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REVIEW OF THE ANIMAL PHARMACOLOGY AND PHARMACOKINETICS OF FLUVOXAMINE

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1 Fluvoxamine maleate is a compound from the series of 2-aminoethyloximethers of aralkylketones which possesses marked inhibition effects on 5-hydroxytryptamine (5-HT) uptake by blood platelets and brain synaptosomes. In contrast, it has no effect on noradrenaline uptake processes.

2 Fluvoxamine is completely absorbed in rats and dogs; the main metabolic path was similar in rat, dog, hamster, mouse and rabbit. The metabolites of fluvoxamine are inactive with regard to aminergic uptake processes.

3 Fluvoxamine is neither sedative nor stimulating, shows a very low cardiotoxic effect and no affinity for the cholinergic receptor. On the basis of the pharmacological profile, a highly favourable therapeutic ratio of antidepressant effects *vs* disturbing side-effects is predicted.

Introduction

Growing support has been accumulating during recent years for the view that a disturbance in 5-hydroxytryptamine (5-HT) metabolism may be an important contributory factor in the development of depressive illness. It is to be expected that in the next few years significant improvement of the diagnostic classification of depressive disorders by biochemical means will clarify which subtypes of depression will benefit most from a correction of 5-HT metabolism. On this basis, it can be postulated that there is an urgent need for a drug with a specific inhibiting effect on neuronal 5-HT re-uptake, beside the available tricyclic antidepressant (TCA) compounds which primarily affect noradrenaline (NA) re-uptake.

Compounds in the series of 2-aminoethyloximethers of aralkylketones possess inhibiting properties both with regard to neuronal NA and 5-HT re-uptake. The relative activity with respect to NA re-uptake and 5-HT re-uptake processes is quite structure-specific. Fluvoxamine was selected from the series as being a compound with a rather selective 5-HT re-uptake inhibiting activity, whereas an effect upon NA re-uptake is almost absent (Claassen *et al.*, 1977) (Figure 1).

In presenting an overview of the pharmacological properties of fluvoxamine relevant to its clinical use, a number of topics have been selected in which the profile of the compound is characterised with regard to its interaction with aminergic processes, adaptational changes upon chronic administration, and its anticholinergic and cardiotoxic properties. In addition, the main aspects of the metabolism of fluvoxamine will be presented where relevant to clinical efficacy.

Acute interaction with aminergic processes

Inhibition of neuronal amine uptake in vitro

Uptake inhibition has been seen over the years as a rather good explanation for the therapeutic activity of antidepressant drugs. It must be realised, however, that this explanation does not fit for a number of compounds. Not all uptake inhibitors are clinically

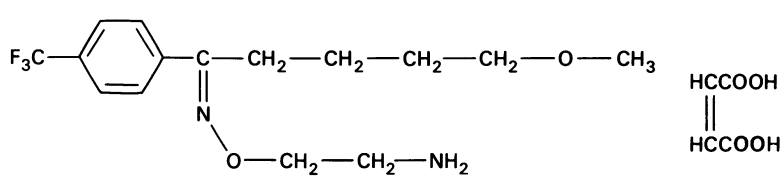

Figure 1 Chemical structure of fluvoxamine maleate

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effective and on the other hand, not all clinically effective antidepressants are uptake inhibitors. Proof of efficacy can only come from clinical studies, which is important to remember when we consider compounds of a new chemical class.

Fluvoxamine is a competitive inhibitor of 5-HT uptake by rat brain synaptosomes, as are the TCAs imipramine and desmethylimipramine (DMI). Fluvoxamine is a more potent inhibitor than other antidepressants tested (Table 1). Of the TCAs chlorimipramine was the most active compound tested and was found to be 2–3 times less active than fluvoxamine. The low activity of zimelidine is likely to be explained by the fact that *in vivo* the metabolite norzimelidine is the active compound.

When comparing the efficacy of the antidepressants with regard to NA uptake, fluvoxamine was found to be markedly less active in this respect (Table 1). The compound is 300 times less active than DMI. The three 5-HT uptake inhibitors tested are also only weakly active. The dopamine uptake inhibiting activity is low for all compounds.

