the 1 mg./kg. dose-level. These include *N,N*-dimethyl-, -diethyl- and -dipropyl-tryptamines, *N,N*-dimethyl-5-hydroxytryptamine (bufotenine) and *N,N*-dimethyl-4-hydroxytryptamine (psilocin). The results of studies in man are not sufficiently quantitative nor are the compounds tested numerous enough to enable any meaningful structure–activity relationships to be worked out. Like LSD 25, however, tryptamines are effective in producing hyperthermia in rabbits (Brimblecombe, Downing, Green & Hunt, 1964) and, although insufficient data exist in the literature to enable correlations to be made between this activity and psychotomimetic activity in man, Brimblecombe in 1967 showed a good correlation between this hyperthermic activity in 36 tryptamine derivatives and their activity in influencing the behaviour of rats in Hall's open-field test (Hall, 1934). The suggestion was made that the tryptamines interact with the same receptors in the CNS as LSD 25 and that the hyperthermic response and the behavioural changes in the open-field situation are both part of the resulting syndrome. The tryptamines studied had the general formula (I).



I

Lower alkyl substitution on the side-chain nitrogen atom conferred higher activity than substitution with higher alkyl groups and, among these more active compounds, the disubstituted ones were more potent than the corresponding monosubstituted derivatives. Only a limited number of compounds with substituents in the benzene ring were studied, but where direct comparison was possible this substitution always reduced activity. Exceptions to these general rules existed in compounds where the side-chain nitrogen was incorporated into a pyrrolidine ring. This tended to confer a high lethality; the most active and the most lethal of all the compounds studied was *N,N*-tetramethylene-5-methoxytryptamine (II).

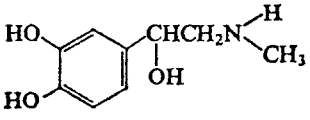


II

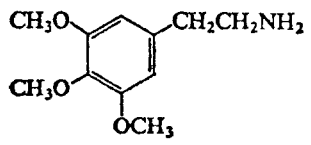
Another study of tryptamines was made by Gessner, Godse, Krull & McMullan (1968). They used compounds with methoxy substitution at positions 4, 5, 6 and 7 in the benzene ring and with alkyl substituents on the side-chain nitrogen atom. Their criterion of activity was blockade of a conditioned avoidance response of rats in a shuttle-box. Methoxy substitution at positions 4 or 5 conferred higher activity than corresponding substitution at positions 6 or 7. Compounds with dimethyl and diethyl substituents on the side-chain nitrogen atom were equiactive. It was noted that *N,N*-dimethyl-5-methoxytryptamine, *N,N*-diethyl-5-methoxytryptamine and *N,N*-methylethyl-5-methoxytryptamine were all more active than the recognized hallucinogens *N,N*-dimethyl-4-hydroxytryptamine and *N,N*-diethyltryptamine.

*c. Phenylethylamines*

The idea that schizophrenia and other mental diseases might result from some disorder of adrenaline metabolism has attracted the attention of many workers. In an attempt to substantiate the hypothesis, many derivatives of adrenaline (III) have been synthesized and tested for possible psychotomimetic activity. It is not possible to review the whole of this work here, and in any case it has been considered at some length by Hoffer & Osmond (1967) and by Smythies (1965). One interesting aspect of the work began with the observation by Osmond & Smythies (1952) that there was a similarity between the symptoms of acute schizophrenia and the effects resulting from mescaline (IV) administration. It was suggested that, in schizophrenia, there may be methylation of the phenolic hydroxyl groups of adrenaline to give a mescaline-like substance. This "M-substance", as it was called, could be considered as an endogenously produced psychotomimetic drug.

