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5-HYDROXYTRYPTAMINE-INTERACTING DRUGS IN ANIMAL MODELS OF ANXIETY DISORDERS: MORE THAN 30 YEARS OF RESEARCH

GUY GRIEBEL*

Laboratoire de Psychophysiologie, 7 rue de l'Université, 67000 Strasbourg, France

Abstract—An overview of the behavioral data arising from the vast literature concerning the involvement of 5-hydroxytryptamine (5-HT) neurotransmission in the regulation of anxiety is presented. More than 1300 experiments were carried out in this area and they provide evidence that: (1) results obtained in ethologically based animal models of anxiety with drugs stimulating 5-HT transmission are most consistent with the classic 5-HT hypothesis of anxiety in that they show an increase in animals' emotional reactivity; (2) no category of anti-anxiety models are selectively sensitive to the anxiolytic-like effects of drugs targetting 5-HT_{1A}, 5-HT_{2A} or 5-HT_{2C} receptor subtypes; (3) anxiolytic-like effects of 5-HT_3 receptor antagonists, in the great part, are revealed by models based on spontaneous behaviors. Taken together, these observations lead to the conclusion that different 5-HT mechanisms, mediated by different receptor subtypes, are involved in the genesis of anxiety.

Keywords—5-HT (serotonin), 5-HT ligands, 5-HT receptors, animal models of anxiety, conditioned paradigms, unconditioned paradigms.

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Abbreviations—CER, conditioned emotional response; DPAG, dorsal periaqueductal gray; 5-HT, 5-hydroxytryptamine; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin; mCPP, 1-(3-chlorophenyl)piperazine; PCPA, *p*-chlorophenylalanine; SRI, 5-hydroxytryptamine reuptake inhibitor; TFMPP, 1-(3-trifluoromethylphenyl)piperazine.

*Present address—*Synthélabo Recherche (L.E.R.S.), CNS Pharmacology Group, 31, avenue Paul Vaillant-Couturier, B.P. 110, 92225 Bagneux Cedex, France.

1. INTRODUCTION

It has been suggested on the basis of previous behavioral studies that 5-hydroxytryptamine (5-HT) could be considered as a central neurotransmitter involved in the modulation of emotional behavior (Sudak and Maas, 1964; Geller and Blum, 1970; Wise *et al.*, 1972; Stein *et al.*, 1973; Crow and Deakin, 1981). This view mainly arose from some observed activity of 5-HT antagonists in operant conflict paradigms (Robichaud and Sledge, 1969), as well as from an association between reduction in turnover of 5-HT and the anxiolytic effects of benzodiazepines (Goldberg *et al.*, 1967). It is now acknowledged that a reduction of the function of brain 5-HT pathways often leads to an anxiolytic-like effect, whereas increased activity of ascending 5-HT pathways usually results in an anxiogenic-like effect (Gardner, 1986; Chopin and Briley, 1987). However, the picture is nowhere near as clear. The behavioral effects of drugs decreasing the activity of the central 5-HT system are often more variable than the effects of standard anxiolytics, and not all findings are accounted for by the classic hypothesis. There are a few instances in which these compounds produce effects opposite to those of standard anxiolytics, suggesting an anxiogenic-like action. Moreover, in some studies, drugs known to possess a 5-HT-stimulating action displayed anxiolytic-like properties, while in others they potentiated animals' emotional reactivity. Finally, a great number of studies found no evidence for an anxiolytic- or anxiogenic-like effect of drugs modulating central 5-HT neurotransmission. This is exemplified by Fig. 2, which illustrates the variability in behavioral effect of some of the most studied compounds interacting with the 5-HT neurotransmission. As an illustration, the central application of 5-HT results in an anxiogenic-like action in half of the studies, whereas in the other half, authors obtained the opposite effect. This variability is probably due to a number of factors, including administration routes (Treit, 1991), doses used (Söderpalm *et al.*, 1989), species differences (Barrett and Gleeson, 1991), the sex of the animals (Hughes, 1993) or the environment in which a test is conducted (Wettstein, 1992; Griebel *et al.*, 1993). Certain authors point to a determining role of the experimental paradigms used when studying 5-HT agents in animal models of anxiety disorders. Variation in the effects might reflect differences in the degree to which the models themselves represent fear or anxiety (Handley, 1991; Treit, 1991; Wettstein, 1992; Barrett and Vanover, 1993; Handley and McBlane, 1993a,b,c). These behavioral tests have been useful in the preclinical testing of benzodiazepine-type anxiolytics, in studying the functional relevance of the benzodiazepine receptor system, and in characterizing the effects of benzodiazepine antagonists, partial agonists, and inverse agonists (for recent reviews, see Barrett and Gleeson, 1991; Treit, 1991). However, the validation of these paradigms has depended primarily on their sensitivity to benzodiazepines only, and the recent introduction to clinical practice of non-benzodiazepine anxiolytics such as buspirone has challenged the validity of these tests as general models of anxiety disorders. The possibility that these tests may be less sensitive to agents not acting at benzodiazepine receptors has been advanced to explain these inconsistencies (Richards *et al.*, 1991).

The main objective of this review is to provide an overview of the developments in research involving the 5-HT system and anxiety. The emphasis will be on a review of the results of animal models used to evaluate these drugs with the help of a synoptic table that summarizes the studies investigating the behavioral effects of 5-HT compounds in this area from 1961 to November 1993 (Table 1). This table is composed of following sections: (1) name of drug (starting with 5-HT, *p*-chlorophenylalanine (PCPA), 5-HT reuptake inhibitors, and ending with 5-HT_3 receptor antagonists); (2) its affinity for 5-HT receptors; (3) animal models of anxiety used; (4) animals and strains used and their weight or age; (5) efficient doses or doses tested; (6) administration route and latency period; (7) effect observed; (8) comments; and finally, in column 9 the pertinent references are indicated.

In Section 2, we will briefly review some aspects of the literature concerning the animal models of anxiety disorders used in investigations of the behavioral actions of psychotropic drugs. Section 3 will focus on the studies evaluating the behavioral actions of 5-HT compounds in animal models of anxiety. The results obtained with these agents will be considered and discussed for the most important 5-HT receptors. Outcomes of some of the most studied compounds, such as 5-HT, 8-OH-DPAT, buspirone, mCPP or ondansetron, will be illustrated graphically with attention to the types of behavioral procedures used. This will allow examination of the possibility that involvement

Table 1: *Effects of Drugs Modulating 5-HT Neurotransmission in Animal Models of Anxiety.*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
5-HT	3.1	3.4	2.8	2500	3.1	22[1]	Geller–Seifter conflict test	Rats	1–10 μg	i.c.v., 10–20	–		Wise *et al.*, 1972
								Rats	20 μg	i.c.v., 0	–		Stein *et al.*, 1973
								Rats (382–446 g)	1–5 μg	Amygdala, 0	–	VI20	Hodges *et al.*, 1987
								Rats	1–10 μg	i.c.v., > 20	+		Wise *et al.*, 1972
								Wistar rats (195–205 g)	10–100 nmol	Dorsal raphé	+	CRF	Thiébot *et al.*, 1982
							Light/dark test	Mice (25–35 g)	10 ng	Dorsal raphé	–	Asymmetric compartments	Costall *et al.*, 1988d
								Swiss mice (10 weeks)	2.5–5 μg	i.c.v., 30	–		Griebel, 1993
							Social interaction	Lister rats (210–280 g)	100–10000 ng	Amygdala, 5	–	LLF	Higgins *et al.*, 1991
									20–100 ng	Dorsal raphé, 5	+	HLU	
							Fear-potentiated startle reflex	Sprague–Dawley rats (320–400 g)	1–15.625 μg	i.c.v.	+		Geyer *et al.*, 1975
								Rats (300–400g)	200 μg	i.c.v., 8 days	+		Davis *et al.*, 1980b
										i.t.	–		
							Conditioned emotional response	Rats	10 nmol	Dorsal raphé	+		Thiébot *et al.*, 1984
							DPAG-stimulation	Wistar rats (250–300g)	5–20 nmol	DPAG, 10	+		Schütz *et al.*, 1985
								Rats	5–20 nmol	DPAG, 10	+		Graeff *et al.*, 1986
5-HTP (5-HT precursor)							Geller–Seifter	Sprague–Dawley rats	15	i.p. 120	–		Geller and Blum, 1970
							Vogel's conflict test	Sprague–Dawley rats (200g)	18	i.p. 30	–	VI21	Kilts *et al.*, 1982
								Sprague–Dawley rats (180–250g)	100–400	i.p. 30	–	Modified Vogel's test	Hjorth *et al.*, 1987
									50		+		
							Conflict test	White Carneau Pigeons (6 months)	50	i.m.	–	FR50	Aprison and Ferster, 1961
							Elevated-plus maze	Sprague–Dawley rats (250–350g)	28–448 μmol	i.p. 30	–		Söderpalm *et al.*, 1989
								Wistar rats (150–200g)	40	30	–	In combination with tranylcypromine	Kshama *et al.*, 1990
							Light/dark test	Wistar rats (150–200g)	40	30	–	In combination with tranylcypromine and asymmetric compartments	Kshama *et al.*, 1990
								Mice	25–100	i.p.	–	Asymmetric compartments	Cheng *et al.*, 1992
							Holeboard	Wistar rats (150–200g)	40	30	–	In combination with tranylcypromine	Kshama *et al.*, 1990
							Fear-potentiated startle reflex	Lister rats (375–415g)	25	i.p. 60	–		Glenn and Green, 1989
							Shock-probe burying test	Wistar rats (250–280g)	2.5–160	s.c. 60	o		Meert and Colpaert, 1986a
							Marble burying test	Female MF1 mice	5–50	i.p. 30	+	Locomotion reduced	Njung'e and Handley, 1991b

Continued

Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{2A}	5-HT_{2C}	5-HT_3	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
							Fear-potentiated startle reflex	Sprague–Dawley rats (320–350g)	100	i.p. 40	–		Svensson and Ahlenius, 1983
								Sprague–Dawley rats (320–350g)	25–50	i.p. 10	–		Svensson, 1985
								Sprague–Dawley rats (310–380g)	125	i.p. 60	o		Walters *et al.*, 1979
							DPAG-stimulation	Rats (250g)	75–150	i.p. 30-120	+		Kiser *et al.*, 1978
Tryptophan-free diet							Fear-potentiated startle reflex	Sprague–Dawley rats (310–380g)			–		Walters *et al.*, 1979
PCPA 5-HT synthesis inhibitor							Geller Seifter conflict test	Long–Evans rats	340	i.p. 1, 3 and 9 days	o	FR12	Blakely and Parker, 1973
								Long–Evans rats	200	p.o. 30 min to 6 days	+	VI2	Robichaud and Sledge, 1969
								Sprague–Dawley rats	200	p.o. 24 hr	+		Geller and Blum, 1970
								Rats	100–400		+		Wise *et al.*, 1972
								Rats	100 400		+		Stein *et al.*, 1973
								Rats	300	p.o. 40	+		Cook and Sepinwall, 1975a
								Sprague–Dawley rats (200–300g)	100	i.p. during 3 days	+		Tye *et al.*, 1979
								Rats	100	i.p. during 2 days	+		Shephard *et al.*, 1982
								Wistar rats (250–350g)	150	i.p. during 3 days	+	Modified Geller–Seifter test	Thiébot *et al.*, 1991
							Vogel's conflict test	Wistar rats (220g)	200–400	i.p. s.c. 72 hr	o	Modified Vogel's test	Petersen and Lassen, 1981
								Sprague–Dawley rats (200g)	400	i.p. 0	+	VI21	Kilts *et al.*, 1982
									200	i.p. during 3 days			
								Sprague–Dawley rats (190–210g)	300	i.p. during 3 days	+	Modified Vogel's test	Engel *et al.*, 1984
								Sprague–Dawley rats (250–350g)	300	i.p. during 3 days	+	Modified Vogel's test	Söderpalm and Engel, 1989
							Elevated-plus maze	Wistar rats (150–200g)	200	72 hr	+		Kshama *et al.*, 1990
								Sprague–Dawley rats (250–350g)	130	i.p. during 4 days	+		Treit *et al.*, 1993
							Light/dark test	Wistar rats (150–200g)	200	72 hr	+	Asymmetric compartments	Kshama *et al.*, 1990
								BKW mice (30–35g)	50–100	i.p. during 3 days	+	Asymmetric compartments	Barnes *et al.*, 1992b
								BKW mice (30–35g)	100	i.p. during 3 days	+	Asymmetric compartments	Barnes *et al.*, 1992a
								Swiss mice (10 weeks)	75–300	i.p. during 3 days	+		Griebel, 1993
							Holeboard	Wistar rats (150 200g)	200	72 hr	o		Kshama *et al.*, 1990
							Social interaction	Rats			o	LLF	File, 1981
								Rats	100–400		+		Ellison, 1977
								Rattus norvegicus rats (200–250g)	400	i.p. 3 days	+		File and Hyde, 1977
								Rats			+	HLU	File, 1981
								Lister rats (250–300g)	100	i.p. during 3 days	+		Barnes *et al.*, 1992b

		Shock-probe burying test	Sprague–Dawley rats (250–350g)	130	i.p. during 4 days	+		Treit *et al.*, 1993
		Disruption of drinking induced by stress	Sprague–Dawley rats (300g)	100	p.o. during 3 days	+		Tenen, 1967
		Freezing	Rats (15–25 days)	300	i.p. during 4 days	+		Hård *et al.*, 1982
		Ultrasonic 'distress' vocalization	Rats (4–16 days)	100	i.p. during 3 days	+		Hård *et al.*, 1982
		Fear-potentiated startle reflex	Long–Evans rats (70 days)	300	s.c. 1–4 days	–		Conner *et al.*, 1970
			Sprague–Dawley rats (175–200g)	100	i.p. 1–4 days	–		Carlton and Advokat, 1973
			Rats	320–900	i.p. during 3 days	o		Fechter, 1974
			Sprague–Dawley rats (300–400g)	300	i.p. during 2 days	o		Davis *et al.*, 1988a
		Stress-induced hyperthermia	Swiss mice (25–30g)	75–150	i.p. during 3 days	o		Lecci *et al.*, 1990
		DPAG-Stimulation	Rats (250g)	316	i.p. 3–18 days	–		Kiser and Lebovitz, 1975
SC-48274 (5-HT stimulant)		Unavoidable stress (gastric lesion)	ICR mice (7–8 weeks)	25–50	p.o. 60 p.o.	+		Ogawa *et al.*, 1993
				5–50	(7–8 weeks)			
		Passive-avoidance test	Wistar rats (7–8 weeks)	25	p.o. 60	+		Ogawa *et al.*, 1993
Fenfluramine (5-HT stimulant)		Vogel's conflict test	Sprague–Dawley rats (200g)	0.25–1	i.p. 60	o	VI21	Kilts *et al.*, 1982
		Marble burying test	Female MF1 mice (23–35g)	1–10	i.p. 30	+		Njung'e and Handley, 1991b
PCA (5-HT neurotoxin)		Vogel's conflict test	Wistar rats (180–220g)	10	i.p. 9 and 8 days	o	Modified Vogel's test	Chojnacka-Wójcik and Przegalinski, 1991
			Wistar rats (180–220g)	10	i.p. 9 and 8 days	o	Modified Vogel's test	Przegalinski *et al.*, 1992
		Fear-potentiated startle reflex	Sprague–Dawley rats (250-300g)	5	i.p. 2–15 hr	–		Davis and Sheard, 1976
			Sprague–Dawley rats (300–400g)	5	i.p. 15	o		Davis *et al.*, 1988a
			Sprague–Dawley rats (250–300g)	5	i.p. 15	+		Davis and Sheard, 1976
5,6-DHT (5-HT neurotoxin)		Geller–Seifter conflict text	Rats	100 μg	i.c.v., 2	+		Stein *et al.*, 1975
5,7-DHT (5-HT neurotoxin)	190[a]	Geller–Seifter conflict tet	Wistar rats (195–205g)	3 μg	Dorsal raphé, 21 days	o	CRF	Thiébot *et al.*, 1982
			Wistar rats	1 μg	Dorsal raphé, 15 days	o	CRF/FR7	Thiébot *et al.*, 1984
			Sprague–Dawley rats (250–300g)	2 μg	Ventromedian tegmentum, 12 days	+		Tye *et al.*, 1977
			Wistar rats	1 μg	Dorsal raphé, 15 days	+	CRF/FR7	Thiébot *et al.*, 1983
				2 μg	Substantia nigra, 15 days	+		

Continued

Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
							Vogel's conflict test	Sprague Dawley rats (180–200g)	100 μg	i.c.v., 15–16 days	–	Modified Vogel's test	Shimizu *et al.*, 1992b
								Wistar rats (180–200g)	50 μg	Dorsal raphé, 7 days	o	Modified Vogel's test	Takao *et al.*, 1992
								Wistar rats	1 μg	Dorsal raphé, 15 days	+		Thiébot *et al.*, 1983
									2 μg	Substantia nigra, 15 days	+		
								Sprague–Dawley rats (250–350g)	450 μg	i.c.v., 14 days	+	Modified Vogel's test	Söderpalm and Engel, 1991
								Sprague–Dawley rats (250–350g)	225 μg	i.c.v., 14 days	+	Modified	Söderpalm and Engel, 1992
							Elevated-plus maze	Sprague–Dawley rats (280–300g)	250 μg	i.c.v., 14 days	+		Briley *et al.*, 1990
							Light/dark test	CD–COBS rats (200–300g)	150 μg	i.c.v., 8 days	o	Transitions only	Carli *et al.*, 1989b
							Open-field	CFHB rats (270–300g)	5 μg	Fornix, 16–20 days	–		Williams *et al.*, 1990
							Holeboard	Sprague–Dawley rats (200–250g)	3–100 μg	i.c.v., Hippocampus or median raphé,12 days	o		Geyer *et al.*, 1980
							Social interaction	Rats (200–250g)	4 μg	Dorsal and median raphé, 15 days	o		File *et al.*,1979
							Freezing	Rats (15 days)	25 μg	i.c.v., 15 days	+		Hård *et al.*, 1982
							Ultrasonic 'distress' vocalization	Rats (4–16 days)	25 μg	i.c.v., 4 days	+		Hård *et al.*, 1982
							Shock–probe burying test	Wistar rats (250–300g)	10 μg	i.c.v., 5 days	+	Copulated males	Saldivar *et al.*, 1991
											o	Non- copulated males	
							Stress-induced hyperthermia	Swiss mice (25–30g)	200 μg	i.c.v., 9 days	o		Lecci *et al.*, 1990
							Conditioned place aversion	Long–Evans rats (280–300g)	100 μg	i.c.v., 8 days	o		Rocha *et al.*, 1993b
Electrolytic lesions							Elevated-plus maze	Sprague–Dawley rats (250–350g)			+	Dorsal raphé and septal lesions	Treit *et al.*, 1993
							Shock–probe	Sprague–Dawley rats (250–350g)			+	Dorsal raphé and septal lesions	Treit *et al.*, 1993
Amitriptyline (5-HT reuptake inhibitor) (IC_{50} = 44 nM)[a22]	960[e]	840[e]		21[f]	5800[e]	260[g]	Geller–Seifter conflict test	Sprague–Dawley rats (200–320g)	1–10	i.p. 20	o	FR40	Kilts *et al.*, 1981
							Vogel's conflict test	Sprague–Dawley rats (200g)	3–10	i.p. 30	–	VI21, also decreased non-punished responding	Kilts *et al.*, 1982
								Sprague–Dawley rats (200–320g)	1–10	i.p. 30	o	VI21	Kilts *et al.*, 1981
								Female Sprague–Dawley rats (225–275g)	0.625–10	i.p. 10	o	Modified Vogel's test	Fontana *et al.*, 1989
									5	i.p. during 5–9 weeks (x1)	+		
							Elevated-plus maze	Sprague-Dawley rats (170–200g)	1–30	p.o., 60	o		Luscombe *et al.*, 1990

