interaction, and this area may also be the site at which the 5-HT antagonists, administered peripherally, are also exerting their effects, although other forebrain areas cannot be ignored. The inability of methysergide and cyproheptadine to completely antagonize the inhibitory action of the larger doses of neuroleptic agents suggests that the reduction in dopamine hyperactivity is not due solely to an enhanced 5-HT activity. Nevertheless, the indication that an enhanced 5-HT function may be important for the action of neuroleptic drugs to inhibit a dopamine response is of interest, particularly for the atypical agents, clozapine, sulpiride and thioridazine. These agents are classified as atypical since they generally fail to cause a marked effect in behavioural tests considered to reflect dopamine blockade, and yet the biochemical experiments to determine the action of these compounds to modify mesolimbic function have invariably assumed a primary drug action on dopamine mechanisms. Thus, the apparent dissociation of extrapyramidal effects (striatal action) from an antipsychotic action (mesolimbic system) using the atypical agents has been investigated experimentally by attempting to correlate a differential action on dopamine turnover in the two areas (Waldmeier & Maitre, 1976; Westerink, Lejeune & van Pragg, 1977). Generally, whilst some differences have been found the degrees of difference are small. It is suggested that future studies should additionally consider an involvement of 5-HT within the two areas.

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REFERENCES

BURKI, H. R., RUCH, W. & ASPER, H. (1975). *Psychopharmacologia (Berl.)*, **41**, 27–33.
COSTALL, B. & NAYLOR, R. J. (1975). *Eur. J. Pharmac.*, **32**, 87–92.
COSTALL, B. & NAYLOR, R. J. (1976). *Ibid.*, **35**, 161–168.
COSTALL, B., FORTUNE, D. H. & NAYLOR, R. J. (1977). *Br. J. Pharmac.*, **60**, 266P.
COSTALL, B., MARSDEN, C. D., NAYLOR, R. J. & PYCOCK, C. J. (1976). *J. Pharm. Pharmac.*, **28**, 523–526.
COSTALL, B., NAYLOR, R. J. & PINDER, R. M. (1976). *Psychopharmacology*, **48**, 225–231.
DE GROOT, J. (1959). *Verh. K. Ned. Akad. Wet.*, **52**, 14–39.
JACKSON, D. M., ANDÉN, N.-E. & DAHLSTRÖM, A. (1975). *Psychopharmacologia (Berl.)*, **45**, 139–149.
LEYSEN, J. E., GOMMEREN, W. & LADURON, P. M. (1978). *Biochem. Pharmac.*, in the press.
LOEW, D. M., DEPOORTERE, H. & BURKI, H. R. (1976). *Arzneimittel-Forsch.*, **26**, 1080–1083.
PIJNENBURG, A. J. J., HONIG, W. M. M. & VAN ROSSUM, J. M. (1975). *Psychopharmacologia (Berl.)*, **41**, 175–180.
PIJNENBURG, A. J. J. & VAN ROSSUM, J. M. (1973). *J. Pharm. Pharmac.*, **25**, 1003–1005.
PYCOCK, C. J., HORTON, R. W. & CARTER, C. J. (1978). *Int. Soc. for Neurochemistry, Satellite Symposium Dopamine* Southampton, U.K., Aug 30th–1st Sept., Editors, Iversen, L., Roberts, P. J. and Woodruff, G. N. New York: Raven Press, in the press.
RUCH, W., ASPER, H. & BURKI, H. R. (1976). *Psychopharmacologia (Berl.)*, **46**, 103–109.
WALDMEIER, P. C. & MAITRE, L. (1976). *J. Neurochem.*, **27**, 589–597.
WESTERINK, B. H. C., LEJEUNE, B. & VAN PRAAG, H. M. (1977). *Eur. J. Pharmac.*, **42**, 179–190.

Receptor interaction for the α-antagonist WB4101 (2-(*N*[2,6-dimethyoxyphenoxyethyl])amino-methyl-1,4-benzodioxane)

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WB4101, a member of the series of benzodioxanes described by Fenton, Green & others (1965) has been evaluated for α-adrenoceptor blocking activity (Mottram & Kapur, 1975). The results indicated that it produced profound post-synaptic α-antagonism against noradrenaline on rat vas deferens, having a pA_2 value (Schild, 1947) of 9·8. Likewise, it has been shown to possess potent α-antagonistic properties in the central nervous system. (Greenberg, U'Prichard & Snyder, 1976). Mottram & Kapur (1975) have suggested that the interaction between WB4101 and the α-receptor involves subsites within the receptor for the nitrogen atom, the benzodioxan moiety and also a possible aromatic subsite though which the dimethoxy benzene may interact. This tertiary interaction may account for the very high potency of WB4101.

To elucidate further the receptor site, a series of benzodioxanes previously described by Green, Shapero & Wilson, 1969 was chosen (1) to study the effect of altering the chain length between amine and aromatic groups, and (2) to examine the effect of ring substitution on drug-receptor interaction.