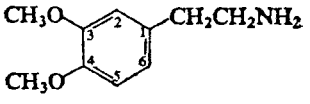


III

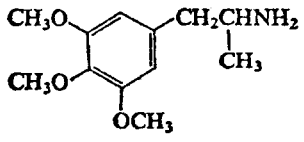


IV

It is of interest that claims have been made in the past few years that 3,4-dimethoxyphenylethylamine (DMPE; V) is present in the urine of schizophrenic, but not in the urine of non-schizophrenic, subjects (Friedhoff & Van Winkel, 1962). However, other workers have refuted this claim (Perry, Hansen, MacDougall & Schwarz, 1966). In 1966, Shulgin, Sargent & Naranjo administered this compound to human volunteers, but it caused no behavioural or autonomic disturbances.



V



VI

Nevertheless, work in this field is still progressing. An amphetamine derivative, 3,4,5-trimethoxyphenylisopropylamine (TMA; VI), has been shown to be psychotomimetic in man (Peretz, Smythies & Gibson, 1955), with about twice the activity of mescaline, and Smythies and his group are engaged

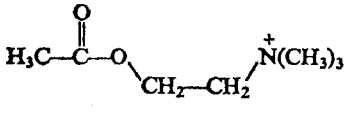
in testing other drugs of this type. Earlier, de Jong (1945) had studied a number of phenylethylamine derivatives for their ability to produce catalepsy and a fear response in cats. Substitution with alkoxy groups in the 4-position was necessary for activity; in considering additional methoxy substitution, position 3 seemed more important than position 5 (see formula V for positions in ring). Ethoxy substitution rather than methoxy substitution reduced activity, whereas substitution at the β-position in the side chain increased activity. In this series of tests on cats, DMPE proved to be as active as mescaline. This is in contrast to Shulgin's finding of its inactivity in man (Shulgin *et al.* 1966).

Apart from TMA, a few other amphetamine derivatives have been studied. Psychoses resulting from prolonged administration of amphetamine itself are not uncommon and, in 1959, Alles reported that 3,4-dimethoxyamphetamine produced marked behavioural changes after a cumulative dose of 126 mg. Recently, a compound which has achieved some notoriety as an hallucinogenic drug is 2,5-dimethoxy-4-methylamphetamine, known as "STP". Limited tests on animals in this laboratory indicated that the drug is likely to have a mescaline-like action, being about fifty times more potent than mescaline itself. Studies in man by Snyder, Faillace & Hollister (1967) suggest a potency of about one hundred times that of mescaline. Recently, Fujimori & Himwich (1968) claimed that STP, unlike amphetamine, acted at the medullary level to facilitate sensory input into the mid-brain. This is, broadly speaking, a mode of action similar to that proposed by Key & Bradley (1960)[1] for LSD 25.

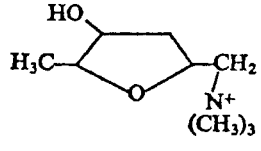
### 2. Anticholinergic Psychotomimetics

#### *a. Muscarinic Receptors in the Central Nervous System*

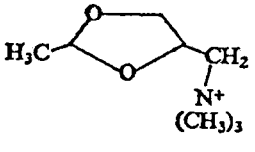
In studying compounds in this class, we have for some years adopted the working hypothesis that there are sites within the CNS which bear a very strong resemblance to peripheral muscarinic receptors. The essential features of these sites have been closely defined by detailed considerations of the structures and conformations of highly active muscarinic substances. Four such compounds which may be considered are acetylcholine (VII), muscarine (VIII), 2-methyl-5-trimethylammonium-methyldioxolane (IX) and oxotremorine (X).



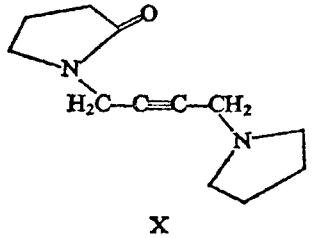
VII



VIII



IX



X

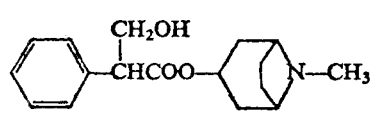
The conformation of acetylcholine in solution has been established recently by Culvenor & Ham (1966), who have shown that the ether oxygen atom is in the *gauche* conformation with respect to the nitrogen atom and that the acetyl group is positioned in such a way that a molecular conformation bearing a strong resemblance to (+)-muscarine results (Chothia & Pauling, 1968). Most deductions about the nature of the muscarinic receptor have of necessity been made in the past on the basis of a consideration of the structures of (+)-muscarine and the dioxolanes, which are conformationally comparatively rigid. It is fortunate that acetylcholine now fits satisfactorily into the picture.