							Sprague-Dawley rats (200–250g)	0.1–1	s.c. 30	o		Klint, 1991
						Light/dark test	BKW mice (20–30g)	30	i.p. 45	–	Asymmetric compartments and sedation (?)	Costall *et al.*, 1989b
						Shock–probe burying test	Wistar rats (250–280g)	0.63–40	s.c. 60	o		Meert and Colpaert, 1986a
						Ultrasonic 'distress' vocalization	Wistar rats (9–12 days)	1–8	i.p. 30	o		Gardner, 1985a
						Novelty-suppressed feeding	Long–Evans rats (300–325g)	10	i.p. 60	–		Bodnoff *et al.*, 1989
									during 21 days (x1)	+		
							Long–Evans rats (300–325g	10	60	o		Bodnoff *et al.*, 1988
									during 21 days (x1)	+		
						Elevated-plus maze	Wistar rats (150–220g)	1-10	i.p. 30 i.p.	–		Griebel *et al.*, 1994
Cianopramine (5-HT reuptake inhibitor) (IC_{50} = 1.5 nM)[a30]								10	during 21 days (x1)	+		
						Light/dark test	Swiss mice (10 weeks)	1–10	i.p. 30	–		Griebel *et al.*, 1994
								10	i.p. during 21 days (x1)	o		
						Free-exploration test	Swiss mice (10 weeks)	10	i.p. 30	–		Griebel *et al.*, 1994
						Geller–Seifter conflict test	Rats	4		+	FR8, weak effect	Hascoët *et al.*, 1992
Citalopram (5-HT reuptake inhibitor) (IC_{50} = 3.8 nM)[a23]	> 10000		> 1000[b]									
						Vogel's conflict test	Rats	10	s.c. 45	–		Broekkamp and Jenck, 1989
						Elevated-plus maze	Wistar rats (150–220g)	10–30	i.p. 30	–		Griebel *et al.*, 1994
						Light/dark test	Swiss mice (10 weeks)	1–30	i.p. 30	–		Griebel *et al.*, 1994
						Free-exploration test	Swiss mice (10 weeks)	30	i.p. 30	–		Griebel *et al.*, 1994
						Marble burying test	Female MF1 mice (23–35g)	1–20	i.p. 30	+		Njung'e and Handley, 1991b
						Ultrasonic 'distress' vocalization	Rats	1	s.c.	+		Winslow and Insel, 1991b
Clomipramine (5-HT reuptake inhibitor)	21000			180	[a22]	Vogel's conflict test	Rats	1–50	30	o		Schoenfeld, 1976
						Social interaction	Rats	3–10	i.p. 30	o	Chronic and acute treatments	File, 1985
						Ultrasonic 'distress' vocalization	Rats	5	s.c.	+		Winslow and Insel, 1991b
							Adult rats	LED = 10	i.p.	+		Molewijk *et al.*, 1993
						DPAG-Stimulation	Rats (250g)	15	i.p. 30-120	+		Kiser *et al.*, 1978
Fluoxetine (5-HT reuptake inhibitor (IC_{50} = 27 nM)[a23]	11500	6170	4266	1820	269	11220 [a19]	Vogel's conflict test	Rats	5–10	i.p. 30	+		Handley and McBlane, 1992
						Elevated-plus maze	Wistar rats (150–200g)	10	30	–		Kshama *et al.*, 1990
							Rats	1.25–10	i.p. 30	–		Handley and McBlane, 1992
						Light/dark test	Wistar rats (150–200g)	10	30	–	Asymmetric compartments	Kshama *et al.*, 1990
						Holeboard	Wistar rats (150–200g)	10	30	–		Kshama *et al.*, 1990
						Ultrasonic 'distress' vocalization	Wistar rats (9–11 days)	5–20	30	o	Warm condition	Mos and Olivier, 1989
							Wistar rats (9–11 days)	20	30	+	Cold condition	Mos and Olivier, 1989
						Novelty-suppressed feeding	Long–Evans rats (300–325g)	10	i.p. 60	–		Bodnoff *et al.*, 1989
									during 21 days (x1)	+		

Continued

Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
Fluvoxamine (5-HT reuptake inhibitor) (ID_{50} = 5 mg/kg)[a23]	> 10000			> 1000[p]			Social interaction	DAP mice (22–30g)	1	i.p.	–	Isolated mice	Olivier *et al.*, 1989
							Marble burying test	Female MF1 mice (23–35g)	1–20	i.p. 30	+		Njung'e and Handley, 1991b
							Ultrasonic 'distress' vocalization	Wistar rats (9–11 days)	5–20	30	o	Warm condition	Mos and Olivier, 1989
								Wistar rats (9–11 days)	5–20	30	+	Cold condition	Mos and Olivier, 1989
								Adult rats	LED = 3	i.p.	+		Molewijk *et al.*, 1993
							Freezing	Wistar rats (250–300g)	3–30	i.p. 30	o		Van Dijken *et al.*, 1992
										i.p. during 14 days (x1)	o		
Imipramine (5-HT reuptake inhibitor)	21000[b]			260[f]	100[t]	570[g]	Geller–Seifter conflict test	Wistar rats (180–200g)	20	i.p. 30	–	VI30	Sanger, 1992
								Rats	0.55–17.7	p.o.	o	VI30/FR10	Cook and Davidson, 1973
								Sprague–Dawley rats (200–320g)	1–10	i.p. 20	o	FR40	Kilts *et al.*, 1981
							Vogel's conflict test	Sprague–Dawley rats (250–300g)	100–300	i.p. 30	–	Modified Vogel's test	McCown *et al.*, 1983
								Female Sprague–Dawley rats (225–275g)	7.1–20	i.p. 10	–	Modified Vogel's test	Fontana and Commissaris, 1988
								Sprague–Dawley rats (200–320g)	1 – 10	i.p. 30	o	VI21	Kilts *et al.*, 1981
								Female Sprague–Dawley rats (225–275g)	2.5	i.p. during 1–5 weeks (x2)	+	Modified Vogel's test	Fontana and Commissaris, 1988
							Conflict test	White Carneau pigeons	1–30	i.m. 15	o		Nanry *et al.*, 1991
							Shuttle box	Rats	8–32	30	+	Caffeine-pretreated rats	Martin, 1993
							Elevated-plus maze	Lister rats (250–400g)	5–15	i.p. 30	o		Pellow *et al.*, 1985
								Sprague–Dawley rats (170–200g)	1–30	p.o. 60	o		Luscombe *et al.*, 1990
							Light/dark test	ICR mice (20–35g)	1–4	i.p. 30	o	Transitions and Asymmetric compartments	Onaivi and Martin, 1989
								Female ICR–DUB mice (17–35g)	3.16	i.p. 30	+	Locomotion decreased and Asymmetric compartments	Young and Johnson, 1991c
							Open-field	Female Long–Evans rat (12 weeks)	20	i.p. 60	–	Saline injection	Dwyer and Roy, 1993
										i.p. during 11 days (x1)	–		
										i.p. 60	o		
										i.p. during 11 days (x1)	o		
							Defense test battery	Long–Evans rats (105–117 days)	15	i.p. during 3 weeks (x1)	+		Blanchard *et al.*, 1993
							Social competition	Wistar rats (120g)	5–10	i.p. 30	o		Joly and Sanger, 1991
							Ultrasonic 'distress' vocalization	Adult rats	LED = 20	i.p.	+		Molewijk *et al.*, 1993
							Conditioned emotional response	Wistar rats (400–500g)	5–20	i.p. 30	–		Sanger, 1990
							Shock–probe burying test	Wistar rats (250–280g)	0.63–40	s.c. 60	+		Meert and Colpaert, 1986a

							Marble burying test	Rats Long–Evans (325–500g)	4–16	i.p. 30	+		Craft *et al.*, 1988
							Fear-potentiated startle reflex	Sprague–Dawley rats (300–400g)	5–10	i.p. 5	o		Cassella and Davis, 1985
										i.p. during 3 weeks (x1)	o		Sanger *et al.*, 1989
							Passive-avoidance test	Wistar rats (220–240g)	7.5–30	i.p. 30	o		Erwin *et al.*, 1987
							Conditioned place aversion	Long–Evans rats (8 weeks)	2–24	i.p. 60	o		Pollard and Howard, 1991
							Cork gnawing	Long–Evans rats (435–640g)	4–32	p.o. 30	o		
Indalpine (5-HT reuptake inhibitor) (IC_{50} = 2.8 nM)[a19]	9120	4467	3630	794	3235	1200[a19]	Marble burying test	Female MF1 mice (23–35g)	1–20	i.p. 30	+		Njung'e and Handley, 1991b
Paroxetine (5-HT reuptake inhibitor) (ED_{50} = 1.9 mg/kg)[c]	> 10000			> 1000[b]			Vogel's conflict test	Wistar rats (220g)	5	i.p. 30	o	Modified Vogel's test	Petersen and Lassen, 1981
							Elevated-plus maze	Lister rats (200–250g)	3	p.o. during 3 weeks (x1)	+		Cadogan *et al.*, 1992
							Social interaction	CD rats	3	p.o. during 3 weeks (x1)	+		Lightowler *et al.*, 1992
							Ultrasonic 'distress'	Rats	1	s.c. 3 weeks (x1)	+		Winslow and Insel, 1991b
S3344 (5-HT reuptake inhibitor)							Social interaction	Rats	2.5–20	i.p. 15	–	Weak effect	File, 1984a
Zimelidine (5-HT reuptake inhibitor)							Elevated-plus maze	Wistar rats (150–200g)	40	30	–		Kshama *et al.*, 1990
							Light/dark test	Wistar rats (150–200g)	40	30	–	Asymmetric compartments	Kshama *et al.*, 1990
							Holeboard	Wistar rats (150–200g)	40	30	–		Kshama *et al.*, 1990
							Marble burying test	Female MF1 mice (23–35g)	1–30	i.p. 30	+		Njung'e and Handley, 1991b
							Ultrasonic 'distress' vocalization	Wistar rats (9–11 days)	1–10	30	o	Warm condition	Mos and Olivier, 1989
								Wistar rats (9–11 days)	3–10	30	+	Cold condition	Mos and Olivier, 1989
							DPAG-Stimulation	Wistar rats (250–300g)	100 nmol	DPAG, 10	+		Schütz *et al.*, 1985
								Rats	100 nmol	DPAG, 10	+		Graeff *et al.*, 1986
								Wistar rats (200–250g)	100 nmol	DPAG, 10 or 20	+		Audi *et al.*, 1988
Tianeptine (5-HT reuptake stimulant)				> 3000[a19]			Elevated-plus maze	Lister rats (200–250g)	10	i.p. 20	+	Weak effect	File and Mabbutt, 1991
									2.5–10	during 5 days (x1)	o		
							Social interaction	Lister rats (200–250g)	2.5–10	i.p. 20	o		File and Mabbutt, 1991
									5–10	during 5 days (x1)	+		
								Rats	2.5–10	i.p. 30	o		Andrews and File, 1993
α-Me-5-HT (non-selective agonist)							Geller-Seifter conflict test	Female CFN rats	0.3–2	i.p.	o	VI30/FR10	Winter, 1972
pK_D [3]	7.1	6.0	6.2	6.6	7.2		Conflict test	White Carneau pigeons	1–3	i.m. 0	–	FI5/FR30	Graeff and Schoenfeld, 1970
2-Me-5-HT (non-selective agonist)	1698[j]		724[j]	1800[a]	> 10000[a]	489[j]	210[a26]	Light/dark test	Mice (25–35g)	0.0000001–0.0001	Dorsal raphé	–	Asymmetric compartments	Costall *et al.*, 1988c
									BKW mice (25–30g)	0.0000001–0.0001	Dorsal raphé	–	Asymmetric compartments	Costall *et al.*, 1989c
											Amygdala or median raphé			
								Social interaction	Lister rats (210–280g)	0.001–0.1	Amygdala, 5	–	LLF	Higgins *et al.*, 1991
										0.001–0.0025	Dorsal raphé	o	HLU and LLF	

Continued

Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
5-CT (non-selective agonist)	0.32[b]	5.12[b]	2.5[b]	633[d]	630[b]		Vogel's conflict test	Lister rats (200–250g)	0.0001–0.001	Dorsal raphé, 5	+		Higgins *et al.*, 1987
								Lister rats (210–270g)	0.00002–0.0005	Dorsal raphé, 5	+		Higgins *et al.*, 1988
							Open-field	Lister rats (200–250g)	1–10 nmol	DPAG, 0	−		Beckett *et al.*, 1992
							Social interaction	Lister rats (200–250g)	0.00002	Dorsal raphé, 5	+	HLU	Higgins *et al.*, 1987
								Lister rats (210–270g)	0.00002–0.0001	Dorsal raphé, 5	+		Higgins *et al.*, 1988
Lisuride (non-selective agonist)	0.8	199	36.6	5.01[b]	19.9		Vogel's conflict test	Wistar rats	0.05–0.1	i.p. 30	+		Akai *et al.*, 1991
							Fear-potentiated startle reflex	Sprague–Dawley rats (320–350g)	0.05–0.8	i.p. 10	−		Svensson, 1985
Bromo-LSD (non-selective antagonist)							Conflict test	White Carneau pigeons	0.1–3	i.m. 0	+	FI5/FR30	Graeff and Schoenfeld, 1970
DMT (non-selective antagonist)							Geller–Seifter conflict test	Female CFN rats	2–7	i.p.	−	VI30	Winter, 1972
Metergoline (non-selective antagonist)	7.9[b]	39.8[b]	0.79[b]	1[b]	0.64[b]	7400[l]	Geller–Seifter conflict test	Rats	20	p.o. 25	o		Deacon and Gardner, 1986
								Rats	2.5–20	p.o.	+	VI30/FR10	Sullivan *et al.*, 1985
							Vogel's conflict test	Sprague–Dawley rats (200–225g)	0.25–2	i.p. 10	o		Commissaris and Rech, 1982
								Sprague–Dawley rats (200g)	0.25–2	i.p. 180	o	VI21	Kilts *et al.*, 1982
								Wistar rats (180–220g)	2–4	i.p. 60	o	Modified Vogel's test	Chojnacka-Wójcik and Przegalinski, 1991
							Conflict test	Pigeons Columbia livia	0.56	i.m. 30	+		Leone *et al.*, 1983
								Squirrel monkeys (550–900g)	0.03–0.3	i.m.	+	FR30	Brady and Barrett, 1985
							Elevated-plus maze	Rats	4		+		File *et al.*, 1987
								Lister rats (250–350g)	4	i.p. 30	+		Pellow *et al.*, 1987
							Light/dark test	Mice (25–35g)	0.05–10	i.p. 40	−	Sedation and asymmetric compartments	Costall *et al.*, 1988c
							Open-field	Sprague–Dawley rats (200–250g)	0.16–0.62	i.p. 60	o		Lucki *et al.*, 1989
							Social interaction	Rats			o	HLU	File, 1981
								Wistar rats (180–200g)	5–20	p.o. 30	o		Guy and Gardner, 1985
								Sprague–Dawley rats (200–250g)	2.5	s.c. 40	o		Kennett *et al.*, 1989
							Shock–probe buring test	Wistar rats (250–280g)	0.63–10	s.c. 60	+		Meert and Colpaert, 1986b
							Marble burying test	Female MF1 mice (23–35g)	0.10–1	i.p. 30	+	Locomotion decreased	Njung'e and Handley, 1991b
							Ultrasonic 'distress' vocalization	Wistar rats (9–12 days)	0.1–10	i.p. 30	+	Myorelaxation	Gardner, 1985a
							Fear-potentiated startle reflex	Sprague–Dawley rats (320–350g)	1	i.p. 70	o		Svensson, 1985

								CD rats (9–13 weeks)	0.5–2	s.c. 180	+	Nanry and Tilson, 1989
							Conditioned emotional response	Rats	10 20		o	Gardner, 1985b
							DPAG–Stimulation	Wistar rats (250–300g)	10 nmol	DPAG, 10	o	Schütz *et al.*, 1985
								Wistar rats (370–450g)	0.1–10	i.p. 35	–	Jenck *et al.*, 1989a
								Rats	10 nmol	DPAG, 10	o	Graeff *et al.*, 1986
Methysergide (non-selective antagonist)	25[b]	1584[b]	3.9[b]	2.5[b]	2.5[b]	19500[k]	Geller–Seifter conflict test	Sprague–Dawley rats (200–320g)	1–18	i.p. 30	o	FR40 Kilts *et al.*, 1981
								Female CFN rats	3	i.p.	+	VI30/FR10 Winter, 1972
								Wistar rats (198–260g)	10	i.p. 30	+	FI1/FR5 Graeff, 1974
								Rats	1.25–5	i.p. 1	+	FR10/VI30 Cook and Sepinwall, 1975b
								Rats	10	i.p. 0	+	Stein *et al.*, 1975
								Rats (382–446g)	0.0005–0.0025	Amygdala, 0	+	VI20 Hodges *et al.*, 1987
									0.25–5	i.p. 15		
								Sprague–Dawley rats (330–370g)	0.1–30	i.p.	+	FR30/FR10 Witkin and Perez, 1989–1990
							Vogel's conflict test	Sprague–Dawley rats (200–320g)	10	i.p. 30	–	VI21 Kilts *et al.*, 1981
								Sprague–Dawley rats (200g)	10	i.p. 30	–	VI21 Kilts *et al.*, 1982
								Sprague–Dawley rats (200–320g)	1–10	i.p. 1	o	VI21 Kilts *et al.*, 1981
								Sprague–Dawley rats (200g)	1–18	i.p. 1	o	VI21 Kilts *et al.*, 1982
								Wistar rats (220g)	0.3–3	i.p. 30	o	Modified Vogel's test Petersen and Lassen, 1981
								Rats	2–20		+	Gardner, 1985b
							Conflict test	White Carneau pigeons	0.1–3	i.m. 0	+	FI5/FR30 Graeff and Schoenfeld, 1970
								Squirrel monkeys (550–900g)	0.1–1	i.m.	+	FR30 Brady and Barrett, 1985
							Conditioned emotional response	Sprague–Dawley rats (200–320g)	1–10	i.p. 30	o	FR40 Kilts *et al.*, 1981
							Light/dark test	Mice (25–35g)	0.05–10	i.p. 40	–	Sedation, ataxia and asymmetric compartments Costall *et al.*, 1988c
							Open-field	Sprague–Dawley rats (200–250g)	5–10	i.p. 30	o	Lucki *et al.*, 1989
							Social interaction	Rats			o	LLF and HLU File, 1981
							Fear-potentiated startle reflex	Sprague–Dawley rats	0.3–10	s.c. 10	–	Mansbach and Geyer, 1988
							Shock–probe burying test	Wistar rats (250–280g)	10	s.c. 60	+	Meert and Colpaert, 1986b
							Marble burying test	Female MF1 mice (23–35g)	5–10	i.p. 30	+	Locomotion decreased Njung'e and Handley, 1991b
							Ultrasonic 'distress' vocalization	Wistar rats (9–11 days)	0.3–3	30	o	Warm condition Mos and Olivier, 1989
							Stress-induced antinociception	ddY mice (18–20g)	2–10	i.p. 30	o +	Cold conditin Tokuyama *et al.*, 1993
							Defecation–micturition	Rats			+	High level of illumination Meert and Colpaert, 1986b
							Stress-induced colonic motor alterations	Wistar rats (250–300g)	0.1	i.p. 30	+	Gué *et al.*, 1993
							DPAG-Stimulation	Rats	10–30	i.p. 30	–	Clarke and File, 1982