When we compare the inhibiting activity *vs* 5-HT uptake and NA uptake, it is clear that fluvoxamine can be seen to be far the most selective 5-HT uptake inhibitor. In contrast, most TCAs are more active NA-uptake inhibitors than 5-HT uptake inhibitors; of these compounds, DMI is the most selective for NA. Chlorimipramine is an exception amongst the TCAs in that blockade of the 5-HT uptake process occurs at a lower concentration than the blockade of NA uptake. The non-tricyclic structures also show selectivity towards the 5-HT process.

Inhibition of neuronal amine uptake in vivo

A measure for the inhibition of the 5-HT uptake process in the *in vivo* situation was obtained by studying the uptake properties of synaptosomes isolated from rats pretreated with the test compounds. Table 2 summarises the uptake of [^{3}H]-labelled 5-HT in synaptosomes of rats treated with fluvoxamine or imipramine. Both compounds already showed a significant inhibition of the uptake process 30 min after drug administration. The effect did not diminish during the longer time-intervals tested. In accordance with the results obtained in the *in vitro* experiments with synaptosomes, fluvoxamine was a stronger inhibitor than imipramine. The same pattern was observed for fluvoxamine after oral administration; the compound is clearly more active than chlorimipramine in this respect. The low efficacy of fluvoxamine *vs* the NA uptake process was also apparent from these *in vivo* studies with rat brain synaptosomes.

Table 1 Inhibition of monoamine uptake by rat brain synaptosomes *in vitro*

	pI_{50}-value		
Compound	*5-HT*	*NA*	*DA*
Fluvoxamine	6.5	4.4	4.3
Chlorimipramine	6.1	5.4	4.8
Imipramine	5.8	6.2	4.5
Amitriptyline	5.5	5.7	4.4
Desmethylimipramine	4.9	7.0	4.4
Nortriptyline	5.0	6.5	4.7
Fluoxetine	5.9	4.8	4.5
Femoxetine	5.7	5.0	4.4
Zimelidine	5.1	4.3	4.1

[^{3}H]-Labelled monoamine uptake was measured in synaptosomal suspension of rat cerebrum (5-HT), hypothalamus (NA) and striatum (DA). Results are expressed as pI_{50}-value, the negative logarithm of the molar concentration giving 50% inhibition of amine uptake.

Table 2 Inhibition of 5-HT uptake by rat brain synaptosomes after *in vivo* dosing

	5-HT uptake (% of control)		
Compound	*30 min*	*60 min*	*90 min*
Fluvoxamine	20	18	16
Imipramine	51	53	50

Compounds were administered in a dose of 25 mg/kg i.p. After the indicated time intervals the animals were killed and 5-HT uptake measured in crude synaptosomal fractions from the homogenate of the cerebral hemispheres. Results were expressed as a percentage of control; the 5-HT uptake of control preparation was 6.10 ± 0.14 (s.e. mean, n = 12) pmol g^{-1} synaptosomal protein 5 min^{-1}.

The prevention of the depleting effects of the tyramine derivatives H 75/12 (4-methyl-α-ethyl-*m*-tyramine) and H 77/77 (4,α-dimethyl-*m*-tyramine), can also be used to study *in vivo* the blockade of the aminergic pump. These compounds apparently enter the neuron by this uptake process before neuronal depletion of the amine can occur. As can be seen from Table 3, fluvoxamine, given twice at 25 mg/kg i.m., effectively inhibited the 5-HT-depleting action of both compounds. Protection against depletion by H 75/12 was found for imipramine at the same dose level, though the effect was far less than that of fluvoxamine. DMI gave a significant but small inhibition of 5-HT depletion by H 77/77. A comparable study was performed after oral administration; the depletion of 5-HT by H 77/77 was antagonised by 50% after two oral doses of fluvoxamine at 25 mg/kg. Chlorimipramine was not effective after oral dosing in these experimental conditions.

After i.p. administration, fluvoxamine did not block the NA-depleting effects of H 77/77 and H 75/12, in accordance with its minimal influence on the NA-uptake pump. Imipramine and especially DMI were clearly effective in this regard.

Table 3 Inhibition of 5-HT depletion by H 75/12 and H 77/77

Compound	*Depletor*	*Brain 5-HT (μg/g tissue)*	*Protective effect (%)*
Control	—	0.67	
Control	H 75/12	0.23	
Fluvoxamine	H 75/12	0.53	68
Imipramine	H 75/12	0.37	31
Control	H 77/77	0.27	
Fluvoxamine	H 77/77	0.51	60
Desmethylimipramine	H 77/77	0.32	12

Compounds were administered twice in a dose of 25 mg/kg i.m. 30 min before an i.p. dose of the depletor (time interval 2 h, individual doses H 75/12 25 mg/kg, H 77/77 12.5 mg/kg). Two hours after the last dose of the depletor the animals were killed and the cerebrum analysed for 5-HT.

