Bioorganic & Medicinal Chemistry Letters, Vol.1, No.12, pp. 717-720, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

5-HT_2 ANTAGONIST ACTIVITY OF 3-AMINOMETHYLTETRALONES

Loza[1], M.; Verde[1], I.; Castro[1], M.E.; Orallo[1], F.; Fontenla[1], J.A.; Calleja[1], J.M.; Ravina[2], E.; Cortizo[2], L and de Ceballos[3], M.L.

[1] Department of Pharmacology and [2] Department of Organic Chemistry (Lab. Pharmaceutical Chemistry), *Faculty of Pharmacy*, University of Santiago de Compostela. 15706 - Santiago de Compostela, **Spain.**

[3] Department of Neuropharmacology, *Cajal Institute, CSIC.* 28006 - Madrid, **Spain.**

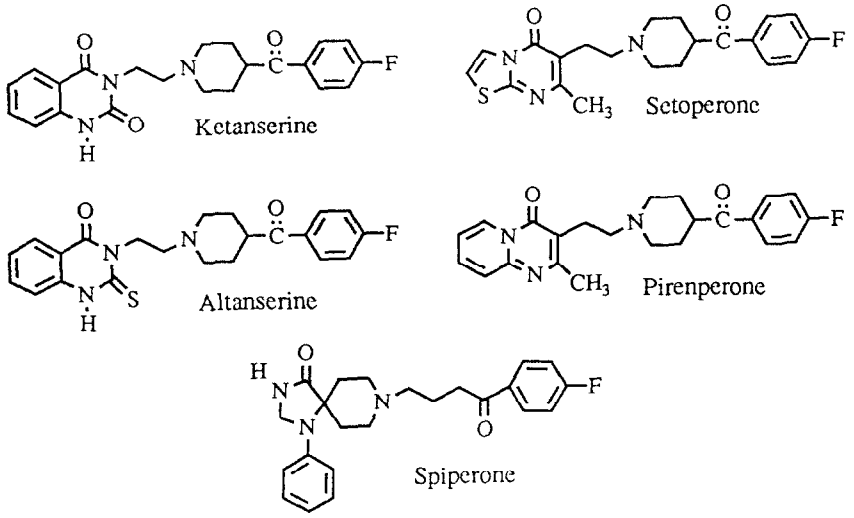
(*Received* 16 *August* 1991)

Abstract: The affinity of four 3-aminomethyltetralones for 5-HT_2 receptors is reported, together with their inhibitory activity against serotonin-induced contractions in rat aorta rings stripped of endothelium. Compound **4**, which has a p-fluorobenzoyl-piperidine fragment, exhibited activity similar to that of methysergyde.

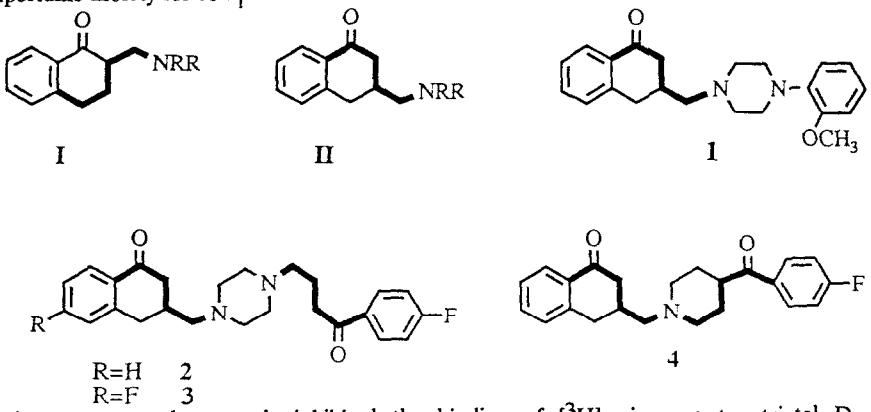
There is now substantial evidence for the existence of multiple 5-HT receptor subtypes recently classified into three major categories designated as 5-HT_1 like, 5-HT_2 and 5-HT_3 (1). The remarkable recent advances in our understanding of 5-HT neurotransmission reflect, in large part, the increasing availability of compounds with selectivity and potency for individual 5-HT receptor subtypes (2), which has led to proposals for the corresponding recognition sites (3-5).