Continued

Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
Alprenolol (non-selective antagonist)							Conflict test	Pigeons	0.63–10	i.m. 5	o	FR30	Colpaert *et al.*, 1992
							Light/dark test	Swiss mice (20–30g)	5	i.p. 30	o		Fernández-Guasti and López-Rubalcava, 1990
								Swiss Webster mice (20–30g)	5	i.p. 30	o		López-Rubalcava *et al.*, 1992
							Shock–probe burying test	Wistar rats (300–350g)	5	i.p. 30	o		Fernández-Guasti *et al.*, 1992a
								Swiss Webster mice (20–35g)	5	i.p. 30	o		Fernández-Guasti *et al.*, 1992a
Cyanopindolol	5.9[a]	17[a]	410[a]	31622[b]	>10000[a]	>10000[a]	Social interaction	Sprague-Dawley rats (200–250g)	6	s.c. 40	o		Kennett *et al.*, 1989
								Sprague-Dawley rats (250–320g)	3–6	s.c. 30	o		Kennett, 1992
Isamoltane (non-selective antagonist)	125[a1]	112[a1]	1174[a14]				Elevated-plus maze	Wistar rats (292–368)	2.5–20	i.p. 30	o	Rats were well-nourished	Almeida *et al.*, 1991
								Wistar rats (144–196g)	2.5–20	i.p. 30	o	Rats were malnourished	Almeida *et al.*, 1991
							DPAG-Stimulation	Wistar rats (180–250g)	4–32 nmol	DPAG	+		Nogueira and Graeff, 1991
(−)Pindolol (non-selective antagonist)	19[b]	15.8[b]	6309[b]	39800[b]	>10000[a]	>10000[a]	Elevated-plus maze	Rats PVG (200–280g)	1 0.10–0.25	i.p. 30	− +	Observations during 10 min	Critchley and Handley, 1987
							Light/dark test	Swiss mice (20–30g)	2	i.p. 30	o		Fernández-Guasti and López-Rubalcava, 1990
								Swiss Webster mice (20–30g)	3.1	i.p. 30	o		López-Rubalcava *et al.*, 1992
							Open-field	Sprague–Dawley rats (200–250g)	10	i.p. 60	+	Locomotion increased	Lucki *et al.*, 1989
							Social interaction	Sprague–Dawley rats (250–320g)	1–6	s.c. 30	o	Locomotion increased	Kennett, 1992
								Rats			+	LLF	Critchley *et al.*, 1987
							Marble burying	Female MF1 mice (23–35g)	5–10	i.p. 30	o		Njung'e and Handley, 1991b
							Shock–probe burying test	Wistar rats (300–350g)	3.1	i.p. 30	o		Fernández-Guasti *et al.*, 1992a
								Swiss Webster mice (20–35g)	3.1	i.p. 30	+		Fernández-Guasti *et al.*, 1992a
							Stress-induced antinociception	ddY mice (18–20g)	1–3	i.p. 30	o	(±)	Tokuyama *et al.*, 1993
							DPAG-Stimulation	Rats			o		Jenck *et al.*, 1989b

Propranolol (non-selective antagonist)		46.8[m] (−)	3162[b] (−)	2490[d] (+)	158[m] (−) 85.1[n] (+)		Vogel's conflict test	Wistar rats (220g)	10–30	i.p. 30	o	Modified Vogel's test	Petersen and Lassen, 1981
							Conflict test	White Carneau pigeons	1–5.6	i.m.	+	FR30	Durel *et al.*, 1986
	140[a] (±)	540[a] (±)	10000[a] (±)	758[n] (±)	588[o] (±)	4000[a] (±)	Elevated-plus maze	Lister rats (250–350g)	5–10	i.p. 30	−	(−)	Pellow *et al.*, 1987
								Wistar rats (150–200g)	10	30	o	Observations during 10 min	Kshama *et al.*, 1990
								CD-1 mice (25–32g)	2.5	i.p. 30	o		Gorman and Dunn, 1993
								Rats	10 nmol	DPAG	+		Graeff *et al.*, 1990
								Wistar rats (200–250g)	10 nmol	DPAG, 10	+	D,L	Audi *et al.*, 1991
									5 nmol		+	L	
								Rats	10 nmol	DPAG	+	D,L	Graeff *et al.*, 1991
									5 nmol		+	L	
								Female CD1 mice (22–24g)	5–10	i.p.30	+	(±)	De Angelis, 1992
								CD-1 mice (25–32g)	2.5	i.p. 30	+	Stressed mice	Gorman and Dunn, 1993
							Light/dark test	CD-COBS rats (200–300g)	0.0001	ICV, 5	o	Transitions only	Carli *et al.*, 1989b
								Wistar rats (150–200g)	10	30	o	DL, Asymmetric compartments	Kshama *et al.*, 1990
								CD1 mice (32–40g)	12.4–24.9 mg/L	p.o. during 12–15 days (x1)	o	Asymmetric compartments	Gao and Cutler, 1992c
								CD1 mice (32–40g)	1.5	i.p. 30	+	DL, Asymmetric compartments	Gao and Cutler, 1992c
							Holeboard	Wistar rats (150–200g)	10	30	o		Kshama *et al.*, 1990
							Social interaction	Wistar rats (180–200g)	10–40	p.o. 30	o		Guy and Gardner, 1985
								Sprague–Dawley rats (200–250g)	16	s.c. 40	o		Kennett *et al.*, 1989
								CD1 mice (32–40g)	1.5–6	i.p. 30	+	DL, Asymmetric compartments	Gao and Cutler, 1992c
									12.4–24.9 mg/L	p.o. during 2–15 days (x1)	+		
							Open-field	Sprague–Dawley rats (200–250g)	10	i.p. 60	+	Locomotion increased	Lucki *et al.*, 1989
							Fear-potentiated startle reflex	Rats	20		+		Davis *et al.*, 1979
							Novelty-suppressed feeding	Rats	1		+		Rex *et al.*, 1991
							Shock–probe burying test	Wistar rats (250–280g)	10–40	s.c. 60	+		Meert and Colpaert, 1986b
							Ultrasonic 'distress' vocalization	Sprague–Dawley rats (9–11 days)	1–10	s.c. 30	o		Winslow and Insel, 1991a
							Restraint stress	CD-1 mice (25–32g)	2.5	i.p. 30	+	L	Gorman and Dunn, 1993
							DPAG-Stimulation	Wistar rats (200–250g)	2.2–8.8 nmol	DPAG, 10 or 20	+		Audi *et al.*, 1988
Eltoprazine (non-selective ligand)	40	52	390	1700	81	1300[e]	Elevated-plus maze	DBA/2 mice (6–8 weeks)	1.25–2.5	i.p. 30	−		Rodgers *et al.*, 1992
								Wistar rats (150–220g)	10	i.p. 30	−		Griebel, 1993
							Light/dark test	Swiss mice (12 weeks)	10	i.p. 30	−		Griebel *et al.*, 1990
							Free-exploratory test	Swiss mice (12 weeks)	5–15	i.p. 30	−		Griebel *et al.*, 1990
							Social interaction	DAP mice (22–30g)	1–20	p.o. 60	−	Isolated mice	Olivier *et al.*, 1989
							Ultrasonic 'distress' vocalization	Wistar rats (9–11 days)	0.3–3	30	o	Warm condition	Mos and Olivier, 1989
								Wistar rats (9–11 days)	1–3	30	+	Cold condition	Mos and Olivier, 1989
							Conditioned place aversion	Long–Evans rats (250–300g)	1–10	i.p.	−		Rocha *et al.*, 1993a

Continued

Table 1. *Continued*

Compounds	Affinities (K_i, nM) 5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{2A}	5-HT_{2C}	5-HT_3	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
Fluprazine (non-selective ligand)	410	4100	510	1800[u]	2600		Elevated-plus maze	DBA/2 mice (6–8 weeks)	1.25–2.5	i.p. 30	–		Rodgers *et al.*, 1992
							Light/dark test	Swiss mice (12 weeks)	5–7.5	i.p. 30	–		Griebel *et al.*, 1990
							Free-exploratory test	Swiss mice (12 weeks)	2.5–10	i.p. 30	–		Griebel *et al.*, 1990
d-LSD (non-selective ligand)	38[c]	151[n]	6.3[b]	2.5[b]	4.4[b]		Vogel's conflict test	Sprague–Dawley rats (200g)	0.0003–0.1	i.p. 1, 10 and 30	o	VI21	Kilts *et al.*, 1982
								Sprague–Dawley rats (200g)	0.001	30	+		Schoenfeld, 1976
								Sprague–Dawley rats (200–225g)	0.05	i.p. 10	+		Commissaris and Rech, 1982
							Holeboard	Sprague–Dawley rats (200–250g)	0.1	i.p. 10	–		Geyer *et al.*, 1980
							Shock–probe burying test	Wistar rats (250–280g)	0.01–0.63	i.p. 15	o		Meert and Colpaert, 1986b
Quipazine (non-selective ligand)	780[c]	260[c]	1258[b]	17[d]	9900[c]	0.22[t]	Vogel's conflict test	Sprague–Dawley rats (200–225g)	2–4	i.p. 10	–	Also decreased non-punished responses	Commissaris and Rech, 1982
							Elevated-plus maze	Rats	2–4		–		File *et al.*, 1987
								Lister rats (250–350g)	2–4	i.p. 30	–		Pellow *et al.*, 1987
								Wistar rats (150–200g)	5	30	o		Kshama *et al.*, 1990
							Light/dark test	Wistar rats (150–200g)	5	30	–	Asymmetric compartments and weak effect	Kshama *et al.*, 1990
								Swiss mice (10 weeks)	5–20	i.p. 30	–		Griebel, 1993
							Free-exploration test	Swiss mice (10 weeks)	5–20	i.p. 30	–		Griebel, 1993
							Holeboard	Wistar rats (150–200g)	5	30	o		Kshama *et al.*, 1990
							Fear-potentiated startled reflex	CD rats (9–13 weeks)	5–10	s.c. 60	+		Nanry and Tilson, 1989
							Ultrasonic 'distress' vocalization	AP mice (4–6 days)	2–4	20	–		Nastiti *et al.*, 1991
Spiperone (non-selective antagonist)	63	5011	5011	1.6[b]	1150		Conflict test	Squirrel monkeys (550–900g)	0.001–0.1	i.m.	o	FR30	Brady and Barrett, 1985
								White Carneau pigeons	0.01–0.1	i.m. 5	o		Gleeson *et al.*, 1989
							Ultrasonic 'distress' vocalization	AP mice (4–6 days)	0.1–0.2	30	+		Nastiti *et al.*, 1991
							DPAG-Stimulation	Wistar rats (370–450g)	0.14–0.2	i.p. 35	+		Jenck *et al.*, 1989a
8-OH-DPAT (*full agonist*)	2.8	1800	930	>10000	7800	4300[a]	Geller–Seifter conflict test	Rats (382–446g)	0.00125–0.005	Amygdala, 0	–	VI20	Hodges *et al.*, 1987
								Rats	0.001		–	FR8	Hascoët *et al.*, 1992
								Rats	0.25	i.p. 25	o		Deacon and Gardner, 1986
								Sprague–Dawley rats (330–370g)	0.1–3	i.p.	o	FR30/FR10	Witkin and Perez, 1989 1990
								Rats	0.015–0.03	s.c.	o	Modified Geller–Seifter test	Thiébot *et al.*, 1990

	Wistar rats (250–350g)	0.007–0.125	s.c. 60	o	Modified Geller–Seifter test	Thiébot *et al.*, 1991
	Wistar rats (180–200g)	0.05–1	i.p. 30	o	VI30	Sanger, 1992
	Wistar rats	0.03–0.1	i.p.	+		Amrick and Bennett, 1986
	Rats (382–446g)	0.25	i.p. 15	+	VI20	Hodges *et al.*, 1987
	Wistar rats	0.1–0.3	i.p. 15	+		De Vry *et al.*, 1991
	Rats	0.5		+	FR8	Hascoët *et al.*, 1992
Vogel's conflict test	Sprague–Dawley rats (170–210g)	0.03–0.15	s.c. 15	o		Moser *et al.*, 1988
	Sprague–Dawley rats	0.05–0.15	s.c.	o		Hibert and Moser, 1990
	Sprague–Dawley rats (200–300g)	0.005–0.15	s.c. 30	o		Moser *et al.*, 1990
	Sprague–Dawley rats (190–210g)	0.062–0.25	i.p. 10	+	Modified Vogel's test	Engel *et al.*, 1984
	Lister rats (200–250g)	0.001	Dorsal raphé, 5	+		Higgins *et al.*, 1987
	CD–COBS rats (200–300g)	0.5–2	i.p. 60	+	Stressed rats	Carli and Samanin, 1988
	Lister rats (210–270g)	0.000004–0.0005	Dorsal raphé, 5	+	Modified Vogel's test	Higgins *et al.*, 1988
	Rats		Hippocampus	+		Plaznik *et al.*, 1991
	Wistar rats (180–220g)	0.025–0.1	i.p. 15	+		Stefanski *et al.*, 1992a
	Rats	0.025–0.05		+		Stefanski *et al.*, 1992b
	Wistar rats	0.5	i.p. 30	+		De Vry *et al.*, 1991
	Lister rats (200–280g)	0.00002–0.005	Dorsal raphé, 5	+		Higgins *et al.*, 1992
	Wistar rats (200–250g)	0.25	i.p. 30	+	Modified Vogel's test	Korneyev and Seredenin, 1993
	Wistar rats (180–220g)	0.0005–0.001	Hippocampus, 5	+		Stefanski *et al.*, 1993a
		0.001–0.0025	Nucleus accumbens, 5	+		
Conflict test	Squirrel monkeys (800–1050g)	0.001–0.3	i.m.	o	FI3	Gleeson and Barrett, 1990
	White Carneau pigeons (480–528g)	0.03–3	i.m. 0	+	FR30	Witkin *et al.*, 1987
	White Carneau pigeons	0.1–3	i.m. 0	+	FR30	Mansbach *et al.*, 1988
	White Carneau pigeons	0.3–3	i.m. 15	+	FR30	Ahlers *et al.*, 1992
	White Carneau pigeons	0.03–1	i.m.0	+	FR30	Barrett, 1992
	Pigeons	0.005–0.81	i.m. 5	+	FR30	Colpaert *et al.*, 1992
Timeout from avoidance procedure	Holtzman specific-pathogen free rats (80–120 days)	0.1–1	i.p. 15	+	VI15	Galizio *et al.*, 1990
Conditioned emotional response	Wistar rats (400–500g)	0.1–1	i.p. 30	+	Weak effect	Sanger, 1990
Elevated-plus maze	Rats (250–280g)	0.01 0.03		–	Observations during 10 min	Critchley and Handley, 1986
	PVG rats (200–280g)	0.015–1	i.p. 15	–	Observations during 10 min	Critchley and Handley, 1987
	Lister rats (250–350g)	0.25	i.p. 10	–		Pellow *et al.*, 1987
	PVG rats (200–260g)	0.05–0.1	i.p. 10	–	Observations during 10 min	Critchley *et al.*, 1988
	Sprague Dawley rats (250 300g)	0.0125–0.1	s.c. 15	–		Moser *et al.*, 1988
	Sprague Dawley rats (200 300g)	0.2	s.c. 15	–	Decreased total open arm entries	Moser, 1989b
	Wistar rats (150 200g)	0.25	30	–		Kshama *et al.*, 1990

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{2A}	5-HT_{2C}	5-HT_3	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								Sprague–Dawley rats (200–250g)	0.1–1	s.c. 30	–	Locomotion decreased	Klint, 1991
								PVG rats (180–260g)	0.05–0.2	i.p. 10	–	Observations during 10 min	Critchley *et al.*, 1992
								Wistar rats (345–405g)	1	i.p. 30	–		Kostowski *et al.*, 1992
								Wistar rats (180–200g)	0.2	i.p. 10	–	172 lux and observations during 10 min	McBlane *et al.*, 1992
								Sprague–Dawley rats (250–350g)	0.1–0.2	s.c. 10	–		Treit *et al.*, 1993
								Rats	0.0625–0.25		o		File *et al.*, 1987
								Sprague–Dawley rats (200–300g)	0.025–0.2	s.c. 30	o		Moser *et al.*, 1990
								Wistar rats (180–200g)	0.2	i.p. 10	o	211 lux and observations during 10 min	McBlane *et al.*, 1992
								Wistar rats (225–250g)	0.1–0.2	i.p. 10	+		Dunn *et al.*, 1989
								Wistar rats (180–220g)	0.001–0.00025	Hippocampus, 10	+		Kostowski *et al.*, 1989
								Sprague–Dawley rats (250–350g)	50–400 nmol	s.c. 10	+		Söderpalm *et al.*, 1989
								CD rats (160–200g)	0.003 0.0001–0.1	p.o. 60 s.c. 60	+		Luscombe *et al.*, 1992
								DBA/2 mice (6–8 weeks)	1	i.p. 15	+		Rodgers *et al.*, 1992
								Wistar rats (150–220g)	1	i.p. 30	+	225 lux above the central area	Griebel, 1993
								Wistar rats (180–220g)	0.2	i.p. 10	+	785 lux and observations during 10 min	Handley and McBlane, 1993b
								Wistar rats	0.01	s.c.	+		Millan and Brocco, 1993
							Zero-maze	Sprague–Dawley rats	0.01	s.c. 30	+		Grewal *et al.*, 1993
							Light/dark test	Wistar rats (150–200g)	0.25	30	–	Asymmetric compartments	Kshama *et al.*, 1990
								CD–COBS rats (200–300g)	0.125–2	i.p. 60	+	Stressed rats	Carli and Samanin, 1988
								Female T/O mice (22–30g)	0.1	s.c. 30	+	Asymmetric compartments	Bill *et al.*, 1989
								Swiss mice (10 weeks)	0.75	i.p. 30	+		Misslin *et al.*, 1990
								Female ICR–DUB mice (17–35g)	0.0005–3.16	i.p. 30	+	Asymmetric compartments	Young and Johnson, 1991c
								BKW mice (30–35g)	0.5	i.p. 45	+	Asymmetric compartments	Barnes *et al.*, 1992a
								Mice	0.125		+	Asymmetric compartments	Fernández-Guasti and López-Rubalcava, 1992
								Swiss Webster mice (20–30g)	0.125	i.p. 30	+	Transitions only	López-Rubalcava *et al.*, 1992