Male Wistar rats (200–300 g) were killed by a blow to the head, their vasa deferentia removed and stripped

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of extraneous tissue and suspended in 10 ml organ baths. The tissues were bathed in Tyrode solution (composition, g litre^{-1}, NaCl 8·0, KCl, 0·2, Mg $Cl_2.6H_2O$, 0·2, $CaCl_2$, 0·2, $NaH_2PO_4.H_2O$, 0·05, $NaHCO_3$, 1·0 and glucose, 1·0) maintained at 37° and aerated with a mixture of 5% CO_2 in oxygen. Isometric contractions were recorded with Devices 2 oz strain gauge transducers and two channel recorders.

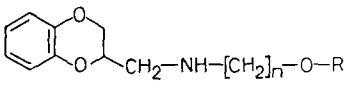
The antagonistic potencies of the compounds were evaluated against noradrenaline by measuring their pA_2 values (Schild, 1947). Table 1 shows the pA_2 values of benzodioxanes with structures similar to WB4101 but bearing dissimilar substituent groups or arrangement of groups on the phenyl ring. Reduction of the methoxy substituents from two to one reduces the α-antagonistic potency markedly. Removal of the second *ortho*-methoxy groups further reduces potency though to a lesser extent. Re-positioning of the methoxy groups around the phenyl ring again affects the pA_2 values adversely.

Replacing the methoxy groups by methyl groups also produces a detrimental effect on the antagonistic potency of these compounds.

The effects of altering the chain length between amine and phenyl groups is also shown in Table 1. Increasing the length by a single methylene group (WB4101 to WB4111) decreases the α-antagonistic potency markedly. Increasing the chain length of WB4082 by one methylene group likewise decreased potency in that WB4093 was devoid of specific α-antagonistic properties. Increasing the chain length of WB4093 by a further methylene group re-established some degree of α-blockade (WB4099).

The results of this study indicate that the contribution of the methoxy group to antagonistic activity may be either through a direct interaction with a constituent of the receptor or as an electron donator to the phenyl ring thereby increasing its attractive force to a phenyl subsite within the receptor. The second of these possibilities seems unlikely since the fall in activity after the loss of one group (4085) is so great, and removal of the second methoxy group (4082) does not decrease activity markedly, in fact there is an increase relative to *p*-methoxy analogue WB4105. With regard to the first possibility, that of a subsite receptive to the methoxy group, perhaps via a hydrogen bond interaction, the substitution of methyl groups for methoxy (WB4110 and WB4108) greatly reduces α-antagonism. It would be expected that WB4085 with one methoxy group in the 2 position would exhibit equal antagonistic potency to WB4101 since the ring would be free to rotate and make the methoxy available for subsite interaction. This is not so. This may indicate that there are two methoxy subsites in the receptor or alternatively that a single methoxy throws the phenyl ring out of plane and therefore disrupts its interaction with an aromatic subsite within the receptor.

Table 1. pA_2 *values of benzodioxanes and showing effects of altering chain length.*



Compound	R	n	pA_2 value
WB4101	2,6-dimethoxy-phenyl	2	9·8 ± 0·04 (6)
WB4085	2-methoxy-phenyl	2	6·62 ± 0·09 (5)
WB4107	3-methoxy-phenyl	2	5·87 ± 0·06 (5)
WB4105	4-methoxy-phenyl	2	4·35 ± 0·07 (5)
WB4082	phenyl	2	4·88 ± 0·02 (5)
WB4110	2,6-dimethyl-phenyl	2	5·39 ± 0·12 (5)
WB4108	6-methyl-phenyl	2	4·92 ± 0·02 (5)
WB4111	2,6-dimethoxy-phenyl	3	4·4 ± 0·08 (6)
WB4093	phenyl	3	< 3·0 (4)
WB4099	phenyl	4	4·3 ± 0·06 (4)

The insertion of a single methylene group into the chain markedly reduced the potency of both the dimethoxy substituted (WB4111) and non-substituted (WB4093) analogues. This would appear to further confirm that the receptor site contains a subsite for aromatic interaction at a specific distance from the primary nitrogen subsite. WB4099 in which two methylene groups have been inserted into the chain exhibits a recovery in antagonistic potency which it is suggested is due to an increased flexibility of the longer chain, allowing a re-alignment of the phenyl group onto its receptor subsite.

Thus the results show that the postsynaptic α-receptor antagonism exhibited by WB4101 depends not only on the benzodioxan moiety but that incorporated into the receptor is at least one other subsite for aromatic interaction at a specific distance from the subsite for nitrogen interaction and that the 2,6-dimethoxy substituents play an important role in the drug-receptor interaction either indirectly through a conformational influence or directly through a receptor subsite interaction.

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REFERENCES

FENTON, H., GREEN, P. N., SHAPERO, M. & WILSON, C. (1965). *Nature*, **206**, 725.
GREEN, P. N., SHAPERO, M. & WILSON, C. (1969). *J. medl Chem.*, **12**, 326.
GREENBERG, D. A., U'PRICHARD, D. C. & SNYDER, S. H. (1976). *Life Sci.*, **19**, 69–76.
MOTTRAM, D. R. & KAPUR, H. (1975). *J. Pharm. Pharmac.*, **27**, 295–296.
SCHILD, H. O. (1947). *Br. J. Pharmac. Chemother.*, **2**, 189–206.