One of the first compounds used to discriminate 5-HT receptor subtypes was spiperone, a butyrophenone derivative originally developed as a dopamine receptor antagonist. The compound has very high affinity for the 5-HT_2 sites but is more active at the D_2 dopamine receptor.

The discovery of the 5-HT receptor antagonist properties of ketanserin, originally designated as a histamine H_1 receptor antagonist, was a key development in this field. The important feature of ketanserin is that it can clearly discriminate 5-HT_2 from 5-HT_1 sites. Numerous analogues (including setoperone, pirenperone, altanserin and ritanserin) have been developed with the aim of improving selectivity, some of which have been investigated as regards their potential for the treatment of anxiety, depression, schizophrenia or other psychic disorders (2). Setoperone, pirenperone and altanserin contain the benzoylpiperidine fragment that is also present in ketanserin and which has been described as a neuroleptic pharmacophore of similar potency to the butyrophenone fragment (6).



In earlier papers (7-9) we reported the potential neuroleptic activity of 2- and 3-aminomethyl tetralones I and II (NRR represents simple amine substituents). These compounds are semirigid variants of the general neuroleptic structure Ar C_4 N. Also recently described the synthesis and antidopaminergic effects of the 3-aminomethyl tetralones **1-4** in both *in vivo* and *in vitro* tests (10). Compound **1** has only one butyrophenone pharmacophore, the semirigid aminomethyl tetralone moiety, while compounds **2-4** have two pharmacophores: the tetralone moiety and a flexible linear butyrophenone fragment for compounds **2** and **3** or a semirigid benzoylpiperidine moiety for compound **4**.



These compounds potently inhibited the binding of [^{3}H]-spiperone to striatal D_2 receptors and moderately inhibited the binding of[^{3}H]-SCH 23390 to striatal D_1 receptors. They had effects similar to those of haloperidol in conventional test of antipsychotic activity, but did not cause catalepsy (10).

In this letter we report the affinity of the above compounds for 5-HT_2 receptors, as measured by their inhibition of [^{3}H]-ketanserine binding to frontal cerebral cortex membranes of rat (15), together with their inhibitory activity against serotonin-induced contractions in rat aorta rings stripped of endothelium (11-14).

All four compounds were active. The most active was compound **4**, which had a pA_2 slightly lower than that of ketanserin in the aorta-rings experiments and a pK_i similar to that of methysergide in the binding experiments. Compounds **2** and **3**, which have p-fluoro-4-aminobutyrophenone moieties instead of the p-fluoro-4-benzoylpiperidine moiety of **4**, were less active than the latter, while compound **1**, which has an o-methoxyphenylpiperazinyl moiety, was only moderately active. The significant activities of compounds **2** and **3**, though 20 times lower than those of ketanserin and methysergide, suggest that their tetralone moieties contributed to antagonism of serotonin at $5\text{-}HT_2$ receptors.

COMPOUND	pA_2	pK_i
1	6.29	6.48
2	7.27	7.25
3	7.25	7.29
4	7.86	8.80
Ketanserine	8.87	---
Methysergide	---	8.84

The most active compound, the p-fluoro-4-benzoylpiperidine derivative **4**, whose inhibition of ketanserin binding to $5\text{-}HT_2$ receptors was similar to that of methysergide, has been selected for further investigation under the code number QF0104B.

Acknowledgement: This work was partially supported by the Xunta de Galicia, Spain.

References and Notes

1. **Bradley, P.B.; Engel, G.; Feniuk, W.; Fozard, J.R.; Humphrey, P.P.A.; Middlemiss, D.N.; Mylecharane, E.J.; Richardson, B.P.; Saxena, P.R.** *Neuropharmacology* **1986**, *25*, 563.

2. **Fozard, J.R.** *Trends Pharmacol. Sci.* **1987**, *8*, 501.

3. **Hibert, M.F.; Gittos, M.W.; Middlemiss, D.N.; Mir, A.K.; Fozard, J.R.** *J. Med. Chem.* **1988**, *31*, 1087.