Holeboard	Wistar rats (150–200g)	0.25	30	–		Kshama *et al.*, 1990
Social interaction	Rats			–	LLF	Critchley *et al.*, 1987
	DAP mice (22–30g)	0.05–6.25	s.c. 30	o	Isolated mice	Olivier *et al.*, 1989
	Lister rats (200–280g)	0.00002–0.001	Dorsal raphé, 5	o	LLF	Higgins *et al.*, 1992
	Lister rats (200–250g)	0.001	Dorsal raphé, 5	+	HLU	Higgins *et al.*, 1987
	Lister rats (210–270g)	0.00004–0.005	Dorsal raphé, 5	+		Higgins *et al.*, 1988
	Wistar rats (225–250g)	0.125–0.25	i.p. 10	+		Dunn *et al.*, 1989
	Lister rats (200–280g)	0.00002–0.001	Dorsal raphé, 5	+	HLU	Higgins *et al.*, 1992
Open-field	Lister rats (200–250g)	3–25 nmol	DPAG, 0	–		Beckett *et al.*, 1992
	Sprague–Dawley rats (280–320g)	0.025–0.4	s.c.	–		Ahlenius *et al.*, 1991
	CD–COBS rats (200–300g)	0.125–0.5	s.c. 60	o	Non-stressed rats	Carli *et al.*, 1989a
	Wistar rats (180–220g)	0.0001–0.005	Nucleus accumbens, 5	o		Stefanski *et al.*, 1993a
	CD–COBS rats (200–300g)	0.125–0.5	s.c. 60	+	Stressed rats	Carli *et al.*, 1989a
	Sprague–Dawley rats (200–250g)	2.5–5	i.p. 0	+	Locomotion increased	Lucki *et al.*, 1989
	Rats		Hippocampus	+		Plaznik *et al.*, 1991
	Wistar rats (180–220g)	0.025–0.1	i.p. 15	+	65 dB noise	Stefanski *et al.*, 1992a
	Rats	0.025–0.05		+		Stefanski *et al.*, 1992b
	CD–COBS rats (200–250g)	0.005	Hippocampus	+		Carli *et al.*, 1993
	Wistar rats (180–220g)	0.0001–0.001	Hippocampus, 5	+	+5,7-DHT	Stefanski *et al.*, 1993a
		0.0005		+		
Anxiety/defense test battery	Male and female Long–Evans rats (98–111 days)	0.01–1	s.c. 30	+		Blanchard *et al.*, 1992
Staircase test	Rats	0.05–0.5	IP	+		Boaventura *et al.*, 1986
Novelty-suppressed feeding	Sprague–Dawley rats (270–320g)	0.032–0.125	s.c. 10	+		Fletcher and Davies, 1990
	Rats	0.03		+		Rex *et al.*, 1991
Marble burying test	Female MF1 mice (23–35g)	0.3–10	i.p. 10	+	Locomotion decreased	Njung'e and Handley, 1991b
Shock–probe burying test	Wistar rats	0.5	i.p. 15	o	+5,7-DHT	Fernández-Guasti *et al.*, 1992b
	Wistar rats (280–350g)	0.125–0.75	i.p. 15	+		Fernández-Guasti and Hong, 1989
	Rats			+		Meert, 1989
	Wistar rats	0.5	i.p. 15	+		Fernández-Guasti *et al.*, 1992b
	Sprague–Dawley rats (250–350g)	0.05–0.2	s.c. 10	+		Treit *et al.*, 1993
Ultrasonic 'distress' Vocalization	AP mice (4–6 days)	0.25–0.5	15	–		Nastiti *et al.*, 1991
	Wistar rats (10 days)	0.0075–0.03	s.c. 10	+		Hård and Engel, 1988
	Wistar rats (9–11 days)	0.1–0.2	30	+	Warm condition	Mos and Olivier, 1989
				+	Cold condition	
	Wistar rats	0.1–1	i.p. 15	+		De Vry *et al.*, 1991
	Sprague–Dawley rats (320–350g)	0.5–0.8	i.p. 10	–		Svensson, 1985

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								Rats	0.63–10 0.1	i.p. 0, IT, 30	–		Davis *et al.*, 1986
								CD rats (9–13 weeks)	1–4	s.c. 5	–		Nanry and Tilson, 1989
								Wistar rats (200–250g)	0.5–8	i.p. 5	–		Hijzen *et al.*, 1991
								Rats	0.05–0.1	i.c.v., 30	o		Davis *et al.*, 1986
								Sprague–Dawley rats (300–400g)	2.5–10	i.p. 0	o		Davis *et al.*, 1988a
								Rats	0.12–0.25	i.p.	o		Davis, 1993
								Sprague–Dawley rats	0.125–0.5	i.p. 10	+		Mansbach and Geyer, 1988
							Aggression-provoked	NMRI mice	1–3	i.p. 30	+		De Vry *et al.*, 1991
							Stress-induced hyperthermia	Swiss mice (25–30g)	2.5–10	s.c. 30	+		Lecci *et al.*, 1990
								Mice	0.3	s.c.	+		Schipper *et al.*, 1991
							Passive-avoidance test	Wistar rats (220–240g)	0.125–0.5	i.p. 30	+		Sanger and Joly, 1989–1990
								Sprague–Dawley rats (200–250g)	0.01–1	s.c. 30	+		Klint, 1991
							Stress-induced colonic motor alterations	Wistar rats (250–300g)	0.05–0.1	i.p. 30	+		Gué *et al.*, 1993
							Hot-plate	Wistar rats (200–250g)	0.1–1	i.p. 30	+		Korneyev and Seredenin, 1993
							DPAG-Stimulation	Wistar rats	0.032–1	i.p. 35	–		Jenck *et al.*, 1989a
Flesinoxan (Full agonist)	1.7	810	160	4500	>10000	>10000[a]	Conflict test	Squirrel monkeys (800–1050g)		i.m.	o	FI3	Gleeson and Barrett, 1990
								White Carneau pigeons (450–600g)	0.03–0.3	i.v.	+		Barrett *et al.*, 1989
								White Carneau pigeons	0.001–3	i.m.0	+	FR30	Barrett, 1992
								pigeons	0.04	i.m. 5	+	FR30	Colpaert *et al*, 1992
							Elevated-plus maze	Mice	0.1–0.5	Acute and chronic	+	Additional measures of anxiety	Rodgers *et al.*, 1993
							Light/dark test	Mice			+		Schipper *et al.*, 1991
								Swiss mice (10 weeks)	0.02–0.1	i.p. 30	+		Griebel, 1993
							Open-field	Sprague–Dawley rats (280–320g)	0.2–3.2	s.c.	–		Ahlenius *et al.*, 1991
							Four hot-plates	Mice			+		Schipper *et al.*, 1991
							Ultrasonic 'distress' vocalization	Wistar rats (9–11 days)	0.3–3	30	+	Warm condition	Mos and Olivier, 1989
											+	Cold condition	
								Rats	0.3–3	i.p.	+		Schipper *et al.*, 1991
								Adult rats	LED = 0.3	i.p.	+		Molewijk *et al.*, 1993
							Stress-induced hyperthermia	Mice	>1	p.o.	+		Schipper *et al.*, 1991
							Freezing	Wistar rats (250–300g)	0.3–3	i.p. 30	+		Van Dijken *et al.*, 1992
										i.p. during 14 days (x1)	+		
LY 165163 (5-HT$_{1A}$ agonist)							Elevated-plus maze	Sprague–Dawley rats (200–300g)	0.5–4	s.c. 30	–		Moser, 1989b
LY 228729 (5-HT$_{1A}$ agonist)							Conflict test	Rats			+		Foreman *et al.*, 1993

MDL 72832 (full agonist)	0.79[b]	630[b]	398[b]	158[b]	501[j]		Elevated-plus maze	Sprague–Dawley rats (200–300g)	0.4–3.2	s.c. 30	–	(+) isomer	Moser, 1989a
								Sprague–Dawley rats (200–300g)	0.05–0.8	s.c. 30	–	(–) isomer	Moser, 1989b
							Passive-avoidance test	Wistar rats (220–240g)	0.25–1	i.p. 30	+		Sanger and Joly, 1989–1990
MKC-242 (full agonist)	0.11[a29]						Conflict test (?)	Rats	LED = 0.0625	Acute and chronic	+		Egawa *et al.*, 1993
S14506 (full agonist)							Conflict test	Pigeons	0.0025–0.63	i.m. 60	+	FR30	Colpaert *et al.*, 1992
pK_i[a17]	9.01	6.55		6.64	7.50	< 6	Elevated plus-maze	Wistar rats	0.0006–2.5	s.c. 30	o		Millan and Brocco, 1993
S14671 (full agonist)													
pKi[a27]	9.3	6.3	7.8	<6	7.8		Conflict test	Pigeons	0.0025–0.16	i.m. 60	+	FR30	Millan and Brocco, 1993
							Elevated plus-maze	Wistar rats	0.0006–2.5	s.c. 30	o		Millan and Brocco, 1993
S20244	0.35[w]						Elevated-plus maze	Sprague–Dawley rats (200–250g)	0.05–1	s.c. 30	+		Curle *et al.*, 1991
							Light/dark test	Swiss mice (10 weeks)	1–3	i.p. 20	+		Griebel *et al.*, 1992
S20499 (full agonist)	0.19[w]						Vogel's conflict test	Wistar rats (195–245g)	4	i.p. 30	+		Porsolt *et al.*, 1992
							Elevated plus-maze	Rats		during 14 days	+		Lesourd *et al.*, 1993
							Light/dark test	Swiss mice (10 weeks)	1–3	i.p. 20	+		Griebel *et al.*, 1992
S20500 (full agonist)	0.95[w]						Vogel's conflict test	Wistar rats (195–245g)	16	i.p. 30	+		Porsolt *et al.*, 1992
							Light/dark test	Swiss mice (10 weeks)	2–4	i.p. 20	+		Griebel *et al.*, 1992
U-93385 (full agonist)							Isolation-induced aggression	Mice	3–10	p.o. and i.p.	+		Schreur *et al.*, 1993
							Shock-induced aggression	Mice	10	i.p.	+		Schreur *et al.*, 1993
							Center test (thigmotaxis)	Rats	1–10	s.c.	o		Schreur *et al.*, 1993
									22	s.c. during 16 days (x1)	+		
							Social interaction	Mice	10	p.o.	+		Schreur *et al.*, 1993
							Stress-induced increases in corticosterone	Rats	3–10	i.p.	–		Lahti *et al.*, 1993
										Subchronic	+		
5-MeODMT (agonist)	2.5[c]	390[c]		15[d]	57[c]		Geller–Seifter conflict test	Female Alderley Park rats (241–315g)	1–3	i.p. 12	o		Shephard *et al.*, 1982
							Elevated-plus maze	PVG rats (200–280g)	0.5–2.5	i.p. 15	–	Observations during 10 min	Critchley and Handley, 1987
							Social interaction	Rats			–	LLF	Critchley *et al.*, 1987
								DAP mice (20–30g)	10	i.p. 30	–	Isolated mice	Olivier *et al.*, 1989
							Marble burying test	Female MF1 mice (23–35g)	0.25–5	i.p. 20	+	Locomotion decreased	Njung'e and Handley, 1991b
							Fear-potentiated startle reflex	Sprague–Dawley rats (300–350g)	0.12–8	i.p. 0	–		Davis *et al.*, 1980a
								CD rats (9–13 weeks)	4	i.p. 5	–		Nanry and Tilson, 1989
							DPAG-Stimulation	Wistar rats (250–350g)	0.5–2 nmol	DPAG, 10	+		Schütz *et al.*, 1985
								Rats	1–2 nmol	DPAG, 10	+		Graeff *et al.*, 1986

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
d-AP159 (selective agonist)	28[x]						Vogel's conflict test	Wistar rats (170–200g)	3–10	p.o.	+	Modified Vogel's test	Nagatani *et al.*, 1991
								Wistar rats (180–200g)	10–60	p.o. 60	+	Modified Vogel's test	Takao *et al.*, 1992
BAY R 1521 (5-HT$_{1A}$ agonist)							Elevated-plus maze	PVG rats (180–260g)	0.1–1.2	i.p. 30	–	Observations during 10 min	Critchley *et al.*, 1992
BMY 7378 (partial agonist)							Conflict test	Squirrel Monkeys (800–1050g)	0.003 0.1	i.m.	o	FI3	Gleeson and Barrett, 1990
pK_i^{5-27}:	8.7	4.4		5.7	6.6	< 6.0		White Carneau pigeons	0.03 3	i.m. 5	+		Gleeson *et al.*, 1989
								White Carneau pigeons	1–5.6	i.m. 15	+	FR30 and weak effect	Ahlers *et al.*, 1992
								pigeons	0.16	i.m. 5	+	FR30	Colpaert *et al.*, 1992
							Light/dark test	Female T/O mice (22–30g)	1	s.c. 30	+	Asymmetric compartments	Bill *et al.*, 1989
							Ultrasonic 'distress' vocalization	Adult rats	LED = 3	i.p.	+		Molewijk *et al.*, 1993
BP 554 (5-HT$_{1A}$ agonist)							Elevated-plus maze	CD rats (160–200g)	0.1–3	p.o. 60	+		Luscombe *et al.*, 1992
Buspirone (partial agonist)	25[b]	125890[b]	31622[b]	794[b]	7940[b]	> 10000[a]	Geller–Seifter conflict test	Rats	1	s.c.	–		Baduel *et al.*, 1986
								Wistar rats (180–200g)	5	i.p. 30	–	VI30	Sanger, 1992
								Rats	1–10	i.p. 15 ou 30	o		Amrick and Bennett, 1986
								Rats	0.5–10	i.p. 30	o		Gardner, 1986
								Rats	2	i.p. 30	o	Trial 2	Soubrié, 1989
									2	i.p. 30	o	Trial 3	
								Wistar rats (250–270g)	0.04–10	s.c. 60	o	VI30	Brocco *et al.*, 1990
								Wistar rats	1–10	i.p. 15	o		De Vry *et al.*, 1991
								Wistar rats (400–500g)	1.25–5	i.p. 30	o		Sanger, 1990
									10–40	p.o. 30	o		
								Wistar rats (229–271g)	0.3	i.p. 30	o	VI/FR4	Zhang and Luo, 1993
								Sprague–Dawley rats	0.25–15	i.p.	+		Hartmann and Geller, 1981
								Sprague–Dawley rats	2.5–5	p.o. 30	+		Geller and Hartmann, 1982
								Rats	10		+	Weak effect	Sullivan *et al.*, 1983
								Rats	0.5	s.c.	+		Baduel *et al.*, 1986
								Sprague–Dawley rats (200–225g)	0.3–3	i.p. 60	+	VI30/FR30	Mason *et al.*, 1987
								Sprague–Dawley rats (420–480g)	5–40	p.o. 30	+		Young *et al.*, 1987
								Rats	2	i.p. 30	+	Trial 1	Soubrié, 1989
									2	i.p. 30	+	Trial 2	
								Sprague–Dawley rats (330–370g)	0.1–5.6	s.c.	+	FR30/FR10	Witkin and Perez, 1989–1990
								Ovariectomised	5–10	p.o. 60	+	FR1 FR10 Rats never treated before (effects were always weak)	Howard and Pollard, 1990
								Long–Evans female rats	5		+		
									5		+		
									1	p.o. 60	+		

	Rats	0.25–2	i.p.	+	Modified Geller–Seifter test	Thiébot *et al.*, 1990
	Wistar rats (250–350g)	0.25–2	i.p. 30	+	Modified Geller–Seifter test	Thiébot *et al.*, 1991
	Rats	0.5–1		+	FR8	Hascoët *et al.*, 1992
	Wistar rats (180–200g)	1.25	i.p. 30	+	VI30	Sanger, 1992
Vogel's conflict test	Wistar rats (180–220g)	0.005	Hippocampus, 5	–		Stefanski *et al.*, 1993a
			Nucleus accumbens, 5	–		
	Rats	50	p.o.	o		Goldberg *et al.*, 1983
	Rats	1.25–20		o		Sullivan *et al.*, 1983
	Wistar rats (300–400g)	1–10	i.p. 30	o		Sanger *et al.*, 1985
	Rats	2–10	p.o.	o		Budhram *et al.*, 1986
	Rats	2–10	p.o.	o		Gardner, 1986
	CD–COBS rats (200–300g)	0.0001–0.01	Dorsal raphé, 10	o		Carli *et al.*, 1989b
	Wistar rats (220–240g)	0.04–10	s.c. 60	o	Modified Vogel's test	Brocco *et al.*, 1990
	Female Long–Evans rats (225–249g)	0.125–0.625	s.c. 15	o	Predictable and moderate predictable shocks	Costello *et al.*, 1991a
	Rats		Hippocampus	o		Plaznik *et al.*, 1991
	CD rats (85–100g)	10–80	p.o. 60	+		Oakley and Jones, 1983
	Sprague–Dawley rats (200g)	0.5–5	p.o. 30	+	Modified Vogel's test	Weissman *et al.*, 1984
	Rats	90	p.o. 30	+		File, 1985
	Rats	1–10	p.o.	+		Taylor *et al.*, 1985
	Sprague–Dawley rats (250–350g)	10	i.p. 15	+	Modified Vogel's test	Eison *et al.*, 1986
	Sprague–Dawley rats (200–250g)	0.6–1.2	s.c. 15	+		Pich and Samanin, 1986
	Rats	5.6–10	i.p.	+		Heym *et al.*, 1987
	Lister rats (200–250g)	0.0004–0.002	Dorsal raphé, 5	+		Higgins *et al.*, 1987
	Female rats (225–250g)	0.25–1	i.p. 10	+	Weak effect	McCloskey *et al.*, 1987
		0.125–1	s.c. 10	+		
	Sprague–Dawley rats (200–300g)	5–10	i.p. 30	+	Modified Vogel's test	Shimizu *et al.*, 1987
		20	p.o. 30			
	Lister rats (210–270g)	0.0004–0.01	Dorsal raphé, 5	+		Higgins *et al.*, 1988
	Sprague–Dawley rats (240–300g)	0.25–4	s.c. 30	+	Modified Vogel's test	Gower and Tricklebank, 1988
		1–50	p.o. 30			
	Sprague–Dawley rats (170–210g)	0.25–2	s.c. 30	+		Moser *et al.*, 1988
	CD–COBS rats (200–300g)	0.001–0.005	Median raphé, 10	+		Carli *et al.*, 1989b
	Sprague–Dawley rats (225–275g)	0.125–2	i.p. 10	+	Modified Vogel's test and weak effect in acute treatment	Schefke *et al.*, 1989
		2–4	i.p. during 8 weeks (x2)	+		
	Wistar rats	5–10	i.p. 30	+		De Vry *et al.*, 1991
	Sprague–Dawley rats	0.05–0.15	s.c.	+		Hibert and Moser, 1990
	Sprague–Dawley rats (200–300g)	0.25–1	s.c. 30	+		Moser *et al.*, 1990
	Female Long–Evans (225–249g)	0.125	s.c. 15	+	Unpredictable shocks	Costello *et al.*, 1991a
	Wistar rats (150–166g)	10–20	p.o. 60	+		Wada and Fukada, 1991
	Lister rats (200–280g)	0.0002	Dorsal raphé, 5	+		Higgins *et al.*, 1992