Unfortunately, no precise information is available on the exact conformation of oxotremorine. The four central carbon atoms, by virtue of the acetylenic link, must be linearly disposed but, because of the free rotation of the C—C bonds, the spatial position of the two nitrogen atoms is not defined. However, we assume that, by analogy with the structures of (+)-muscarine iodide and of acetylcholine in solution, the two nitrogen atoms in oxotremorine bear a *gauche* relationship to each other, and in this conformation the molecule is capable of interaction with the three essential sites on the receptor (Bebbington, Brimblecombe & Shakeshaft, 1966). The factors influencing potency in muscarinic agents of this class have been described by us in detail (Bebbington & Brimblecombe, 1965).

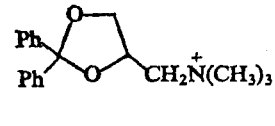
Oxotremorine exhibits peripheral effects which are typical of muscarinic agents; in addition it produces a marked and sustained tremor originating in the CNS (George, Haslett & Jenden, 1962). To shed further light on this tremorogenic action we synthesized a number of acetylenic tertiary amines related to oxotremorine and compared their peripheral muscarinic activity with their ability to produce tremors (blocked by atropine but not by atropine methonitrate). A marked parallelism between peripheral muscarinic activity and central tremorogenic activity was observed. The exact site of the tremorogenic receptors in the CNS is not known, but these results support the view that the structure of the site is essentially similar to that of the peripheral muscarinic receptor. All muscarinic substances possessing a tertiary amine group (i.e., capable of penetrating into the CNS) would thus be expected to have tremorogenic properties, and in general this is found to be the case.

#### *b. Actions of Antagonists*

When the resemblance between peripheral and central cholinergic receptors was established, it was reasonable to re-examine the central properties of known peripheral antagonists. Whereas active muscarinic agents have compact structures, highly active antagonists possess, in addition, groups which are capable of van der Waals binding, thereby increasing the affinity of the drug for the receptor. Potent anticholinergics may, in fact, be considered to be derived from muscarinic agents by the introduction of large substituent groups into the agonist molecule. These groups must, however, be positioned in such a way as to be capable of interaction with closely defined areas of the receptor, remote from the anionic site. Thus, atropine (XI) is related to acetylcholine, and the 2,2-diphenyl-1,3-dioxolane-4-trimethylammonium-methyl salt (XII) is related to the most active muscarinic agent known (IX).



XI



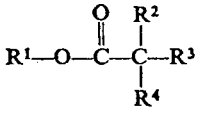
XII

[1] See also Key, *Br. med. Bull.* 1965, 21, 30.—Ed.

The behavioural effects produced by atropine in high dosage have been known since ancient times but, largely as a result of the work of Abood & Biel (1962), very highly active anticholinergics of the glycollate class are now available for studies of the effects of blocking cholinergic receptors in the CNS.