Effect on 5-HT- or NA-mediated behaviour

Further evidence for the prominent activity of fluvoxamine as a 5-HT uptake inhibitor was obtained in a series of experiments in which the brain 5-HT content of mice, rats or rabbits was increased by pretreatment with tryptophan, 5-HTP and/or MAO-inhibitors. Marked efficacy of fluvoxamine was demonstrated in mice through the potentiating activity on the induction of behavioural effects by 5-HTP. As can be seen from Table 4, fluvoxamine is clearly more active than the various TCAs, some of which did not show any activity at the highest dose tested. These 5-HTP-induced effects must be due to the formation of an increased amount of 5-HT, as these phenomena are suppressed by centrally acting anti-5-HT compounds and by high doses of centrally acting decarboxylase inhibitors.

The prominent 5-HT uptake-inhibiting properties of fluvoxamine also become apparent from the induction of a 5-hydroxytryptaminergic syndrome when the compound is given in combination with a long-acting MAO-inhibitor such as pargyline; the oral ED_{50}-value under our test conditions was 33 mg/kg. Chlorimipramine was only active at a five-times higher dosage, whereas the other TCAs were inactive.

The activity of fluvoxamine in comparison with chlorimipramine and fluoxetine was further demonstrated by the induction of the hyperactivity syndrome in rats pretreated with a MAO-inhibitor and tryptophan. In rabbits, additional evidence was obtained for the 5-HT uptake inhibiting properties of fluvoxamine from the potentiation of the hyperthermic effects of 5-HTP. In this respect, fluvoxamine and chlorimipramine showed comparable activity.

Convincing evidence has accumulated that, in a large number of cases, adrenergic mechanisms are involved in the antagonism of effects of reserpine (and reserpine-like compounds). In contrast to the TCAs fluvoxamine is not or is only weakly active as an antagonist in this respect. For example, fluvoxamine showed an ED_{50}-value of about 100 mg/kg in antagonising tetrabenazine-induced ptosis in mice and was 9-130 times less active than the TCAs tested (Table 4). In antagonising tetrabenazine-induced ptosis in rats, fluvoxamine was even less active. Reserpine-induced hypothermia in mice was reversed by fluvoxamine, but at much higher dose levels than TCAs. In contrast to most TCAs, fluvoxamine did not produce compulsive hyperactivity in the rat when administered in combination with compounds such as

Table 4 Specificity of fluvoxamine in *in vivo* experiments in mice to potentiate 5-HT effects compared with NA effects

Compound	*Oral ED_{50} (mg/kg) Potentiation 5-HTP**	*Antagonism tetrabenazine***	*Ratio ED_{50}-values*
Fluvoxamine	36	107	0.34
Chlorimipramine	84	12	7
Imipramine	135	5.2	26
Amitriptyline	> 100	11.1	> 9
Desmethylimipramine	> 320	0.80	> 400
Nortriptyline	> 320	5.6	> 57

*The ED_{50}-value is the dose of the test compound which potentiates the 5-HTP effect to 50% of the maximal score. Induction of 5-hydroxytrypaminergic behaviour (head-searching, hindlimb abduction, tremor, escape tendency, forelimb clonus, lordosis) was scored upon i.p. injection of (±)-5-hydroxytryptophan (150 mg/kg).

**The ED_{50}-value is the dose of the test compound required to reduce ptosis to half of that of the control tetrabenazine group. The ability of the test compounds to prevent ptosis was measured using s.c. injected tetrabenazine (80 mg/kg).

tetrabenazine and Ro 4-1284, which rapidly release brain NA.

The comparison of the activity ratios in mice between potentiating 5-HTP and antagonising tetrabenazine for the various compounds, shows fluvoxamine to be a highly specific 5-HT uptake inhibitor *in vivo*.

Affinity for aminergic receptors

The affinity of fluvoxamine for various aminergic receptor types was determined in receptor binding studies, together with that of a number of TCAs. As is apparent from Table 5, fluvoxamine has no significant affinity for any of these receptors. This, in contrast with the profiles of the various TCAs, suggests that side-effects related to occupation of these sites, are unlikely to occur with fluvoxamine.