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								SPRD rats (200g)	0.04	i.p. 30	+		Horváth *et al.*, 1992
								Wistar rats (195–245g)	8	i.p. 30	+		Porsolt *et al.*, 1992
								Wistar rats (180–220g)	0.62–2.5	i.p. 30	+	Modified Vogel's test	Stefanski *et al.*, 1992a
								Rats	0.62		+		Stefanski *et al.*, 1992b
								Wistar rats (180–200g)	3–60	p.o. 60	+	Modified Vogel's test	Takao *et al.*, 1992
								Sprague–Dawley rats (211–347g)	10	p.o. 30 p.o. during 7 days	+	Modified Vogel's test	Amano *et al.*, 1993
								Wistar rats (200–250g)	3–5	i.p. 30	+	Modified Vogel's test	Korneyev and Seredenin, 1993
								Wistar rats (12 weeks)	10	i.p. 30	+	0.16 and 0.32 mA shocks	Meneses and Hong, 1993
								Rats			+		Miyauchi *et al.*, 1993
							Conflict test	Squirrel monkeys	5		−		Sullivan *et al.*, 1983
								Squirrel monkeys	10	p.o.	o		Goldberg *et al.*, 1983
								Squirrel monkeys	1.25–2.5		o		Sullivan *et al.*, 1983
								Monkeys	0.01–0.3	i.v. 10	o		Wettstein, 1988
								Squirrel Monkeys (800–1050g)	0.003–0.1	i.m.	o	FI3	Gleeson and Barrett, 1990
								Squirrel monkeys	0.25–15	i.m.	+		Hartmann and Geller, 1981
								Cynomolgus monkeys (4–7 kg)	0.5–5	i.m. 60	+		Geller and Hartmann, 1982
								Squirrel monkeys (0.7–0.8 kg)	3–30	p.o. 30	+		Weissman *et al.*, 1984
								pigeons	0.03–10	i.m.	+		Barrett *et al.*, 1984
								White Carneau pigeons	0.03–10	i.m. 5	+		Barrett *et al.*, 1986
								pigeons	0.03–3	i.m. 0	+		Witkin and Barrett, 1986
								White Carneau pigeons (480–528g)	0.1–5.6	i.m. 5	+	FR30	Witkin *et al.*, 1987
								White Carneau pigeons	0.1–10	i.m. 0	+	FR30	Mansbach *et al.*, 1988
								White Carneau pigeons	0.1–10	i.m. 0	+	FR30	Mansbach *et al.*, 1988
								White Carneau pigeons (500–600g)	0.63	i.m. 5	+	FR30	Brocco *et al.*, 1990
								White Carneau pigeons	0.3–5.6		+	FR30	Nader, 1991
								White Carneau pigeons	0.1–3	i.m. 15	+	FR30	Nanry *et al.*, 1991
								pigeons	0.63	i.m. 5	+	FR30	Colpaert *et al.*, 1992
								White Carneau pigeons	0.03–3	i.m. 0	+		Barrett and Vanover, 1993
								White Carneau pigeons (1 year)	0.1–3	i.m. 0	+	VI1/VI3/FR10	Wojnicki and Barrett, 1993
											+	VI3/VI1/FR10	
							Timeout from avoidance procedure	Holtzman specific-pathogen free rats (80–120 days)	0.5–2	i.p. 15	o	VI	Galizio *et al.*, 1990
								Holtzman specific-pathogen free rats (80–120 days)	0.3–1	i.p. 15	o	VI15	Galizio *et al.*, 1993
							Conditioned emotional response	Wistar rats (400–500g)	1.25–5	i.p. 30	+		Sanger, 1990

Shuttle box	Rats	1	30	+	Caffeine-pretreated rats	Martin, 1993
Elevated-plus maze	Lister rats (250–350g)	4–8	i.p. 30	–		Pellow *et al.*, 1987
	Sprague–Dawley rats (250–300g)	0.125–2	s.c. 30	–		Moser *et al.*, 1988
	Sprague–Dawley rats (200–300g)	0.25–1	s.c. 30	–		Moser, 1989a
		1	s.c. during 16 days (x2)	–		
		0.125–2	s.c. 30	–	PCPA pretreatment	
	Sprague–Dawley rats (200–300g)	1–2	s.c. 30	–	Decreased total open arm entries	Moser, 1989b
	Sprague–Dawley rats (140–230g)	1		–		Redfern and Williams, 1989
	Rats	1–4		–		Kostowski *et al.*, 1990
	Sprague–Dawley rats (200–300g)	0.015–2	s.c. 30	–		Moser *et al.*, 1990
	Lister rats (180g)	0.8	s.c. 15	–		File and Andrews, 1991
	Sprague–Dawley rats (200–250g)	0.1–1	s.c. 30	–	Locomotion decreased	Klint, 1991
	Long–Evans rats (320–340g)	1.25	i.p. 15	–		Lal *et al.*, 1991
	PVG rats (180–260g)	0.025–5	i.p. 30	–	Locomotion decreased and observations during 10 min	Critchley *et al.*, 1992
	Wistar rats (345–405g)	0.06, 0.25–4	i.p. 30	–		Kostowski *et al.*, 1992
	Rats			–		Onaivi, 1993
	Lister rats (250–350g)	0.5–20	i.p. 30	o		Pellow and File, 1986
	Rats	0.5–20		o		File *et al.*, 1987
	Lister rats (300–400g)	2	i.p. 40	o		Moulton and Morinan, 1990
	Wistar rats (151–202g)	2.5–20	p.o. 60	o		Wada and Fukada, 1991
	PVG rats (200–260g)	0.05	i.p. 30	o	Observations during 10 min	Critchley *et al.*, 1988
	SPRD rats (200g)	0.08–1.25	i.p. 30	o		Horváth *et al.*, 1992
	Wistar rats (225–250g)	0.5–1	i.p. 30	+		Dunn *et al.*, 1989
	Wistar rats (180–220g)	0.0025	Hippocampus, 20	+		Kostowski *et al.*, 1989
	Sprague–Dawley rats (250–350g)	8–2048 nmol	s.c. 10	+		Söderpalm *et al.*, 1989
	Wistar rats (150–200g)	2	30	+		Kshama *et al.*, 1990
	DBA/2 mice (12–14 weeks)	1–10	i.p. 15	+		Lee and Rodgers, 1991
	Wistar rats (345–405g)	0.125	i.p. 30	+		Kostowski *et al.*, 1992
	CD rats (160–200g)	0.01–3	p.o. 60	+		Luscombe *et al.*, 1992
	Mice	0.63–5	Acute and chronic	+	Additional measures of anxiety	Rodgers *et al.*, 1993
	Sprague–Dawley rats (250–350g)	10	i.p. during 5 weeks (x2)	+		Söderpalm *et al.*, 1993
	Wistar rats (213–263g)	1	i.p. 20	+		Zhang and Luo, 1993
Light/dark test	Wistar rats (150–200g)	2	30	o	Asymmetric compartments	Kshama *et al.*, 1990
	Rats	0.1	s.c. 15	+	Weak effect	Pich and Samanin, 1986
	Mice (25–35g)	0.06–4	i.p. 30	+	Asymmetric compartments	Costall *et al.*, 1988a
	Mice	3.16–10	i.p.	+		Young and Johnson, 1988
		10–56.2	p.o.	+		
	Female T/O mice (22–30g)	1	s.c. 30	+	Asymmetric	Bill *et al.*, 1989

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								CD–COBS rats (200–300g)	0.1	s.c. 15	+	Transitions only	Carli *et al.*, 1989b
									0.005	Median raphé, 10	+		
								Mice C57Bl/6J (18–20g)	0.1–10	s.c. 20	+		Kilfoil *et al.*, 1989
								BKW mice (20–30g)	0.25–1	i.p. 45	+	Asymmetric compartments and rears	Costall *et al.*, 1989b
								ICR mice (20–35g)	1–5	i.p. 30	+	Transitions and asymmetric compartments	Onaivi and Martin, 1989
								BKW mice (30–35g)	0.125–4	i.p. 45	+	Asymmetric compartments	Barnes *et al.*, 1991
								Mice	0.25–2	i.p. during 7 days (x1)	+	Asymmetric compartments	Costall and Naylor, 1991
								Female ICR-DUB mice (17–35g)	3.16–17.8	i.p. 30	+	Asymmetric compartments	Young and Johnson, 1991b
								BKW mice (25–30g)	0.25–2	i.p. 40	+	Asymmetric	Costall *et al.*, 1992a
							Holeboard	Wistar rats (150–200g)	2	30	+	compartments	Kshama *et al.*, 1990
							Social interaction	Wistar rats	2.5	i.p. 15	–		De Vry *et al.*, 1991
								Rats			o	HLU	File, 1984a
								Rats	0.25–2.5	30	o		File, 1984b
								Wistar rats (180–200g)	5–10	p.o. 30	o	Familiar congener	Guy and Gardner, 1985
								DAP mice (22–30g)	0.3–10	i.p. 30	o	Isolated mice	Olivier *et al.*, 1989
								Sprague–Dawley rats (225–275g)	0.125–2	i.p. 45	o	HLU	Barnes *et al.*, 1991
								Lister rats (180g)	0.2–0.8	s.c. 15	o		File and Andrews, 1991
								Lister rats (200–280g)	0.00004–0.0002	Dorsal raphé, 5	o		Higgins *et al.*, 1992
								Rats	0.2	s.c. 15	o		Andrews and File, 1993
								Wistar rats (180–200g)	5–20	p.o. 30	+	Familiar congener	Guy and Gardner, 1985
								Lister rats (200–250g)	0.0004–0.002	Dorsal raphé, 5	+	HLU	Higgins *et al.*, 1987
								Lister rats (210–270g)	0.004–0.01	Dorsal raphé, 5	+	LLF	Higgins *et al.*, 1988
								Mice	10	s.c. 30	+		Schreur, 1988
								Wistar rats (225–250g)	5–10	i.p. 30	+		Dunn *et al.*, 1989
								Male and female DBA/2 mice (24–36g)	2.3–2.6	p.o. during 5–10 days (x1)	+	HLU	Cutler, 1991a
								Wistar rats	1.25	i.p. 15	+		De Vry *et al.*, 1991
								Lister rats (250–300g)	1–2	i.p. 40	+	HLU	Costall *et al.*, 1992a
								CD1 mice (40–44g)	3.4	p.o. during 12–14 days	+	HLU and LLF	Gao and Cutler, 1992a
								Lister rats (200–280g)	0.00004–0.0002	Dorsal raphé, 5	+	HLU	Higgins *et al.*, 1992
								CD1 mice (35–45g)	1–5	i.p. 30	+	Home cage	Gao and Cutler, 1993a
											+	Neutral cage	
								Female CD1 mice (30–35g)	12.8 mg/L	Drinking fluid during 6–8 days	+	Oestrous mice	Gao and Cutler, 1993b
											+	Dioestrous mice	
								Wistar rats (213–263g)	1	i.p. 15	+		Zhang and Luo, 1993
							Open-field	Sprague–Dawley rats (330–420g)	0.04–10	i.p. 20	–	15W	Panickar and McNaughton, 1991
								CD–COBS rats (200–300g)	0.1–1	s.c. 15	o	Non-stressed rats	Carli *et al.*, 1989a

	Wistar rats (180–220g)	0.0001–0.005	Nucleus accumbens, 5	o		Stefanski *et al.*, 1993a
	CD–COBS rats (200–300g)	0.1–1	s.c. 15	+	Stressed rats	Carli *et al.*, 1989a
	Rats		Hippocampus	+		Plaznik *et al.*, 1991
	SPRD rats (200g)	0.62	i.p. 30	+		Horváth *et al.*, 1992
	Wistar rats (180–220g)	0.3–2.5	i.p. 30	+	65 dB noise	Stefanski *et al.*, 1992a
	Rats	0.62–2.5		+		Stefanski *et al.*, 1992b
	Male and female Wistar rats (180 days)	1.25–2.5	i.p. 30	+	Sedation?	Hughes, 1993
	Wistar rats (180–220g)	0.0025–0.005	Hippocampus, 5	+		Stefanski *et al.*, 1993a
Staircase test	Rats	10–20	p.o.	+		Boaventura *et al.*, 1986
Defense test battery	Adult male and female R. rattus	10–20	i.p. 30	+		Blanchard *et al.*, 1989
Ultrasonic 'distress' vocalization	Wistar rats (9–11 days)	1–3	30	+	Warm condition	Mos and Olivier, 1989
				+	Cold condition	
	Wistar rats	1–10	i.p. 15	+		De Vry *et al.*, 1991
	Rats			+		Schipper *et al.*, 1991
	AP mice (4–6 days)	3–6	30	+		Nastiti *et al.*, 1991
	Sprague–Dawley rats (9–11 days)	0.3–3	s.c. 30	+		Winslow and Insel, 1991a
	Rats	0.03–0.3	s.c.	+		Winslow and Insel, 1991b
	Adult rats	LED = 1	i.p.	+		Molewijk *et al.*, 1993
Social competition	Wistar rats (120g)	0.6–1.25	i.p. 30	+		Joly and Sanger, 1991
Marble burying test	Female mice MF1 (23–35g)	1–20	i.p. 30	+	Locomotion decreased	Njung'e and Handley, 1991b
Shock–probe burying test	Wistar rats (250–280g)	0.63–40	s.c. 60	o		Meert and Colpaert, 1986a
	Sprague–Dawley rats (250–350g)	0.05–1	s.c.	+		Treit and Fundytus, 1988
	Wistar rats	5	i.p. 30	+ +	+5,7-DHT	Fernández-Guasti *et al.*, 1992b
Conditioned burying	Long–Evans rats (325–500g)	8–64	i.p. 30	o		Craft *et al.*, 1988
Fear-potentiated startle reflex	Wistar rats (200–250g)	5–20	p.o. 10	–		Hijzen *et al.*, 1991
	Rats	0.6		+		Davis, 1988
	Sprague–Dawley rats (300–400g)	5–10	s.c. 0	+		Davis *et al.*, 1988a
	Sprague–Dawley rats (300–400g)	0.6–5	s.c. 0	+		Kehne *et al.*, 1988
	Sprague–Dawley rats	1.25–5	s.c. 10	+		Mansbach and Geyer, 1988
	Sprague–Dawley rats (330–400g)	5		+ +	Lesion of the septum	Melia and Davis, 1991
	Wistar rats (200g)	5		+		Munonyedi *et al.*, 1991
Aggression-provoked	NMRI mice	3–30	i.p. 30	+		De Vry *et al.*, 1991
Stress-induced hyperthermia	Swiss mice (25–30g)	10	i.p. 45	+		Lecci *et al.*, 1990
	Mice	10	p.o.	+		Schipper *et al.*, 1991
Unavoidable stress (gastric lesion)	ICR mice (7–8 weeks)	2.5–5	p.o. 60	o		Ogawa *et al.*, 1993
		2–10	p.o. during 3 days			
Avoidance test	Sprague–Dawley rats	0.5–7.5	i.p. 30	+	Auditive stimulus	Geller and Hartmann, 1982
Conditioned avoidance test	Wistar rats	ED_{50} = 3.64, 18.2	i.p. p.o.	+		Allen *et al.*, 1974

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								Sprague–Dawley rats (200–300g)	ED_{50} = 69	p.o. 30	+		Shimizu *et al.*, 1987
							Active-avoidance test	Wistar rats (220–240g)	5–10	i.p. 30	+		Sanger *et al.*, 1989
							Passive-avoidance test	Wistar rats (220–240g)	5–10	i.p. 30	+		Sanger *et al.*, 1989
								Wistar rats (220–240g)	5	i.p. 30	+		Sanger and Joly, 1989–1990
								Sprague–Dawley rats (200–250g)	0.01–1	s.c. 30	+		Klint, 1991
								Wistar rats (7–8 weeks)	25	p.o. 60	+		Ogawa *et al.*, 1993
							Conditioned place aversion	Long–Evans rats (8 weeks)	0.5–5	i.p. 60	+		Ervin *et al.*, 1987
									1–10	p.o. 60	+		
							Novelty-suppressed	Long–Evans rats (300–325g)	4	i.p. 60 during 21 days (x1)	o +		Bodnoff *et al.*, 1989
								Sprague–Dawley rats (270–320g)	0.5–2.5	s.c. 30	+		Fletcher and Davies, 1990
							Human threat	Marmoset Callithrix jacchus (350–440g)	0.05–1	s.c. 45	+		Barnes *et al.*, 1991
								Marmoset Callithrix jacchus (350–440g)	0.1–1	s.c. 45	+		Costall *et al.*, 1992a
							Cork gnawing	Long–Evans rats (435–640g)	8–32	p.o. 30	+		Pollard and Howard, 1991
								Ovariectomised Long–Evans CD (300g)	3	p.o. 30	+		Pollard *et al.*, 1992
							Straw suspension	Sprague–Dawley rats (140–170g)	0.5–5	i.p. 30	+		Nishimura *et al.*, 1993
							Stress-induced antinociception	ddY mice (18–20g)	1–10	i.p. 30	+		Tokuyama *et al.*, 1993
							Stress-induced colonic motor alterations	Wistar rats (250–300g)	1	i.p. 30	+		Gué *et al.*, 1993
							Hot-plate	Wistar rats (200–250g)	2.5–10	i.p. 30	+		Korneyev and Seredenin, 1993
E-4424 (selective agonist)	101[a12]						Elevated-plus maze	Rats	0.0001–0.5	i.p.	+		Costall *et al.*, 1991a
							Light/dark test	Mice	0.0001–0.5	i.p.	+	Asymmetric compartments	Costall *et al.*, 1991a
								BKW mice (25–30g)	0.0001–0.5	i.p. between 25 and 24 hr	+	Asymmetric compartments	Costall *et al.*, 1992a
										i.p. during 3, 7 or 14 days (x2)	+		
							Social interaction	Rats	0.0001–0.5	i.p.	+		Costall *et al.*, 1991a
								Lister rats (250–300g)	0.001–0.5	i.p. 40	+	HLU	Costall *et al.*, 1992a
							Human threat	Marmoset Callithrix jacchus (295–335g)	0.0001–0.001	s.c. between 40 and 96 hr	+		Costall *et al.*, 1992a
FG5893 (agonist)	0.7			4[a13]			Ultrasonic 'distress' vocalization	Rats	0.05		+		Andersson *et al.*, 1992
							Passive-avoidance test	Rats	0.1		+		Andersson *et al.*, 1992