There has been, and still is, some dispute about whether the drugs produce their psychotomimetic effect by virtue of their anticholinergic action in the CNS. Some of the earlier work from which it was concluded that no correlation existed between anticholinergic potency and psychotomimetic activity was not very meaningful, in that the tests of anticholinergic activity were carried out on such preparations as the isolated guinea-pig ileum, i.e., they were a measure of peripheral, rather than central, anticholinergic activity. Later, studies by Herz (1963) and White & Carlton (1963) demonstrated a parallelism between the effects of a series of anticholinergic drugs on the electrical activity of the brain and the behaviour of animals. These results supported the hypothesis that the psychotomimetic benzilates acted via a central anticholinergic mechanism. Brimblecombe & Green (1968a, 1968b) measured the peripheral and central anticholinergic activity of atropine, hyoscine and some piperidyl benzilates. There was a highly significant degree of correlation between the potency of the drugs in blocking oxotremorine-induced tremors in mice (taken as a measure of central anticholinergic activity) and their activity in elevating the threshold level for electrical stimulation of the brain-stem reticular formation to produce an electrocortical arousal. The implication of this finding is that, to produce their characteristic effects on the electrical activity of the cortex, the drugs are blocking cholinergic synapses somewhere in the pathway between reticular formation and cortex—possibly at the level of the diffuse thalamic projections (Bradley & Key, 1958). Whether this effect is associated with the psychotomimetic activity of these drugs, or indeed what it means in terms of behaviour, is not clear. We have been able to show some degree of parallelism between the central anticholinergic activity of a short series of drugs and their potency in blocking the acquisition of a conditioned avoidance response. Again, the significance of this finding in terms of human behaviour is not clear, but it may be relevant to the reported amnesic properties of many of these drugs.

Recently, Abood (1968) has reviewed the psychotomimetic glycollate esters (XIII). Some of his main conclusions regarding the relationship between the chemical structure of the drugs and their psychotomimetic activity are:



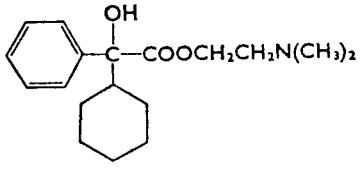
XIII

i. in the series where $R^1$ = *N*-substituted piperidine or pyrrolidine, the *N*-substituent must be a lower alkyl group for maximum activity;
ii. $R^2$ must be an OH group;
iii. $R^3$ and $R^4$ can be the following combinations (in decreasing order of potency): cycloalkyl + phenyl; phenyl + phenyl; phenyl + unsaturated alkyl; cycloalkyl + unsaturated alkyl; phenyl + alkyl; cycloalkyl + alkyl; alkyl + alkyl;
iv. activity is lost following substitution (of halides, alkyl, alkoxy or phenyl) in one or both phenyl rings of the acid moiety;
v. in the piperidyl series, greatest potency is found with the ester in the 4-position of the ring. The 3-position is less potent and the 2-position least potent of all;
vi. the thiol esters (i.e., —S— substituted for —O—) are less potent and shorter acting than their oxygen analogues.

Abood (1968) reviewed the behavioural, electrophysiological and biochemical effects of these esters, but reached no definite conclusion as to whether their psychotomimetic activity was a direct result of anticholinergic action in the CNS.

One additional aspect that is of interest concerns the stereochemical requirements of the active site, which can be studied

**TABLE I. The anticholinergic activities of enantiomers of**



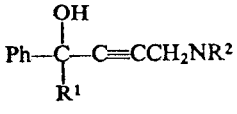
| Derivative and enantiomer used | | Antagonism of acetylcholine on isolated guinea-pig ileum ($pA_2$*) | $ED_{50}$ (μmoles/kg.) for blocking, in mice, of oxotremorine-induced: | | Production of mydriasis in mice | | |
|---|---|---|---|---|---|---|---|
| | | | Salivation | Tremors | Potency relative to atropine | Time to peak (min.) | Duration (min.) |
| Hydrochloride | R | 8.45 | 0.8 | 5.1 | 0.8 | 7 | 80 |
| | S | 7.55 | >100 | >100 | 0.1 | 4 | 50 |
| Methiodide | R | 8.8 | 0.04 | >25 | 2.6 | 24 | 100 |
| | S | 7.4 | 8.8 | >25 | 0.1 | 4 | 60 |

* $pA_2$: the negative logarithm of the molar concentration of the drug which reduces the effect of a double dose of acetylcholine to that of a single one

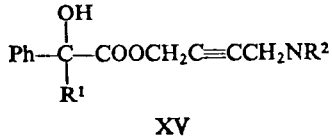
with the aid of enantiomeric pairs of esters. Fortunately, pure enantiomers are now available as a result of the development of an elegant asymmetric synthesis of benzylic centres devised by Inch, Ley & Rich (1968). The absolute configuration of these esters was found to be in agreement with that which had been postulated by Ellenbroek, Nivard, van Rossum & Ariëns (1965) on the basis of a comparison of the pharmacological activities of these compounds with those of the enantiomeric hyoscyamines of known absolute configuration. The R and S enantiomers of dimethylaminoethyl phenyl cyclohexyl glycollate and of its methiodide were tested for anticholinergic activity, as shown in Table I.

