Antidepressant Activity of New 3-Amino-5-disubstituted Benzylidene-6-methyl-(4H)-pyridazine Derivatives

CATHERINE RUBAT, a PASCAL COUDERT, b PIERRE BASTIDE a and PIERRE TRONCHE a,b

Laboratoire de Pharmacologie, a and Laboratoire de Chimie Thérapeutique, b
Faculté de Pharmacie, Université de Clermont-Ferrand 1,
28, place Henri-Dunant, F-63001 Clermont-Ferrand,
Cedex, France

(Received May 23, 1988)

By the reaction of various amines with 3-chloropyridazines, several minaprine analogues were prepared. Most of them exhibited significant antidepressant activity. Compound 2a antagonizes reserpine action and neuroleptic-induced catalepsy in a dose-dependent manner.

Keywords—disubstituted benzylidene pyridazine; 3-amino pyridazine derivative; minaprine analogue; antidepressant activity

Recently, it was reported that minaprine proved to be effective in the treatment of various depressive disorders. 1) This 3-amino-6-phenylpyridazine derivative is known to represent a new class of psychotropic drugs. 2) This prompted us to synthesize analogues containing a 5-disubstituted benzylidene pyridazine moiety. Most of them were found to be effective in antidepressant activity tests.

\[
\text{minaprine}
\]

Results and Discussion

The selected compounds were synthesized according to the scheme shown.

3-Chloro-5-disubstituted benzylidene-6-methyl-4H-pyridazines (1) were prepared as described in a previous paper. 3) They were refluxed with an excess of the requisite amine to afford 3-amino-5-disubstituted benzylidene-6-methyl-4H-pyridazine derivatives (2a—g). All compounds were evaluated for antidepressant activity as described in the experimental section. Physical and spectral data are summarized in Tables I and II; pharmacological data are reported in Table III.
The experimental study on animals indicated that most derivatives antagonized reserpine-induced ptosis as well as prochlorperazine-induced catalepsy. Compounds 2a, 2c, 2f exhibited remarkable activities as shown in Table III. They antagonized reserpine-induced ptosis in a dose-dependent manner, in the range of 25 to 100 mg/kg. Maximal antagonism of ptosis was achieved 1 h after reserpine administration. Four hours after treatment, all...
compounds failed to antagonize reserpine-induced ptosis even at doses of 100 mg/kg. The nature and the length of the amino-chain at the 3-position on the pyridazine ring did not have a clear influence in terms of the pharmacological data. Compounds 2a—d with a dimethylamino group were not significantly more potent than compounds 2e—g containing a morpholino group. In the same way, compounds 2a, 2b and compounds 2c, 2d with an additional carbon on the alkylamino chain did not present significant different activities. In addition, the presence of one chlorine atom on the phenyl nucleus in the case of compounds 2a and 2f seemed to be favorable for antidepressant effect. In the first test, compound 2a showed an activity comparable to that of minaprine, but with a shorter duration of effect. The same compounds 2a, 2c and 2f significantly and potently antagonized catalepsy induced by prochlorperazine. All the other tested drugs were less active in this test.

The antidepressant potential of the target compounds 2a—g seemed to be partly determined by the number of chlorine atoms on the phenyl nucleus. With regard to structure—activity relationships, introduction of two chlorine atoms at the 2' and 6' positions of the phenyl nucleus did not enhance antidepressant activity.

In conclusion, the present study revealed that 3-amino-5-disubstituted benzylidene-6-methyl-4H-pyridazines 2 were relatively potent as antidepressant drugs. Compound 2a showed a dose-dependent antidepressant activity as potent as that of minaprine in the two tests used.

**Experimental**

Melting points were determined on a Kofler apparatus and are uncorrected. The infrared spectra were recorded
on a Beckman 4240 spectrophotometer. The proton nuclear magnetic resonance (1H-NMR) spectra were recorded on a Varian EM 360 A spectrometer. Resonance positions are given on the δ scale (parts per million) relative to internal tetramethylsilane. The NMR signals are designated as follows: s, singlet; br s, broad singlet; m, multiplet.

Chemistry — (2',6'-Disubstituted benzylidene)-6-methyl-3-(dimethylaminoalkylamino)-4H-pyridazine (2a—d): A solution of a 3-chloropyridazine 1 (0.01 mol) in an excess of a suitable amine (0.1 mol) was refluxed for 24 h. After evaporation in vacuo the residue was triturated with diethyl ether and washed with water to provide the expected aminopyridazines. Compounds 2a—d were recrystallized from mixtures of ethanol-water.

(2,6-Disubstituted benzylidene)-6-methyl-3-(2-morpholinoethylamine)-4H-pyridazine (2e—g): A solution of a 3-chloropyridazine 1 (0.01 mol) in an excess of 4-(2-aminoethyl)morpholine (13 g, 0.1 mol) was refluxed for 24 h. After cooling, the solid residue which separated was filtered off and triturated with water until crystallization. Compounds 2e—g were recrystallized from mixtures of ethanol—water.

Pharmacology — All compounds were administered orally in a 0.5% hydroxypropyl methyl cellulose aqueous suspension. Ifa Credo OF1 male mice (20 g) and OFA male Wistar rats (200 g) were used.

Antagonism of Reserpine-Induced Ptosis 4): This test was performed on groups of 10 mice weighing 20 ± 2 g. Test drugs were administered p.o. 1 h before the test. Reserpine was dissolved in a 1% solution of citric acid and administered i.p. at a dose of 2.5 mg/kg: 1, 2 and 4 h later, ptosis was assessed. Animals were hung up by the tail individually for 10 s; when animals did not exhibit ptosis during these 10 s, ptosis was considered as antagonized. Mice were scored individually according to the criteria of Rubin et al. 5) Results are expressed as the percentage of protection in comparison with controls.

Antagonism of Prochlorperazine-Induced Catalepsy: Test drugs were administered p.o. to groups of 6 rats. One hour later, prochlorperazine was administered i.p. at a dose of 12 mg/kg. Catalepsy was assessed 5 h after the administration of prochlorperazine; each rat was individually placed with its forepaws on a stand 11 cm high and the animals were forced to maintain this abnormal position. A rat which kept the posture for over 20 s was considered as cataleptic. Rats were scored individually according to the following criteria: 2, catalepsy; 1, ambiguous posture; 0, no catalepsy. Results are expressed as the percentage of noncataleptic rats in comparison with the control group.

Data Analysis: Statistical analysis of the results was performed using the method of Schwartz. 7) The data on antagonism of reserpine-induced ptosis were analyzed by using Student’s t-test. All values of percentage protection in Table III were expressed as mean ± S.E. Qualitative data on the antagonism of prochlorperazine-induced catalepsy were compared by means of the chisquare test with Yates correction.

References