Gepirone (partial agonist)	79.4[b]	125893[b]	>10000[a]	3800[a]	25118[b]	>10000[a]	Geller–Seifter conflict test	Sprague–Dawley rats (420–480g)	20–80	p.o. 30	+		Young *et al.*, 1987
								Sprague–Dawley rats (330–370g)	0.3–10	s.c.	+	FR30/FR10 and weak effect	Witkin and Perez, 1989–1990
								Rats	0.125–1	s.c.	+	Modified Geller–Seifter test	Thiébot *et al.*, 1990
								Wistar rats	10	i.p. 15	+		De Vry *et al.*, 1991
								Wistar rats (250–350g)	0.125–1	s.c. 15	+	Modified Geller–Seifter test	Thiébot *et al.*, 1991
							Vogel's conflict test	Female Long–Evans rats (225–249g)	1.25–5	s.c. 15	–	Unpredictable shocks	Costello *et al.*, 1991b
								Sprague–Dawley rats (250–350g)	10	i.p. 15	+	Modified Vogel's test	Eison *et al.*, 1986
								Wistar rats	2.5–10	i.p. 30	+		De Vry *et al.*, 1991
								Female Long–Evans rats (225–249g)	1.25	s.c. 15	+	Shocks moderate	Costello *et al.*, 1991b
								Lister rats (200–280g)	0.001	Dorsal raphé 5	+		Higgins *et al.*, 1992
								Wistar rats (180–220g)	0.3–1.25	i.p. 30	+	Modified Vogel's test	Stefanski *et al.*, 1992a
								Rats	0.3–0.62		+		Stefanski *et al.*, 1992b
								Wistar rats (200–250g)	3–5	i.p. 30	+	Modified Vogel's test	Korneyev and Seredenin, 1993
							Conflict test	White Carneau pigeons	0.1–1	i.m. 0	+	FR30	Mansbach *et al.*, 1988
							Conditioned emotional response	Wistar rats (400–500g)	5–20	i.p. 30	+		Sanger, 1990
							Elevated-plus maze	Wistar rats (220–250g)	3–10	i.p. 30	–		Motta *et al.*, 1992
								PVG rats (180–260g)	0.1–5	i.p. 30	o	Observations during 10 min	Critchley *et al.*, 1992
								Wistar rats (220–250g)	10	i.p. 30	o	Isolated rats	Motta *et al.*, 1992
								Wistar rats (220–250g)	1–10	i.p. 30	o	After a 2-hr period of isolation	Maisonnette *et al.*, 1993
									10		o	After a 2-week period of isolation	
								Wistar rats (225–250g)	1–2.5	i.p. 30	+		Dunn *et al.*, 1989
								Sprague–Dawley rats (250–350g)	8–2048 nmol	s.c. 10	+		Söderpalm *et al.*, 1989
								CD rats (160–200g)	0.001–3	p.o. 60	+		Luscombe *et al.*, 1992
								Wistar rats (220–250g)	10	i.p. during 2 weeks (x1)	+	Isolated rats	Motta *et al.*, 1992
								Wistar rats (220–250g)	10	Added to drinking water during 14 days	+	After a 2-weeks period of isolation	Maisonnette *et al.*, 1993
							Light/dark test	Female T/O mice (22–30g)		s.c. 30	o	Asymmetric compartments	Bill *et al.*, 1989
							Open-field	Sprague–Dawley rats (441g)	2.3–4.6	i.p. 30	–		Knapp *et al.*, 1992
								Wistar rats (180–220g)	0.16–0.62	i.p. 30	+	65 dB noise	Stefanski *et al.*, 1992a
								Rats	0.3–0.62		+		Stefanski *et al.*, 1992b
							Social interaction	Wistar rats	2.5–5	i.p. 15	–	LLF	De Vry *et al.*, 1991
								Lister rats (200–280g)	0.0002–0.001	Dorsal raphé 5	o	LLF	Higgins *et al.*, 1992
								Wistar rats (225–250g)	5–10	i.p. 30	+		Dunn *et al.*, 1989
								Wistar rats	1.25	i.p. 15	+	HLU	De Vry *et al.*, 1991
								Lister rats (200–280g)	0.0002–0.001	Dorsal raphé 5	+	HLU	Higgins *et al.*, 1992
							Defense test battery	Adult male and female R. Rattus	5–20	i.p. 30	+		Blanchard *et al.*, 1989
							Ultrasonic 'distress' vocalization	Wistar rats	1–10	i.p. 15	+		De Vry *et al.*, 1991

Continued

Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								AP mice (4–6 days)	2.5–5	40	+		Nastiti *et al.*, 1991
								Adult rats	0.1–1	i.p.	+		Vivian and Miczek, 1993
							Marble burying test	Female MF1 mice (23–35g)	5–20	i.p. 30	+	Locomotion decreased	Njung'e and Handley, 1991b
							Novelty-suppressed feeding	Long–Evans rats (300–325g)	4	i.p. 60	o		Bodnoff *et al.*, 1989
										during 21 days (x1)	+		
							Fear-potentiated startle reflex	Sprague–Dawley rats (300–400g)	1.25–10	s.c. 0	+		Kehne *et al.*, 1988
								Sprague–Dawley rats	3–10	i.p. 10	+		Mansbach and Geyer, 1988
							Active-avoidance test	Wistar rats (220–240g)	10–20	i.p. 30	+		Sanger *et al.*, 1989
							Passive-avoidance test	Wistar rats (220–240g)	2.5–10	i.p. 30	+		Sanger *et al.*, 1989
							Aggression-provoked	NMRI mice	20–30	i.p. 30	+		De Vry *et al.*, 1991
							Center test (thigmotaxis)	Rats	10	s.c.	+		Schreur *et al.*, 1993
									67	s.c. during 21 days (x1)	+		
							Cork gnawing	Long–Evans rats (435–640g)	8–32	p.o. 30	+		Pollard and Howard, 1991
							Hot-plate	Wistar rats (200–250g)	5–10	i.p. 30	+		Korneyev and Seredenin, 1993
Ipsapirone (partial agonist)	19[b]	125892[b]	12589[b]	2700[a]	31622[b]	>10000[a]	Geller–Seifter conflict trest	Rats	2.5	i.p. 25	o		Deacon and Gardner, 1986
								Wistar rats (400–500g)	2.5–20	i.p. 30	o		Sanger, 1990
								Wistar rats	3–5.4	i.p.	+		Amrick and Bennett, 1986
								Sprague–Dawley rats (420–480g)	0.5–60	p.o. 30	+		Young *et al.*, 1987
								Wistar rats (180–200g)	5–20	i.p. 30	+	VI30	Sanger, 1992
							Vogel's conflict test	Wistar rats (12 weeks)	1–10	i.p. 30	o	0.32 mA shocks	Meneses and Hong, 1993
								Rats			+		Schuurman *et al.*, 1986
								Lister rats (200–250g)	0.002	Dorsal raphé, 5	+		Higgins *et al.*, 1987
								Lister rats (210–270g)	0.004–0.01	Dorsal raphé, 5	+		Higgins *et al.*, 1988
								Wistar rats	2.5–15	i.p. 30	+		De Vry *et al.*, 1991
								Wistar rats (180–220g)	1.25–20	i.p. 30	+	Modified Vogel's test	Chojnacka–Wójcik and Przegalinski, 1991
								Lister rats (200–280g)	0.002	Dorsal raphé, 5	+		Higgins *et al.*, 1992
								Wistar rats (180–220g)	1.25–10	i.p. 30	+	Modified Vogel's test	Przegalinski *et al.*, 1992
								Wistar rats (180–220g)	0.3–1.25	i.p. 30	+	Modified Vogel's test	Stefanski *et al.*, 1992a
								Rats	0.3–0.62		+		Stefanski *et al.*, 1992b
								Wistar rats (200–250g)	3–10	i.p. 30	+	Modified Vogel's test	Korneyev and Seredenin, 1993
								Wistar rats (12 weeks)	3.1–10	i.p. 30	+	0.16 mA shocks	Meneses and Hong, 1993
							Conflict test	Squirrel monkeys (800–1050g)	0.01–1	i.m.	o	FI3	Gleeson and Barrett, 1990
								White Carneau pigeons	0.1–10	i.m. 5	+		Gleeson *et al.*, 1989
								White Carneau pigeons	1–3	i.m. 15	+	FR30	Nanry *et al.*, 1991
								White Carneau pigeons	0.1–53	i.m. 0	+	FR30	Barrett, 1992
							Conditioned emotional response	Sprague–Dawley rats (300–325g)	0.5–5	i.p. 15	o		Lorens *et al.*, 1989
								Wistar rats (400–500g)	2.5–20	i.p. 30	+		Sanger, 1990

Elevated-plus maze	Lister rats (250–350g)	2.5–10	i.p. 30	–		Pellow *et al.*, 1987
	Sprague–Dawley rats (200–300g)	0.15–10	s.c. 30	–		Moser, 1989a
	Sprague–Dawley rats (200–300g)	10	s.c. 30	–	Decreased total open arm entries	Moser, 1989b
	Lister rats (200–270g)	0.1	i.p. 30	–		Wright *et al.*, 1992a
	Rats	2.5–10		o		File *et al.*, 1987
	Wistar rats (144–196g)	0.5–5	i.p. 30	o	Rats were malnourished	Almeida *et al.*, 1991
	Lister rats (200–270g)	0.01–1	i.p. during 2 weeks (x2)	o		Wright *et al.*, 1992a
	Lister rats (240–300g)	1	i.p. 5–20	o		Wright *et al.*, 1992b
	PVG rats (200–260g)	1	i.p. 30	+	Observations during 10 min	Critchley *et al.*, 1988
	Rats Sprague Dawley (250–350g)	8–2048 nmol	s.c. 10	+		Söderpalm *et al.*, 1989
	Rats	0.5–2.5	i.p. 30	+	Observations during 10 min	Graeff *et al.*, 1990
	Wistar rats (292–368)	0.5	i.p. 30	+	Rats were well nourished	Almeida *et al.*, 1991
	PVG rats (180–260g)	0.25–5	i.p. 30	+	Observations during 10 min	Critchley *et al.*, 1992
	CD rats (160–200g)	0.01–1	p.o. 60	+		Luscombe *et al.*, 1992
Light/dark test	Female T/O mice (22–30g)	1.5	s.c. 30	+	Asymmetric compartments	Bill *et al.*, 1989
	Swiss mice (20–30g)	2.5–5	i.p. 30	+	Transitions only	Fernández-Guasti and López-Rubalcava, 1990
	Female ICR–DUB mice (17–35g)	17.8–31.6	i.p. 30	+	Asymmetric compartments	Young and Johnson, 1991c
	BKW mice (25–30g)	1–5	i.p. 40	+	Asymmetric compartments	Costall *et al.*, 1992a
	Mice	5		+	Asymmetric compartments	Fernández-Guasti and López-Rubalcava, 1992
	Swiss Webster mice (20–30g)	5	i.p. 30	+	Transitions only	López-Rubalcava *et al.*, 1992
Open-field	Wistar rats (180–220g)	0.31–1.25	i.p. 30	+	65 dB noise	Stefanski *et al.*, 1992a
	Rats	0.3–0.62		+		Stefanski *et al.*, 1992b
Social interaction	Lister rats (200–280g)	0.0002	Dorsal raphé, 5	o	LLF	Higgins *et al.*, 1992
	Rats			+		Schuurman *et al.*, 1986
	Lister rats (200–250g)	0.002	Dorsal raphé, 5	+	HLU	Higgins *et al.*, 1987
	Rats			+	LLF	Critchley *et al.*, 1987
	Lister rats (210–270g)	0.0004–0.01	Dorsal raphé, 5	+		Higgins *et al.*, 1988
	DAP mice 22–30g)	10	i.p. 30	+	Isolated mice	Olivier *et al.*, 1989
	Wistar rats	1.25 0.63–4	i.p. 15	+ +	HLU et LLF	De Vry *et al.*, 1991
	Rats	0.025–10	i.p.	+		Carter and Smith, 1992
	Lister rats (250–300g)	1–5	i.p. 40	+	HLU	Costall *et al.*, 1992a
	Lister rats (200–280g)	0.0002	Dorsal raphé, 5	+	HLU	Higgins *et al.*, 1992
Staircase test	Rats	1–2.5	i.p.	+		Boaventura *et al.*, 1986
Novelty-suppressed feeding	Rats	2		+		Rex *et al.*, 1991
Ultrasonic 'distress' vocalization	Wistar rats (9–11 days)	1 1–3	30	+	Warm condition	Mos and Olivier, 1989
		1–3		+	Cold conditions	
	Wistar rats (220–240g)	5	i.p. 30	+		Kaltwasser, 1991

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								AP mice (4–6 days)	2.5–5	30	+		Nastiti *et al.*, 1991
								Rats			+		Schipper *et al.*, 1991
								Wistar rats (200–220g)	0.5 g/l	p.o. 48 hr and during 21 days (x1)	+		Baudrie *et al.*, 1993
								Adult rats	LED = 3	i.p.	+		Molewijk *et al.*, 1993
								Wistar rats (200–250g)	0.3–10	s.c. 15	+		Sommermeyer *et al.*, 1993
							Marble burying test	Female MF1 mice (23–35g)	5–20	i.p. 30	o		Njung'e and Handley, 1991b
							Shock–probe burying test	Wistar rats (280–350g)	2.5–10	i.p. 30	+		Fernández-Guasti and Hong, 1989
								Rats	0.5–2.5	i.v.	+		Bouws *et al.*, 1991
								Wistar rats (300–350g)	2.5–5	i.p. 30	+		Fernández-Guasti *et al.*, 1992a
								Swiss Webster mice (20–35g)	2.5–5	i.p. 30	+		Fernández-Guasti *et al.*, 1992a
								Wistar rats	5	i.p. 30	+	+5,7-DHT	Fernández-Guasti *et al.*, 1992b
											+		
								Wistar rats (300–360g)	0.625–10	i.p. 30	+		Korte and Bohus, 1990
								Wistar rats (290–340g)	0.5–2.5	i.v., 10	+		Korte *et al.*, 1992
							Fear-potentiated startle reflex	Sprague–Dawley rats (300–400g)	10–40	i.p. 0	+		Davis *et al.*, 1988a
								Sprague–Dawley rats	1–10	s.c. 10	+		Mansbach and Geyer, 1988
							Stress-induced hyperthermia	Mice		p.o.	o		Schipper *et al.*, 1991
							Active-avoidance test	Wistar rats (220–240g)	20–40	i.p. 30	+		Sanger *et al.*, 1989
							Passive-avoidance test	Wistar rats (220–240g)	1.2–10	i.p. 30	+		Sanger *et al.*, 1989
							Aggression-provoked	NMRI mice	ED_{50} = 2.2	i.p. 30	+		Traber *et al.*, 1984
								NMRI mice	10–30	i.p. 30	+		De Vry *et al.*, 1991
							Cork gnawing	Ovariectomised Long–Evans CD rats (330g)	1–3	p.o. 30	+		Pollard *et al.*, 1992
							Hot-plate	Wistar rats (200–250g)	3–10	i.p. 30	+		Korneyev and Seredenin, 1993
							DPAG-Stimulation	Rats			o		Jenck *et al.*, 1989b
								Rats	10–40 nmol	DPAG	+	Weak effect	Graeff *et al.*, 1990
LY 165,163 (agonist)							Elevated-plus maze	CD rats (160–200g)	0.03–3	p.o. 60	+		Luscombe *et al.*, 1992
pK_D[y]	8.2	6	6	5.7	6.2								
RS-30199 (5-HT$_{1A}$ ligand)							Elevated plus-maze	Sprague–Dawley rats	0.3–30	i.p.	–		Redfern *et al.*, 1989
pK_D[a31]	7.9	< 5	< 5	5.9	< 5			Lister rats (300–400g)	3	i.p. 40	–		Moulton and Morinan, 1990
Spiroxatrine (agonist)	7.94	125892	7943	630[b]	7943		*Conflict test*	White Carneau pigeons	0.01–0.3	i.m. O	+	FR30	Barrett, 1992
							Elevated-plus maze	CD rats (160–200g)	0.3–3	p.o. 60	+		Luscombe *et al.*, 1992

Tandospirone (partial agonist)	27	>100000	>100000	1300[a19]	2600	Geller–Seifter conflict test	Ovariectomised Long–Evans CD rats (300g)	1–100	p.o. 60	o		Pollard *et al.*, 1992
							Sprague–Dawley rats (320–370g)	1.25–20	i.p. and p.o. 0	+	Modified Geller–Seifter test	Shimizu *et al.*, 1992a
						Vogel's conflict test	Sprague–Dawley rats (200–300g)	5–10	i.p. 60	+	Modified Vogel's test	Shimizu *et al.*, 1987
								10	i.p. 5–10 days p.o. 60			
							Sprague–Dawley rats (180–200g)	1	s.c. 60	+	Modified Vogel's test	Shimizu *et al.*, 1992b
										+	+ 5,7-DHT	
						Conflict test	Squirrel monkeys (800–1050g)	0.01–0.1	i.m.	o	FI3	Gleeson and Barrett, 1990
							White Carneau pigeons	1	i.m. 15	+	FR30	Pollard *et al.*, 1992
							White Carneau pigeons	0.3–10	i.m. 0	+		Barrett and Vanover, 1993
						Conditioned avoidance reaction	Sprague–Dawley rats (200–300g)	$ED_{50} > 300$	p.o. 60	o		Shimizu *et al.*, 1987
						Straw suspension	Sprague–Dawley rats (140–170g)	5–20	i.p. 30	+		Nishimura *et al.*, 1993
						Cork gnawing	Ovariectomised Long–Evans CD rats (300g)	10–60	p.o. 30	+		Pollard *et al.*, 1992
Umespirone (agonist)	15.7[a15]					Light/dark test	BKW mice (30–35g)	0.0001–100	p.o. 45	+	Asymmetric compartments	Barnes *et al.*, 1991
						Social interaction	Sprague–Dawley rats (225–275g)	0.001–10	p.o. 45	+	HLU	Barnes *et al.*, 1991
						Human threat	Marmoset *Callithrix jacchus* (350–440g)	0.001–0.1	s.c. 45	+		Barnes *et al.*, 1991
HT-90B (agonist/antagonist) (IC_{50})[a28]	0.4			20		Vogel's conflict test	Rats	3–30	p.o.	+		Miyauchi *et al.*, 1993
WY-47,846 (agonist)	16.7			458[a16]		Geller–Seifter	CD rats (200g)	1–20	i.p. 30	o	VI2	Haskins *et al.*, 1989
						Vogel's conflict test	CD rats (200–250g)	1–20	i.p. 30	o		Haskins *et al.*, 1989
						Conflict test	Squirrel monkeys (800–1050g)	0.01–0.3	i.m.	o	FI3	Gleeson and Barrett, 1990
							White Carneau pigeons (450–600g)	0.1–10	i.m. 20	+	FR30	Barrett and Zhang, 1991
WY-48,723 (agonist)	0.3			272[a16]		Geller–Seifter conflict test	Rats			o		Andree *et al.*, 1988
						Conflict test	White Carneau pigeons (450–600g)	0.03–10	i.m. 20	+	FR30	Barrett and Zhang, 1991
						Conditioned avoidance reaction	Rats			+		Andree *et al.*, 1988
WY-50,324 (agonist)	1			66[a16]		Geller–Seifter conflict test	Rats	10	i.p.	+		Morris *et al.*, 1989
						Conflict test	White Carneau pigeons (450–600g)	0.03–10	i.m. 20	+	FR30	Barrett and Zhang, 1991
MDL 73005EF (partial agonist)						Geller Seifter conflict test	Wistar rats (180–200g)	0.3–10	i.p. 30	o	VI30	Sanger, 1992
pK_D'	8.4	5.4	6.0	5.7	6.2	Vogel's conflict test	Sprague–Dawley rats (170–210g)	0.3–3	s.c. 30	+		Moser *et al.*, 1988
							Sprague–Dawley rats	0.1–3	s.c.	+		Hibert and Moser, 1990