Adaptational changes upon chronic administration

Discussions have arisen about the validity of single-dose *vs* repeated-dose testing methods. Acute experiments may be inappropriate for the prediction of clinical antidepressant activity because of the delay that occurs in obtaining a (maximal) therapeutic response in man (Sulser, 1979). It is generally assumed that a functional neuronal (re-)adaptation, occurring over a longer time interval, must proceed before recovery can become apparent. Chronic tests in animals have demonstrated such adaptational changes to drug treatment. Though some of these adaptational changes are comparable for a great series of antidepressant drugs, there is no consensus of opinion amongst investigators about the essential characteristics that predict clinical effectivity. Without doubt, effects after chronic administration make an important contribution to the description of the pharmacological profile of a psychotropic drug. However, it seems worth stating that this does not invalidate the characterisation achieved by acute experiments. In cases where there are maladapted neuronal circuits due to a primary local deficit in one transmitter function, the knowledge of the effect of a drug on that synapse process remains of prime importance. The predictability of clinical activity on the basis of measurement of the quantitative EEG, indicates that specific changes are brought about after a single dose of the antidepressant to humans.

Recent studies have made clear that various types of antidepressants, when administered to animals over a period of some weeks, down-regulate the NA coupled adenylate cyclase system located in the post-synaptic membrane of brain neurons. This down-regulation is not due to a change in the affinity of NA for the receptor site but is in most cases caused by a decrease in the number of β-adrenoceptors. For some compounds, (such as mianserin and possibly zimelidine), however, a reduction in the density of the β-adrenoceptor population does not occur, although a down-regulation of the sensitivity of the adenylate cyclase system is observed. The mechanism of action resulting in this effect is not yet resolved.

In studies of the effect of chronic fluvoxamine administration, the compound was administered twice daily (10 mg/kg i.p.) during a 14-day period. In such preliminary experiments it was found that upon chronic treatment, in contrast to DMI, fluvoxamine did not decrease the number of β-adrenoceptors to a marked extent. Nevertheless, a marked subsensitivity of the adenylate cyclase system was induced by this chronic fluvoxamine treatment and according to these results the adaptational changes in this system are comparable with those described by Mishra *et al.* (1980) for mianserin and zimelidine. These effects occur without any indication of a direct interaction with NA processes.

Adaptational changes of 5-HT receptor populations have been described in the literature on chronic treatment with antidepressant drugs, although also in this case differences between investigators occur. In correspondence with Peroutka we found that DMI decreases the 5-HT_2 receptor population, while not affecting the number of 5-HT_1 receptors. Fluvoxamine, under our conditions, does not influence either of the two types of 5-HT receptors.

Table 5 Binding affinity for aminergic receptors

	IC_{50}-value for ligand displacement (nM)				
Compound	α_1	α_2	β	*5-HT_2*	*DA_2*
Fluvoxamine	5.000	30.000	24.000	13.500	> 100.000
Chlorimipramine	117	20.000	28.000	150	700
Imipramine	300	11.000	77.000	180	2.700
Amitriptyline	200	1.400	19.500	170	1.300
Desmethylimipramine	660	37.000	41.000	880	5.700

Binding experiments were performed *in vitro*: α_1—WB 4101 – rat brain; α_2 – clonidine – rat brain; β – dihydroalprenolol – rat frontal cortex; 5-HT_2 – spiroperidol – rat frontal cortex; DA_2 – spiroperidol – calf caudate

Anticholinergic effects

One of the most disturbing clinical side-effects of TCAs is the appearance of atropine-like effects such as dry mouth, constipation and disturbances of accommodation. The affinity of fluvoxamine for the muscarinic receptor was determined by receptor-binding studies using [^{3}H]-labelled quinuclidinyl-benzilate ([^{3}H]-QNB) as ligand. In Table 6 the affinity of the various antidepressants is given in terms of IC_{50}-values. Fluvoxamine has no significant affinity for the muscarinic receptor; in contrast, all TCAs possessed a moderate activity for reduction of QNB binding to this cholinergic receptor.

