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The hydroxy-hexahydronaphthoxazines: a new group of very potent and selective dopamine agonists

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Replacement of the pyrrole ring system in the dopaminergic oxaergolines (e.g. RU 29717) by a phenolic OH group leads to the hydroxy-hexahydronaphthoxazines, a new group of potent dopamine agonists which exhibit increased selectivity due to their lower affinity for adrenergic and 5-HT receptors.

The ergolines, such as bromocriptine and lergotrile, are one of the most potent and well-studied groups of dopamine (DA) receptor agonists (Loew et al 1978). However, they are structurally complex and they exhibit various side effects which are possibly due to their actions on α-adrenergic and 5-hydroxytryptaminergic (5-HT) receptors (Müller-Schweinitzer & Weidmann 1978; Barbeau et al 1979; McPherson & Beart 1983). There is thus currently much interest in developing simpler analogues which are purer DA agonists. Recently, the chemically less complex oxaergolines such as EOE (Martin et al 1982) and RU 29717 (Boissier et al 1983) have also been shown to be strong DA agonists, however, they also possess considerable activity at α and 5-HT receptors (Anderson et al 1983; Nedelec et al 1983). We now report that the replacement of the pyrrole ring of the oxaergolines by a phenolic hydroxyl group (see Table 1) leads to the hydroxy-hexahydronaphthoxazines which are compounds having a very high dopaminergic potency combined with selectivity with regard to their affinity for other receptor types. The two isomers N-0499 (7-OH) and N-0500 (9-OH) were tested against the corresponding oxaergoline RU 29717 (see Table 1).

Four tests of dopaminergic activity were used, i.e. rat brain striatal homovanillic acid (HVA) decrease and the antagonism of the GBL-induced rise in dopa levels, both of which reflect pre-synaptic dopaminergic activity (Feenstra et al 1983), induction of stereotypy in rats which is an indication of post-synaptic dopaminergic actions (Horn et al 1979) and finally the inhibition of the in-vitro binding to rat striatal homogenates of [^{3}H]DiPr-5,6-ADTN, which is a measure of D-2 DA activity (Mulder et al 1984). In addition α_1/α_2 adrenergic and 5-HT_1/5-HT_2 potencies were investigated in-vitro by studying the ability of the compounds to displace

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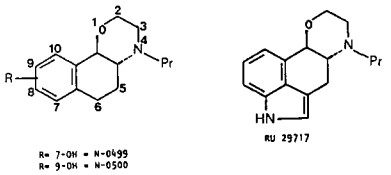
Table 1. Pharmacological activities of N-0499 and N-0500 at dopaminergic, adrenergic and 5-HT receptors.

Test	N-0499	N-0500	RU 29717
[^{3}H]DiPr-5,6-ADTN[1] (IC50, nM)	80·0	2·8	3·0
% Decrease HVA[2]	13·6	56·1	55·8
GBL-DOPA[3] (ED50, μmol kg^{-1})	0·86	0·09	—
Stereotypy[4] (μmol kg^{-1})	7·5	0·5	0·5*
α_1[5] (IC50, nM)	9000	34000	—
α_2[6] (IC50, nM)	1050	1500	31**
5-HT_1[7] (IC50, nM)	2100	480	25*
5-HT_2[8] (IC50, nM)	15 000	12 500	—



[1] The IC50 is the concentration of drug required to inhibit the binding of the labelled ligand by 50%. Each concentration (range 10^{-11}–10^{-5} M) was analysed in triplicate.

[2] Percentage decrease in HVA levels after 1 h following a dose of 0·4 μmol kg^{-1} i.p. Values are the means of 8 determinations.

[3] The ED50 is the dose of drug required to inhibit the GBL-induced rise in dopa levels by 50%. Values are the means of 4 determinations.

[4] Dose (s.c.) inducing a state of continuous sniffing behaviour in rats, corresponding to a score of 2 according to Costall et al (1977).

[5] Displacement of [^{3}H]prazosin binding to rat brain membranes, see 1 for definition of IC50. Values are the means of 4 experiments run in duplicate.

[6] Displacement of [^{3}H]clonidine binding to rat brain membranes. Number of experiments as in 5. IC50 clonidine = 2·9 nM.

[7] Displacement of [^{3}H]5-HT binding to rat frontal cortex membranes. Number of experiments as in 5. IC50 5-HT = 2·5 nM.

[8] Displacement of [^{3}H]mianserin binding to rat frontal cortex membranes. Number of experiments as in 5.

* Boissier et al (1983).

** Anderson et al (1983).

[^{3}H]prazosin, [^{3}H]clonidine, [^{3}H]5-HT and [^{3}H]mianserin binding to rat brain membranes, respectively (Kalkman et al 1983; Timmermans et al 1984).

As can be seen the 9-OH isomer (N-0500) rather than the 7-OH compound (N-0499) had the same potency as RU 29717 with regard to dopaminergic activities. This is a most surprising finding and it means that the hypothesis that the NH group of the pyrrole ring of the ergolines and oxaergolines is in some way equivalent to one of the -OH groups in DA may be an oversimplification (Müller-Schweinitzer & Weidmann 1978). It is noteworthy in this context that the ergoline derivative lergotrile is metabolized to the more active 13-OH compound (Parli et al 1978) and this position corresponds to the 9-OH position in the hexahydronaphthoxazines. It is also of interest that not only is N-0500 as potent as RU 29717 as a DA agonist but that its affinity for α_2 and 5-HT$_1$ receptors is very much less than that of RU 29717. The pressor effects of N-0499 and N-0500 at high doses (1–3 mg kg^{-1} i.v.) were very small and their effects on heart rate (β_1-mimetic) were negligible. Taken together these results show that N-0500 is not only a very potent DA agonist but that it is a much more specifically acting drug than many of the dopaminergic ergolines. An additional advantage with the hydroxy-hexahydronaphthoxazines is that the synthesis and purification of these compounds is much easier than that of the corresponding carbon analogues i.e. the hydroxyoctahydrobenzol[f]quinolines (Cannon et al 1979).

Recently Martin et al (1984) have come to similar conclusions regarding the high potency of the (+)-enantiomer of N-0500, which they refer to as (+)-PHNO. To our knowledge, however, this is the first report regarding the high selectivity of action of this compound. The present findings show that with a careful manipulation of molecular structure it is possible to greatly reduce certain additional pharmacological actions which occur in some DA agonists which are based on the ergoline ring system.

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