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								Sprague–Dawley rats (200–300g)	0.1–3	s.c. 30	+		Moser *et al.*, 1990
							Elevated-plus maze	Sprague–Dawley rats (250–300g)	0.03–0.25	s.c. 30	+		Moser *et al.*, 1988
									0.25–1	p.o. 30	+		
								Sprague–Dawley rats	0.03–2	s.c.	+		Hibert and Moser, 1990
								Sprague–Dawley rats (200–300g)	0.03–4	s.c. 30	+		Moser *et al.*, 1990
							Light/dark test	Female T/O mice (22–30g)	2	s.c. 30	+	Asymmetric compartments	Bill *et al.*, 1989
								Swiss mice (10 weeks)	1.25–5	i.p. 30	+		Misslin *et al.*, 1990
							Fear-potentiated startle reflex	Rats	1.25–10		+		Hitchcock *et al.*, 1991
NAN-190 (partial agonist)	1.3[j]	616[j]	790[a]	218[j]	602[j]	1202[j]	Vogel's conflict test	Wistar rats (180–220g)	0.25–1	i.p. 60	o	Modified Vogel's test	Chojnacka-Wójcik and Przegalinski, 1991
							Conflict test	White Carneau pigeons	1–3	i.m. 15	o	FR30	Ahlers *et al.*, 1992
								pigeons	0.16–2.5	i.m. 5	o	FR30	Colpaert *et al.*, 1992
							Elevated-plus maze	CD rats (160–200g)	0.003–3	p.o. 60	+		Luscombe *et al.*, 1992
							Passive-avoidance test	Wistar rats (220–240g)	2	i.p. 30	–		Sanger and Joly, 1989–1990
NDO 008 (5-HT$_{1A}$ agonist)							Elevated-plus maze	Rats	1–4		–		Kostowski *et al.*, 1990
								Wistar rats (345–445g)	0.06–0.125, 2–4	i.p. 30	–		Kostowski *et al.*, 1992
									0.125		+		
SDZ 21009 (antagonist)	10[b]	0.42[m]	398[b]	10000[b]	5011[b]		Vogel's conflict test	Wistar rats (180–220g)	2–8	i.p. 60	o	Modified Vogel's test	Chojnacka-Wójcik and Przegalinski, 1991
(S)-UH-301 (antagonist)							Geller–Seifter conflict test	Wistar rats	0.3–30	s.c. 30	o		Moreau *et al.*, 1992
IC$_{50}$[26]	98	100000		7200	7150		Elevated-plus maze	Wistar rats	1	i.p. 30	+		Moreau *et al.*, 1992
							Light/dark test	Swiss mice (10 weeks)	1	i.p. 30	+		Moreau *et al.*, 1992
(+)WAY 100135 (antagonist)							Elevated-plus maze	Lister rats (250–280g)	1	s.c. 45	o		Bickerdike *et al.*, 1993
IC$_{50}$[a21]	25	>10000		>10000	>10000		Light/dark test	Mice	3–10	s.c.	+		Fletcher *et al.*, 1991
								Mice	1–30	s.c.	+		Fletcher *et al.*, 1992
							Fear-potentiated startle reflex	Rats	2	s.c.	+		Fletcher *et al.*, 1992
Indorenate (5-HT$_{1A}$ antagonist)							Vogel's conflict test	Wistar rats (12 weeks)	3.1–10	i.p. 30	+	0.16 mA shocks	Meneses and Hong, 1993
									5.6–10		+	0.32 mA shocks	
							Light/dark test	Swiss mice (20–30g)	2.5–10	i.p. 90	+	Transitions only	Fernández-Guasti and López-Rubalcava, 1990
								Mice	5		+	Asymmetric compartments	Fernández-Guasti and López-Rubalcava, 1992
								Swiss Webster mice (20–30g)	5	i.p. 90	+	Transitions only	López-Rubalcava *et al.*, 1992

							Shock–probe burying test	Wistar rats (280–350g)	10	i.p. 90	+		Fernández-Guasti and Hong, 1989
								Wistar rats (300–350g)	5	i.p. 90	+		Fernández-Guasti *et al.*, 1992a
								Swiss Webster mice (20–35g)	5	i.p. 90	+		Fernández-Guasti *et al.*, 1992a
								Wistar rats	5	i.p. 90	+	+5,7-DHT	Fernández-Guasti *et al.*, 1992b
											+		
1-PP (zapirone's metabolite)	1040			>10000	[a10]		Geller–Seifter	Sprague–Dawley rats (420–480g)	5–80	p.o. 30	o		Young *et al.*, 1987
							Vogel's conflict test	Sprague–Dawley rats (240–300g)	1–4	s.c. 30	+	Modified Vogel's test	Gower and Tricklebank, 1988
								Wistar rats	5–10	i.p. 30	+		De Vry *et al.*, 1991
								Sprague–Dawley rats (211–347g)	25	p.o. 30	+	Modified Vogel's test	Amano *et al.*, 1993
									5–25	p.o. during 7 days	o		
							Conflict test	White Carneau pigeons	0.01–3	i.m. 5	o		Barrett *et al.*, 1986
							Elevated-plus maze	Sprague–Dawley rats (250–350g)	8–2048 nmol	s.c. 10	–		Söderpalm *et al.*, 1989
							Social interaction	Wistar rats	1.25	i.p. 15	o		De Vry *et al.*, 1991
							Ultrasonic 'distress' vocalization	Wistar rats	3–10	i.p. 15	+		De Vry *et al.*, 1991
							Passive-avoidance test	Wistar rats (220–240g)	1.25–10	i.p. 30	o		Sanger and Joly, 1989–1990
							Fear-potentiated startle reflex	Sprague–Dawley rats (300–400g)	0.5–40	s.c. 0	o		Kehne *et al.*, 1988
CGS 12066B (non-selective agonist)	64.5[a1]	114[a1]	446[a1]		12882[o]		Elevated-plus maze	Swiss mice NIH (20–30g)	3.125	i.p. 30	o		Benjamin *et al.*, 1990
								DBA/2 mice (6–8 weeks)	2.5–10	i.p. 20	–		Rodgers *et al.*, 1992
							Social interaction	Lister rats (200–280g)	0.0025	Dorsal raphé 5	+	HLU	Higgins *et al.*, 1992
							Ultrasonic 'distress' vocalization	Sprague–Dawley rats (9–11 days)	1–3	s.c. 30	–		Winslow and Insel, 1991a
								Rats	1–3	s.c.	–		Winslow and Insel, 1991b
RU 24969 (non-selective agonist)	7.9[b]	3.8[m]	50[b]	42[d]	316[b]	3800[f]	Geller–Seifter conflict test	Rats	2	p.o. 25	o		Deacon and Gardner, 1986
							Vogel's conflict test	Wistar rats (200–250g)	0.5–2	i.p. 30	+	Modified Vogel's test	Korneyev and Seredenin, 1993
							Conflict test	Squirrel monkeys (800–1050g)	0.003–0.1	i.m.	o	F13	Gleeson and Barrett, 1990
								White Carneau pigeons	0.03–3	i.m. 5	+		Gleeson *et al.*, 1989
							Elevated-plus maze	Rats (250–280g)	0.08–3.6		–	Observations during 10 min	Critchley and Handley, 1986
								PVG rats (200–280g)	0.5–3	i.p. 30	–	Observations during 10 min	Critchley and Handley, 1987
								Rats	0.1875–1.5		–		File *et al.*, 1987
								Lister rats (250–350g)	0.1875–1.5	i.p. 30	–		Pellow *et al.*, 1987
								PVG rats (180–260g)	0.5–2	i.p. 30	–	Observations during 10 min	Critchley *et al.*, 1992
							Social interaction	Rats			–	LLF	Critchley *et al.*, 1987
							Ultrasonic 'distress' vocalization	Wistar rats (9–11 days)	0.3–3	30	o	Warm condition	Mos and Olivier, 1989

Continued

Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								Rats			+		Gardner, 1985c
								Wistar rats (9–11 days)	1–3	30	+	Cold condition	Mos and Olivier, 1989
							Marble burying test	Female MF1 mice (23–35g)	0.1–10	i.p. 30	+	Locomotion increased	Njung'e and Handley, 1991b
							Shock–probe burying test	Wistar rats (280–350g)	0.25–0.75	i.p. 15	+		Fernández-Guasti and Hong, 1989
							Hot-plate	Wistar rats (200–250g)	2–5	i.p. 30	+		Korneyev and Seredenin, 1993
1-NP (agonist)							Social interaction	Sprague–Dawley rats (250–320g)	0.2–1	s.c. 30	+		Kennett, 1992
pK_D[25]	7.2	6.6	7.8	7.2	8.3	6.9							
DOI (agonist)	3938[i]	2041[i]	7200[a]	1.3[d]	6.45[i]	>10000[a]	Elevated-plus maze	Lister rats	0.1	i.p.	o		Tomkins *et al.*, 1990
								Rats			+		Heaton *et al.*, 1988
								Rats			+		Njung'e, 1990
							Ultrasonic 'distress' vocalization	AP mice (4–6 days)	0.25–0.5	30	–		Nastiti *et al.*, 1991
								Wistar rats (9–11 days)	0.3–3	30	+	Warm condition	Mos and Olivier, 1989
											+	Cold condition	
								Sprague–Dawley rats (9–11 days)	0.03–0.3	s.c. 30	+	Locomotion decreased	Winslow and Insel, 1991a
							Marble burying test	Female MF1 mice (23–35g)	0.01–5	i.p. 30	+		Njung'e and Handley, 1991b
mCPP (non-selective agonist)	210	79	1100	140	29	5.6[a]	Vogel's conflict test	Sprague–Dawley rats (200g)	1–2	i.p. 10	–	VI21, also decreased non-published responding	Kilts *et al.*, 1982
							Shuttle box	Rats	4		–		Martin, 1993
							Elevated-plus maze	Swiss mice NIH (20–30g)	1.56–3.125	i.p. 30	–		Benjamin *et al.*, 1990
								Sprague–Dawley rats	0.5	i.p.	–		Gibson *et al.*, 1991
								DBA/2 mice (6–8 weeks)	1–4	i.p. 30	–		Rodgers *et al.*, 1992
								Sprague–Dawley rats (250–300g)	0.5	s.c. 20	–		Blackburn *et al.*, 1993
								Wistar rats (150–220g)	0.3–3	i.p. 30	–		Griebel, 1993
								Long–Evans rats (320–340g)	5	i.p. 15	–		Rezazadeh *et al.*, 1993
								Wistar rats (200–240g)	1	i.p. during 21 days (x1)	o		Griebel, 1993
							Zero-maze	Sprague–Dawley rats	1	s.c. 30	–		Grewal *et al.*, 1993
							Light/dark test	Sprague–Dawley rats (200–250g)	0.5–0.75	i.p. 20	–		Kennett *et al.*, 1989
								Swiss mice (10 weeks)	1–3	i.p. 30	–		Griebel *et al.*, 1991
								Swiss mice (10 weeks)	2	i.p. during 21 days (x1)	o		Griebel, 1993
							Open-field	Wistar rats (200–250g)	1–5	i.p. 30	–	Sedation?	Klodzinska *et al.*, 1989
								Sprague–Dawley rats (200–250g)	2.5–5	i.p. 20	–	Locomotion decreased	Lucki *et al.*, 1989
							Free-exploratory test	Swiss mice (10 weeks)	3–4	i.p. 30	–		Griebel *et al.*, 1991
							Social interaction	Sprague–Dawley rats (250–280g)	0.001	Amygdala, 0	o		Whitton and Curzon, 1990
								Lister rats (200–280g)	0.0005–0.0125	Dorsal raphé, 5	o		Higgins *et al.*, 1992

								Sprague–Dawley rats (200–250g)	0.1–1	i.p. 20	–		Kennett *et al.*, 1989
								Sprague–Dawley rats (250–280g)	0.0002–0.0004	i.c.v., 0	–		Whitton and Curzon, 1990
									0.001	Hippocampus, 0	–		
								Sprague–Dawley rats	0.5	i.p.	–		Gibson *et al.*, 1991
							Novelty-suppressed feeding	Rats			o		Rex *et al.*, 1991
							Fear-potentiated startle reflex	Sprague–Dawley rats	0.25–1	s.c. 10	–	Locomotion increased	Mansbach and Geyer, 1988
								Rats	0.1	i.t., 30	o		Davis *et al.*, 1986
								Rats	2.5–10 0.1	i.p. 0 i.c.v. 30	+		Davis *et al.*, 1986
							Ultrasonic 'distress' vocalization	Sprague–Dawley rats (9–11 days)	0.1–1	s.c. 30	+		Winslow and Insel, 1991a
							Shock–probe burying test	Rats			+		Meert, 1989
							Marble burying test	Female MF1 mice (23–35g)	1–20	i.p. 30	+		Njung'e and Handley, 1991b
							Stress-induced hyperthermia	Swiss mice (25–30g)	2.5–5	i.p. 45	o		Lecci *et al.*, 1990
							Conditioned place aversion	Long–Evans rats (250–300g)	0.1–1	i.p.	o		Rocha *et al.*, 1993a
							DPAG-Stimulation	Wistar rats	0.1–1	i.p. 35	+		Jenck *et al.*, 1989a
MK-212 (non-selective agonist)							Conflict test	White Carneau pigeons (480–528g)	0.01	i.m. 0	o	FR30	Witkin *et al.*, 1987
pK_D[a,24]	5.32	5.03		4.76	6.16		Elevated-plus maze	Wistar rats (150–200g)	0.5	30	o		Kshama *et al.*, 1990
							Light/dark test	Wistar rats (150–200g)	0.5	30	o	Asymmetric compartments	Kshama *et al.*, 1990
							Holeboard	Wistar rats (150–200g)	0.5	30	–		Kshama *et al.*, 1990
							Open-field	Sprague–Dawley rats (200–250g)	0.31–0.62	i.p. 20	–	Locomotion decreased	Lucki *et al.*, 1989
							Ultrasonic 'distress' vocalization	Wistar rats (9–12 days)	0.2–1	i.p. 30	+	Myoclonus	Gardner, 1985a
TFMPP (non-selective agonist)	200	49	690	780	13	2100[a]	Elevated-plus maze	Swiss NIH mice (20–30g)	1.56–6.25	i.p. 30	–		Benjamin *et al.*, 1990
								DBA/2 mice (6–8 weeks)	2.5–5	i.p. 30	–		Rodgers *et al.*, 1992
								Wistar rats (150–220g)	1–10	i.p. 30	–		Griebel, 1993
							Open-field	Wistar rats (200–250g)	1–5	i.p. 30	–	Sedation?	Klodzinska *et al.*, 1989
								Sprague–Dawley rats (200–250g)	2.5–5	i.p. 20	–	Locomotion decreased	Lucki *et al.*, 1989
							Social interaction	Sprague–Dawley rats (200–250g)	0.2–1	i.p. 20	–		Kennett *et al.*, 1989
							Ultrasonic 'distress' vocalization	Sprague–Dawley rats (9–11 days)	0.3–3	s.c. 30	–		Winslow and Insel, 1991a
								Wistar rats (9–11 days)	0.3–3	30	o	Warm condition	Mos and Olivier, 1989
								Wistar rats (9–11 days)	3	30	+	Cold condition	Mos and Olivier, 1989
								AP mice (4–6 days)	0.5–1	30	+		Nastiti *et al.*, 1991
							Shock–probe burying test	Rats			+		Meert, 1989

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Table 1. *Continued*

Compounds	Affinities (K_i, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
							Marble burying test	Female MF1 mice (23–35g)	1–20	i.p. 30	+		Njung'e and Handley, 1991b
							Stress-induced hyperthermia	Swiss mice (25–30g)	5–20	i.p. 45	o		Lecci *et al.*, 1990
							DPAG-Stimulation	Rats			+		Jenck *et al.*, 1989b
Altanserin (antagonist): pK_D[a3]	5.6	6.0		8.6	6.9		Social interaction	Sprague–Dawley rats (250–320g)	0.5–5	s.c. 30	o	Locomotion decreased	Kennett, 1992
Cinanserin (antagonist)	740[c]	6200[c]		19[b]	199[b]		Geller–Seifter conflict test	Female CFN rats	3–25	i.p. 0 or 80	o	VI30/FR10	Winter, 1972
								Rats	60		o		Sepinwall and Cook, 1978
								Sprague–Dawley rats (200–320g)	10–56	i.p. 60	o	FR40	Kilts *et al.*, 1981
								Sprague–Dawley rats (4 months)	60	i.p. 60	+		Geller *et al.*, 1974
								Rats	15–60	i.p. 60	+	FR10/VI30	Cook and Sepinwall, 1975b
							Vogel's conflict test	Wistar rats (220g)	10–60	i.p. 30	o	Modified Vogel's test	Petersen and Lassen, 1981
								Sprague–Dawley rats (200–320g)	56	i.p. 60	+	VI21	Kilts *et al.*, 1981
								Sprague–Dawley rats (200g)	56	i.p. 60	+	VI21	Kilts *et al.*, 1982
							Conflict test	Squirrel monkeys (550–900g)	1–3	i.m.	+	FR30	Brady and Barrett, 1985
							Fear-potentiated startle reflex	Sprague–Dawley rats (300–400g)	10	i.p. 15	o		Davis *et al.*, 1988b
ICI 169369 (antagonist)							Social interaction	Sprague–Dawley rats (250–320g)	6	s.c. 30	+		Kennett, 1992
IC_{50}[a20]:	2600	2000	6100	17.9	19.2	1100	Marble burying test	Female MF1 mice (23–35g)	1–10	i.p. 30	o		Njung'e and Handley, 1991b
Methiotepin (antagonist)	79[b]	50[b]	50.1[b]	1.58[b]	25[b]	3000[l]	Light/dark test	Swiss mice (20–30g)	0.25	i.p. 30	o		Fernández-Guasti and López-Rubalcava, 1990
								Swiss Webster mice (20–30g)	0.31	i.p. 30	o		López-Rubalcava *et al.*, 1992
							Shock–probe burying test	Swiss Webster mice (20–35g)	0.31	i.p. 30	o		Fernández-Guasti *et al.*, 1992a
								Wistar rats (300–350g)	0.31	i.p. 30	+		Fernández-Guasti *et al.*, 1992a
							Fear-potentiated startle reflex	Sprague–Dawley rats (320–350g)	0.1	i.p. 70	o		Svensson, 1985
Clozapine (Non-selective 5-HT$_{2C}$ antagonist)	pKi[a32]:			7.6	8.1		Geller–Seifter conflict test	Sprague–Dawley rats (260–320g)	2.5–5	i.p. 60	+	FI60/FR1	Wiley *et al.*, 1993