Table 6 Binding affinity for the muscarinic receptor

Test compound	*IC_{50} (nM)*
Fluvoxamine	90.000
Chlorimipramine	160
Imipramine	400
Amitriptyline	68
Desmethylimipramine	460

IC_{50} = concentration of drug necessary to reduce the specific binding of [^{3}H]-QNB to the muscarinic receptor by 50%.

When antagonism *vs* carbachol was studied in guinea pig isolated ileum, fluvoxamine did not produce a parallel shift of the dose-response curve of carbachol. This indicates that no competitive antagonism occurs between fluvoxamine and carbachol for the muscarinic receptor.

In various *in vivo* studies, the absence of a parasympatholytic activity of fluvoxamine was also shown. Fluvoxamine does not block oxotremorine effects in mice—effects due to a central muscarinic action. In interaction studies with pilocarpine in mice there is essentially no antagonism of pilocarpine-induced effects, neither of the peripheral effects such as salivation and lacrimation, nor of the effects that are due to central effects of this cholinomimetic.

Cardiotoxic properties

TCAs have caused serious clinical concern because of their effects on the cardiovascular system at therapeutic doses and especially in situations of overdose (Bigger *et al.*, 1978). Deviations in the ECG have been reported of both atrial and ventricular origin. In addition, postural hypotension and a decrease of the inotropic state of the heart are known to occur.

The cardiovascular effects of TCAs have been attributed to a series of their pharmacological properties such as inhibition of NA re-uptake, anticholinergic and 'quinidine-like' effects. The second generation, non-tricyclic antidepressants are claimed to produce less cardiovascular disturbances.

Conscious rabbits were constantly infused with fluvoxamine till death. The left ventricular pressure, LV dP/dt and ECG lead I, II and III were recorded. For purposes of comparison the effects of mianserin and amitriptyline were studied in a parallel fashion. ECG abnormalities were scored at their first appearance in three broad categories: gross changes in QRS-complex wave form, typical rhythm disturbances and fibrillation/flutter. In Table 7 the cumulative dose for appearance of the ECG abnormalities is given, together with the numbers of animals affected. The cumulative lethal dose for the compounds is indicated.

Amitriptyline induced severe ECG abnormalities in all three categories at doses half the lethal dose. Mianserin produced fewer QRS abnormalities, but still produced arrhythmias and fibrillation/flutter in two animals. The doses at which these abnormalities occurred were, however, much higher also relative to the lethal dose, than in the amitryptyline group.

In the fluvoxamine group of nine animals, none died of fibrillation/flutter and only one showed rhythm disturbances. Gross QRS changes developed in most animals but only at doses approaching the lethal dose.

At the end of the infusion, just before death, amitriptyline showed a severe, statistically significant, decrease in contractility (Table 8). In contrast, both mianserin and fluvoxamine showed only a small, non-significant decrease in dP/dt_{max}. During the infusion,

Table 7 Induction of gross ECG effects

Effect	*Median effect dose (mg/kg i.v.)* *Fluvoxamine*		*Amitriptyline*		*Mianserin*	
QRS changes	54.3	(8/9)	4.0	(6/6)	24.5	(3/6)
Arrhythmias	39.2	(1/9)	4.2	(3/6)	40.3	(2/6)
Fibrillation/flutter	—	(0/9)	6.3	(2/6)	61.6	(2/6)
Lethal dose	59.5		13.6		56.0	

Conscious rabbits were continuously infused with drug solution till death. ECG abnormalities were scored at their first appearance. Cumulative dose is given as median effect dose and, in parentheses, the number of animals effected over the total number of animals tested.

Table 8 Effect on heart contractility

Dose	*Left ventricular dP/dt_{max} (% control)* Fluvoxamine	Amitriptyline	Mianserin
Half lethal dose	76* (59–106)	—	102 (29–133)
End of infusion	86 (45–144)	47* (23–75)	96 (35–156)
n	9	6	6

* $P < 0.01$, Student's *t*-test, with respect to control (100%). Conscious rabbits were continuously infused with drug solution till death, and the first derivative of the left ventricular pressure was registered. The mean value for dP/dt_{max} is given as % of control and, in parentheses, the range of individual values.

at half lethal dose, the mean dP/dt_{max} was essentially unchanged for mianserin, whereas a small significant decrease occurred with fluvoxamine. There was, however, a marked overlap of the ranges of the dP/dt_{max} of both drugs.