It is clear that in all the tests employed, the R enantiomers were more potent than the corresponding S enantiomers. None of these tests gives a direct indication of the psychotomimetic potency of the compounds; but the central anticholinergic activity of the R enantiomer of the free base, as measured by blockade of oxotremorine-induced tremors, is about three times that of atropine, and thus it would not be unreasonable to expect the compound to show appreciable psychotomimetic activity.

Since it has been shown that active anticholinergics can be derived from acetylcholine-like structures by the introduction of phenyl cycloalkyl carbinol groups, it seemed reasonable to suppose that highly active compounds based on the structure of oxotremorine could be similarly devised. This has in fact been found to be the case. Compounds of the type XIV and XV, possessing groups capable of interaction with the areas of van der Waals binding adjacent to the receptor (Bebbington & Brimblecombe, 1965), have pronounced peripheral and central activity.



XIV



XV

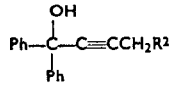
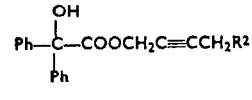
A comparison of the activities of corresponding compounds in these two series reveals that structural changes do not have similar effects. This is shown in Table II.

Maximum central activity (as measured by blockade of oxotremorine-induced tremors) in the acetylenic carbinol series was found with the piperidyl derivative, whereas in the acetylenic glycollate series maximum activity occurred with the dimethylamine derivative. In general, these compounds were all rather less active than the corresponding non-acetylenic glycollates examined by Abood (1968). This suggests that the rigidity imposed on the molecule by the acetylenic bond, which is so important in the case of the agonist oxotremorine, in fact hinders access of the corresponding antagonist to the receptor, thus reducing binding by the ring structures to the appropriate sites on the receptor.

### 3. Conclusions

It is clear that the precise mode of action of the two main groups of psychotomimetic drugs, the sympathomimetics and the anticholinergics, is still not understood. Nevertheless, using rather empirical methods, it has been possible to find some relationship between the activity of these drugs and their chemical structure. Continuing studies of this type should lead to a better understanding of the mode of action of the drugs and to the development of specific antagonists. If future work reveals that naturally occurring mental disorders result from the endogenous production of psychotomimetic substances, then it seems possible that these antagonist drugs may be useful in the treatment of such disorders.

**TABLE II. A comparison of the activity of acetylenic carbinols and acetylenic glycollates**

| $R^2$ |  | | | |  | | | |
|---|---|---|---|---|---|---|---|---|
| | $pA_2$* | $ED_{50}$ (μmoles/kg.) for antagonism, in mice, of oxotremorine-induced: | | Mydriasis in mice (potency relative to atropine) | $pA_2$* | $ED_{50}$ (μmoles/kg.) for antagonism, in mice, of oxotremorine-induced: | | Mydriasis in mice (potency relative to atropine) |
| | | Salivation | Tremors | | | Salivation | Tremors | |
| $N(CH_3)_2$ | 7.8 | 22.1 | >100 | 0.02 | 7.95 | 5.7 | 11.7 | 0.34 |
|  | 8.1 | 10.2 | 50.0 | 0.11 | 7.45 | 29.9 | >100 | 0.05 |
|  | 8.1 | 8.8 | 7.5 | 0.60 | 7.10 | >100 | >100 | 0.02 |
|  | 8.1 | >100 | >100 | 0.02 | 7.00 | >100 | >100 | <0.01 |

*$pA_2$: the negative logarithm of the molar concentration of the drug which reduces the effect of a double dose of acetylcholine to that of a single one

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