4. **Hibert, M.F.; McDermott, I.; Middlemiss, D.N.; Mir, A.K.; Fozard, J.R.** *Eur. J. Med. Chem.* **1989**, *24*, 31.

5. **Hibert, M.F.** *Actual. Chim. Ther.* **1989**, *16*.

6. **Boswell, R.F., Jr.; Welstead, W.J.,Jr.; Duncan, R.L., Jr.; Johnson, D.N.; Funderburk, W.H.** *J. Med. Chem.* **1978**, *21*, 136.

7. **Eirin, A.; Ravina, E.; Montanes, J.M.; Calleja, J.M.** *Eur. J. Med. Chem.* **1976**, *11*, 29.

8. **Eirin, A.; Santana, L.; Ravina, E.; Fernandez, F.; Sanchez-Abarca, E.; Calleja, J.M.** *Eur. J. Med.*

Chem. **1978**, *13*, 533.

9. **Santana, L.; Ravina, E.; Eirin, A.; Sanchez-Abarca, E.; Calleja, J.M.** *Proceedings of the VII International Symposium on Medicinal Chemistry.* Torremolinos (Spain), **1980**, p 173.

10. **Cortizo, L.; Santana, L.; Ravina, E.; Orallo, F.; Fontenla, J.A. Castro, E.; Calleja, J.M.; de Ceballos, M.L.** *J. Med. Chem.*, **1991**, *(In press)*.

11. **Aorta-ring experiments:** Aorta rings from 275 ± 25 g male Sprague-Dawley rats stripped of endothelium were mounted under a resting tension of 1.5 g in a 20 mL organ bath containing Krebs solution (composition (mM): NaCl, 118.07; KCl, 4; $CaCl_2$ H_2O, 2.5; $MgSO_4 \cdot 7H_2O$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; Glucosa, 11) at 37°C bubbled with carbogen (95% O_2, 5% CO_2). Isometric contraction forces were measured using a CPUL 0-25 g transducer connected to a Celaster IOS-1 apparatus. After 60 min stabilization, accumulative concentration-response curves were recorded as per Van Rossum, increasing serotonin concentration from 30 nM to 10 mM, in the absence and in the presence of increasing concentrations of ketanserine or the new compounds. Competitive antagonism was quantified as pA_2, which was calculated from a Schild plot of log (dose ratio - 1) for three antagonist concentrations; six replicate experiments were performed.

12. **Cohen, M.L.; Fuller, R.W.; Wiley, K.S.** *J. Pharmacol. Exp. Ther.* **1981**, *218*, 421.

13.- **Van Rossum, J.M.** *Arch. Int. Pharmacodyn.* **1963**, *143*, 299

14. **Tallarida, R.J.; Murray, R.B.** *Manual of Pharmacologic Calculations with Computer Programs.* Springer-Verlag, New York, **1987**.

15. **(^{3}H)-Ketanserin binding to frontal cortex membrane preparations:** Frontal cortex tissue from male Wistar rats weighing 190 ± 10 g were dissected on a cold plate, weighed and stored at -20°C until assayed. Frontal cortex from each rat was homogenized (Ultraturrax, 5 sec at 20,000 rpm) in 50 vol of Tris HCl 50 mM, pH 7.4, and centrifuged at 30,000 g for 10 min at 4°C. The pellet was rehomogenized and centrifuged at again. The final pellet was reconstituted in 2000 vol of buffer. Aliquots of membrane preparations (200 ul) were incubated with 25 ul of 1 nM (^{3}H)-ketanserin (NEN; 60 Ci/mmol specific binding was defined by the incorporation of 25 ul of methysergide, 1 uM final concentration. Samples were incubated for 15 min at 37°C, incubation was terminated by vacuum filtration.

All experiments were performed in duplicate, using at least six increasing concentrations of the drug under study. Inhibition constant (Ki) values were calculated from the Cheng-Prussof equation. $K_I = IC_{50}/(1+(F/K_D))$, were F is the total concentration of ^{3}H-ligand used, K_D is the equilibrium dissociation constant and IC_{50} is the drug concentration required to inhibit 50% of specific binding, percentage specific binding being calculated as (dpm sample-dpm non specific binding/ dpm total-dpm non specific binding)*100.