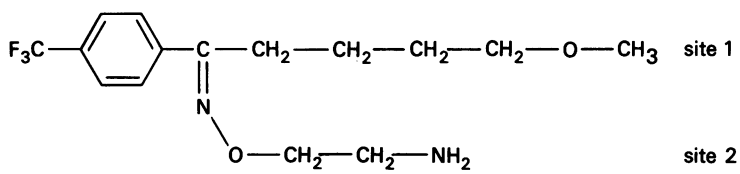
From these results it is apparent that fluvoxamine induced far less cardiotoxic effects than did amitriptyline. The compound also had a lesser tendency to cause ECG disturbances than mianserin.

Pharmacokinetic properties and metabolism

Fluvoxamine is rapidly absorbed after oral administration. Important for clinical use is the relatively long half-life of 15 h and the fact that fluvoxamine is not extensively bound to plasma proteins (77% in man).

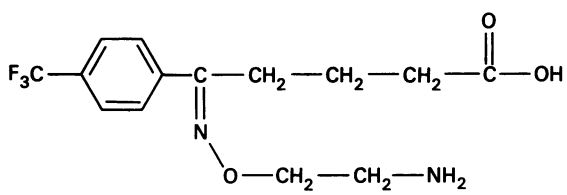
To help interpret the therapeutic activity of fluvoxamine, it is useful to know to what extent metabolites may contribute to the antidepressant effect. Metabolism of fluvoxamine has been studied in both animals and man. [^{14}C]-Labelled fluvoxamine was used to establish the metabolite pattern in urine by thin-layer chromatography and high performance liquid chromatography. Plasma levels of fluvoxamine were measured by means of a gas-chromatographic method.

Fluvoxamine was extensively metabolised in all species studied and unchanged fluvoxamine was not found in the urine. Two major routes of metabolic



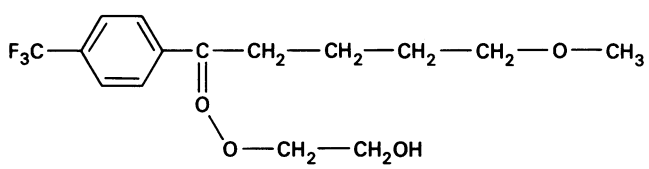
Fluvoxamine

% of total urinary excretion (free + conjugated)



Metabolite A

35 + 8



Metabolite B

5

Figure 2 Metabolic routes of fluvoxamine.

Table 9 Pharmacological properties of the main urinary metabolites of fluvoxamine

Test	*Fluvoxamine*	*Metabolite A*	*Metabolite B*
Inhibition NA uptake pI_{50}-value	4.5	< 4	< 4
Inhibition 5-HT uptake pI_{50}-value	6.6	5.0	< 4
Antagonism tetrabenazine oral ED_{50}-value (mg/kg)	99	> 215	> 215
Potentiation 5-HTP oral ED_{50}-value (mg/kg)	39	> 215	> 215

Testing conditions as indicated in Tables 1 and 4.

transformation occur (Figure 2). In the first place, there is an elimination of the methoxyl group followed in most species, including man, by oxidation to the carboxylic acid, the main metabolite found in urine. In the mouse only, the alcohol, in conjugated form, is the major metabolite.

The second most important metabolic path is oxidative deamination leading, via the alcohol, to the carboxylic acid. Small amounts of the corresponding oximes are also formed, probably by further oxidative breakdown of this metabolite.

Transformation at both sites of the molecule simultaneously produces a further series of acidic metabolites; only, however, to a minor extent. A minor metabolite is also formed by hydrolysis of the oxime or oximether; this may be a further breakdown product of several different metabolites. Some of the various metabolites occur in a conjugated form (acetylated, glucuronated or glycinated).

Nine metabolites are detected in the urine after oral administration of fluvoxamine in man, constituting 85% of the urinary excretion products. The two metabolites shown in Figure 2, one a compound with an intact oxime ethylamine group and an acidic side chain, and the other a compound in which no amine nitrogen is present, were investigated for their effects on 5-HT and NA uptake processes. As can be seen from Table 9 these compounds have no effect on the NA uptake process. The carboxylic acid derivative shows only a weak inhibition of the 5-HT uptake process in comparison to fluvoxamine.

From these results it seems reasonable to postulate that the antidepressant activity of fluvoxamine is due to the activity of the parent compound and that metabolism leads to therapeutically inactive products.

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