Mianserin (antagonist)	1000[b]	6390[b]	398[b]	7.9[b]	10[b]	64.5[a4]	Geller–Seifter conflict test	Sprague–Dawley rats (330–370g)	0.3–17	i.p.	o	FR30/FR10	Witkin and Perez, 1989–1990
								Rats			+		Van Riezen *et al.*, 1981
								Rats	0.7–0.5	i.p.	+	VI30/FR10	Sullivan *et al.*, 1985
								Sprague–Dawley rats (200–225g)	3	i.p. 60	+	VI30/FR30	Mason *et al.*, 1987
							Conflict test	Squirrel monkeys (550–900g)	0.1–10	i.m.	+	FR30	Brady and Barrett, 1985
							Elevated-plus maze	Wistar rats (150–220g)	10	i.p. 30	–		Griebel, 1993
								Lister rats (250–400g)	10–20	i.p. 30	o		Pellow *et al.*, 1985
								Swiss mice NIH (24–28g)	5	i.p. 30	o		Benjamin *et al.*, 1992
									2.5–20	i.p. 48 hr	+		
									20	i.p. 18 days	+		
							Light/dark test	Swiss mice (10 weeks)	1–10	i.p. 30	o		Griebel, 1993
							Open-field	Sprague–Dawley rats (200–250g)	2.5–5	i.p. 60	o		Lucki *et al.*, 1989
							Social interaction	Sprague–Dawley rats (200–250g)	2	s.c. 40	o	Locomotion increased	Kennett *et al.*, 1989
								Sprague–Dawley rats (250–320g)	1–2	s.c. 30	+		Kennett, 1992
							Novelty-suppressed feeeding	Long–Evans rats (300–325g)	10	i.p. 60 during 21 days (x1)	o +		Bodnoff *et al.*, 1989
							Shock–probe burying test	Wistar rats (250–280g)	0.63–40	s.c. 60	o		Meert and Colpaert, 1986b
							Conditioned place aversion	Rats			–		Rocha *et al.*, 1992
								Long–Evans rats (250–300g)	10	i.p.	–		Rocha *et al.*, 1993a
								Long–Evans rats (280–300g)	10 0.1–10	i.p.	– –	+5,7-DHT	Rocha *et al.*, 1993b
							DPAG-Stimulation	Wistar rats (370–450g)	1–32	i.p. 35	–		Jenck *et al.*, 1989a
(+)Mianserin (antagonist)							Social interaction	Sprague–Dawley rats (250–320g)	2–4	s.c. 30	+		Kennett, 1992
pK_D:[a3]	6.2	5.5		8.6	7.9	6.6							
(−)Mianserin (antagonist)							Social interaction	Sprague–Dawley rats (250–320g)	1	s.c. 30	o		Kennett, 1992
pK_D:[a3]	5.4	4.9		7.2	7.0	8.0							
Cyproheptadine (antagonist)	316[b]	840[c]		3.16[d]	12.6[b]	263[a4]	Geller–Seifter conflict test	Rats	10	p.o. 25	o		Deacon and Gardner, 1986
								Wistar rats (198–260g)	5.6	i.p. 30	+	FI1/FR5	Graeff, 1974
								Rats	5–40	p.o.	+	FR10/FR30	Sepinwall and Cook, 1980
								Sprague–Dawley rats (330–370g)	0.1–1	i.p.	+	FR30/FR10	Witkin and Perez, 1989–1990
							Vogel's conflict test	Sprague–Dawley rats (200g)	1–18	i.p. 30	o	VI21	Kilts *et al.*, 1982
								Wistar rats (220g)	1–10	i.p. 30	o	Modified Vogel's test	Petersen and Lassen, 1981
								Rats	3	30	+		Schoenfeld, 1976
							Conflict test	White Carneau pigeons (480–528g)	0.01	i.m. 0	o	FR30	Witkin *et al.*, 1987

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								Squirrel monkeys (550–900g)	0.1–1	i.m.	+	FR30	Brady and Barrett, 1985
							Elevated-plus maze	Wistar rats (150–200g)	0.5	30	o		Kshama *et al.*, 1990
							Light/dark test	Mice (25–35g)	0.05–10	i.p. 40	–	Sedation and Asymmetric compartments	Costall *et al.*, 1988c
								Wistar rats (150–200g)	0.5	30	–	Asymmetric compartments and weak effect	Kshama *et al.*, 1990
							Holeboard	Wistar rats (150–200g)	0.5	30	o		Kshama *et al.*, 1990
							Social interaction	Sprague–Dawley rats (200–250g)	2	s.c. 40	o		Kennett *et al.*, 1989
							Fear-potentiated startle reflex	Sprague–Dawley rats (300–400g)	5	i.p. 15	o		Davis *et al.*, 1988b
							Shock–probe burying test	Wistar rats (250–280g)	2.5–40	s.c. 60	+		Meert and Colpaert, 1986b
							Marble burying test	Female MF1 mice (23–35g)	1–5	i.p. 30	+		Njung'e and Handley, 1991b
							Defecation–micturition	Rats			o		Meert and Colpaert, 1986c
							Conditioned emotional response	Rats	10		o		Gardner, 1985b
							DPAG-Stimulation	Rats	3	i.p. 30	–		Clarke and File, 1982
EGIS-3886 (5-HT$_{2A}$ selective antagonist)							Vogel's conflict test	Rats			+		Gacsályi *et al.*, 1991
Pitozifen (antagonist)	630[h]			4.4[v]	7.9[b]	42[g]	Social interaction	Sprague–Dawley rats (250–320g)	0.5–1	s.c. 30	+		Kennett, 1992
							Shock–probe burying test	Wistar rats (250–280g)	40	s.c. 60	+		Meert and Colpaert, 1986b
R 56413 (5-HT$_{2A}$ antagonist)							Geller–Seifter	Sprague–Dawley rats conflict test	1–30 (330–370g)	i.p.	o	FR30/FR10	Witkin and Perez, 1989–1990
							Vogel's conflict test	Wistar rats (250–280g)	25–40	s.c. 60	+	Modified Vogel's test	Colpaert *et al.*, 1985
							Light/dark test	Wistar rats (250–280g)	0.16	s.c. 60	+	Transitions and Asymmetric compartments	Colpaert *et al.*, 1985
							Open-field	Rats	0.01–0.63		+		Meert and Colpaert, 1986b
							Shock–probe burying test	Rats	2.5		+		Meert and Colpaert, 1986b
Ritanserin (antagonist)	6309[h]	1737[i]	1584[h]	1.48[h]	1.25[h]	7244[j]	Geller–Seifter conflict test	Rats	10	i.p. 25	o		Deacon and Gardner, 1986
								Sprague–Dawley rats (330–370g)	0.1–10	i.p.	o	FR30/FR10	Witkin and Perez, 1989–1990
								Wistar rats (250–270g)	0.16–40	s.c. 60	o	V130	Brocco *et al.*, 1990
								Wistar rats	3	p.o.	+		Amrick and Bennett, 1986
								Rats	2		+	FR8, weak effect	Hascoët *et al.*, 1992

Vogel's conflict test	Wistar rats (220–240g)	0.16–40	s.c. 60	o	Modified Vogel's test	Brocco *et al.*, 1990
	Wistar rats (180–220g)	0.25–0.5	i.p. 60	o	Modified Vogel's test	Chojnacka-Wójcik and Przegalinski, 1991
	Wistar rats (250–280g)	2.5	s.c. 60	+	Modified Vogel's test	Colpaert *et al.*, 1985
	Wistar rats (180–220g)	1–5	i.p. 30	+	Modified Vogel's test	Stefanski *et al.*, 1992a
	Rats	2.5–5		+		Stefanski *et al.*, 1992b
Conflict test	White Carneau pigeons	0.03–10	i.m. 5	+		Gleeson *et al.*, 1989
	White Carneau pigeons (500–600g)	0.16–2.5	i.m. 5	+	FR30	Brocco *et al.*, 1990
Elevated-plus maze	Rats	0.25–10		–		File *et al.*, 1987
	Lister rats (250–350g)	0.25–10	i.p. 30	–		Pellow *et al.*, 1987
	Lister rats (200–270g)	0.05–0.25	i.p. 30	o		Wright *et al.*, 1992a
	Wistar rats (292–368)	0.05–1	i.p. 30	o	Rats were well nourished	Almeida *et al.*, 1991
	CD–COBS mice (24g)	0.25–4	p.o. 90	o		Stutzmann *et al.*, 1991
	Lister rats (240–300g)	0.05–0.25	i.p. 30	o		Wright *et al.*, 1992a
	Wistar rats	0.63–10	s.c. 30	o		Millan and Brocco, 1993
	PVG rats (200–280g)	0.025–5	i.p. 30	+	Observations during 10 min	Critchley and Handley, 1987
	Lister rats	0.1	i.p.	+		Tomkins *et al.*, 1990
	Wistar rats (144–196g)	0.05–0.1 and 1	i.p. 30	+	Rats were malnourished	Almeida *et al.*, 1991
	Lister rats (200–270g)	0.25	i.p. during 2 weeks (x2)	+		Wright *et al.*, 1992a
	Lister rats (200–250g)	10 nmol	DPAG, 10	+		Audi *et al.*, 1991
	Lister rats (200–270g)	0.25	i.p. during 2 weeks (x2)	+		Wright *et al.*, 1992a
	Rats	1		+		Onaivi, 1993
Light/dark test	Mice (25–35g)	0.05–10	i.p. 40	–	Sedation, ataxia and Asymmetric compartments	Costall *et al.*, 1988c
	CD1 mice	0.1–0.6 0.32–0.7	i.p. 30 p.o. 12–15 days	o	Asymmetric compartments	Gao and Cutler, 1993a
	Swiss mice (10 weeks)	0.12–4	i.p. 30	o		Griebel, 1993
	Wistar rats (250–280g)	0.04–10	s.c. 60	+	Transitions and Asymmetric compartments	Colpaert *et al.*, 1985
	BKW mice (30–35g)	1	i.p. 45	+	Asymmetric compartments	Barnes *et al.*, 1992a
Open-field	Wistar rats (220–240g)	2.5–10	s.c. 60	–	Sedation ?	Meert, 1992
	Wistar rats (250–280g)	0.01–40	s.c. 60	+		Meert, 1986
	Rats	0.04–10		+		Meert and Colpaert, 1986b
	Wistar rats (220–240g)	0.04–0.63	s.c. 60	+		Meert, 1992
	Wistar rats (180–220g)	1–5	i.p. 30	+	65 dB noise	Stefanski *et al.*, 1992a
	Rats	5		+		Stefanski *et al.*, 1992b
Social interaction	Rats			o	LLF	Critchley *et al.*, 1987
	Sprague–Dawley rats (200–250g)	0.6	s.c. 40	o		Kennett *et al.*, 1989
	CD1 mice	0.1–0.6 0.32–0.7	i.p. 30 p.o. 12–15 days	+	Unfamiliar and neutral box	Gao and Cutler, 1993a
Novelty-suppressed feeding	Rats	0.25		+		Rex *et al.*, 1991

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Table 1. *Continued*

Compounds	Affinities (K_i, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
							Shock–probe burying test	Rats			o		Meert and Colpaert, 1986b
								Wistar rats (250–280g)	2.5	s.c. 60	+		Meert and Colpaert, 1986a
							Marble burying test	Female MF1 mice (23–35g)	1–20	i.p. 30	+	Locomotion decreased	Njung'e and Handley, 1991b
							Ultrasonic 'distress' vocalization	Sprague–Dawley rats (9–11 days)	0.3–3	s.c. 30	–		Winslow and Insel, 1991a
								Wistar rats (9–11 days)	0.3–3	30	o o	Warm condition Cold condition	Mos and Olivier, 1989
								AP mice (4–6 days)	2.5–5	30	+		Nastiti *et al.*, 1991
							Stress-induced antinociception	ddY mice (18–20g)	1–5	i.p. 30	+		Tokuyama *et al.*, 1993
							Stress-induced hyperthermia	Swiss mice (25–30g)	0.1–0.2	i.p. 60	o		Lecci *et al.*, 1990
							Passive-avoidance test	Wistar rats (220–240g)	2.5–20	i.p. 30	o		Sanger and Joly, 1989–1990
							Defense test battery	Male and female Long–Evans rats (100–103 days)	0.1–10	i.p. 30	o		Shepherd *et al.*, 1992
							DPAG-Stimulation	Rats			–		Jenck *et al.*, 1989b
								Wistar rats (200–250g)	10 nmol	DPAG	o		Audi *et al.*, 1988
								Rats	10 nmol	DPAG	o		Graeff, 1988
								Wistar rats (180–250g)	10 nmol	DPAG	o		Nogueira and Graeff, 1991
Ketanserin (antagonist)	1258[b]	1910[b]	1000[b]	3.1[c]	97.7[b]	>10000[a]	Geller–Seifter conflict test	Sprague–Dawley rats (330–370g)	0.3–30	i.p.	o	FR30/FR10	Witkin and Perez, 1989–1990
								Wistar rats	10	p.o.	+		Amrick and Bennett, 1986
							Conflict test	Squirrel monkeys (550–900g)	0.1–3	i.m.	+	FR30	Brady and Barrett, 1985
								White Carneau pigeons	0.3–10	i.m. 5	+		Gleeson *et al.*, 1989
							Elevated-plus maze	Wistar rats (220–250g)	1	i.p. 30	–		Motta *et al.*, 1992
								PVG rats (200–280g)	0.1–0.5	i.p. 30	+	Observations during 10 min	Critchley and Handley, 1987
							Open-field	Sprague–Dawley rats (200–250g)	10	i.p. 60	o		Lucki *et al.*, 1989
							Social interaction	Rats			o	LLF	Critchley *et al.*, 1987
								Sprague–Dawley rats (200–250g)	0.2	s.c. 40	o		Kennett *et al.*, 1989
								Sprague–Dawley rats (250–320g)	0.2–1	s.c. 30	o		Kennett, 1992
							Fear-potentiated	CD rats (9–13 weeks) (250–320g)	1–4	s.c. 180	o		Nanry and Tilson, 1989
							Marble burying test	Female MF1 mice (23–35g)	1–10	i.p. 30	+	Locomotion decreased	Njung'e and Handley, 1991b
							Stress-induced colonic motor alterations	Wistar rats (250–300g)	0.1–1	i.p. 30	o		Gué *et al.*, 1993

						Conditioned place aversion	Long–Evans rats (250–300g)	1–10	i.p.	o	Rocha *et al.*, 1993a
						DPAG-Stimulation	Wistar rats (250–300g)	10 nmol	DPAG 10	o	Schütz *et al.*, 1985
							Rats	10 nmol	DPAG 10	o	Graeff *et al.*, 1986
							Wistar rats (370–450g)	1–10	i.p. 35	+	Jenck *et al.*, 1989a
LY 53857 (antagonist)		3162		50[b]	7.9		Geller–Seifter conflict test	Sprague–Dawley rats (330–370g)	0.03–3	i.p.	o	FR30/FR10	Witkin and Perez, 1989–1990
							Social interaction	Sprague–Dawley rats (250–320g)	2–5	s.c. 30	+		Kennett, 1992
							Stress-induced hyperthermia	Swiss mice (25–30g)	1.5–3	i.p. 60	o		Lecci *et al.*, 1990
Pirenperone (antagonist)	1258			1.58[b]	50		Geller–Seifter conflict test	Sprague–Dawley rats (330–370g)	0.03–3	i.p.	o	FR30/FR10	Witkin and Perez, 1989–1990
							Conflict test	Squirrel monkeys (550–900g)	0.001–0.3	i.m.	o	FR30	Brady and Barrett, 1985
							DPAG-Stimulation	Wistar rats (370–450g)	0.1–1	i.p. 35	+		Jenck *et al.*, 1989a
RP 62203 (antagonist)	68.5[a5]			0.42[r]	29[r]	>1000[a5]	Elevated-plus maze	Mice CD–COBS (24g)	0.25–4	p.o. 90	+		Stutzmann *et al.*, 1991
Seganserin (5-HT_{2A} antagonist)							Elevated-plus maze	PVG rats (200–280g)	0.5	i.p. 30	+	Observations during 10 min	Critchley and Handley, 1987
Phenylbiguanide (agonist)						130[k]	Light/dark test	Female ICR–DUB mice (17–35g)	1–31.6	i.p. 30	o	Asymmetric compartments	Young and Johnson, 1991c
Anpirtoline (antagonist)	151	28				30[a18]	Light/dark test	BKW mice (25–30g)	0.000001–0.001	i.p. 45	+	Asymmetric compartments	Metzenauer *et al.*, 1992
BRL 46470A (Selective antagonist)	>4000	>10000	>10000	>10000	>10000	0.32[a9]	Elevated-plus maze	Sprague–Dawley rats (250–300g)	0.0001–0.1	p.o. 30	+	Asymmetric compartments	Blackburn *et al.*, 1993
							Light/dark test	CD1 mice (40–55g)	0.0025	i.p. 30	+	Asymmetric compartments	Gao and Cutler, 1992b
							Social interaction	CD1 mice (40–55g)	0.0025–2.5	i.p. 30	+	Familiar and neutral box	Gao and Cutler, 1992b
								CD1 mice (40–44g)	0.01	p.o. during 12–14 days (x1)	+	Familiar and neutral box	Gao and Cutler, 1992a
								Sprague–Dawley rats (250–300g)	0.0001–0.1	s.c. 30	+		Blackburn *et al.*, 1993
								Female CD1 mice (30–35g)	40 μg/l	Drinking fluid	+	Oestrous mice	Gao and Cutler, 1993b
										during 6–8 days	+	Dioestrous mice	
							Free observation	Cynomolgus monkeys	0.001–0.1	p.o. during 15 days	+		Piper *et al.*, 1992
DAU 6215 (5-HT_3 antagonist)							Geller–Seifter conflict test	Wistar rats	0.01–1	p.o. 60	o		Borsini *et al.*, 1993
							Elevated-plus maze	Wistar rats	0.015–0.15	s.c. 25 or 45	o		Borsini *et al.*, 1993
							Light/dark test	CD-1 mice (20–22g)	0.01–1	i.p. 45	+	Asymmetric compartments	Borsini *et al.*, 1993
							Staircase test	NMRI mice	0.001–0.1	i.p. 45	o		Borsini *et al.*, 1993
							Four hot-plates	NMRI mice	0.01–0.1	i.p. 45	o		Borsini *et al.*, 1993

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{3C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
							Aggression-provoked	Cynomolgus monkeys	0.001–0.01	p.o. during 5 h	+		Borsini *et al.*, 1993
							Stress-induced hyperthermia	CD-1 mice	0.001–0.1	i.p. 45	o		Borsini *et al.*, 1993
							Conditioned place aversion	CD–COBS rats	0.015–0.3	s.c. 30	+		Borsini *et al.*, 1993
							Stress-suppressed feeding	Wistar rats	0.001–0.1	i.p. 30	o		Borsini *et al.*, 1993
Granisetron (selective antagonist)	>10000[a]	>1000[a]	>10000[a]	>10000[a]	>10000[a]	1.41[a4]	Geller–Seifter conflict test	Lister rats (200–250g)	0.0005–50	p.o.	o		Piper *et al.*, 1988
							Vogel's conflict test	Lister rats (200–250g)	0.0005–50	p.o.	o		Piper *et al.*, 1988
							Elevated-plus maze	Rats	0.01–1	p.o. 60	o		Johnston and File, 1988
							Light/dark test	Wistar rats (21 days)	0.001–1	i.p. 50	o		Morinan, 1989
								Mice	0.00001–0.001	i.p.	+	Asymmetric compartments	Costall *et al.*, 1988a
								BKW mice (20–30g)	0.00001–0.001	i.p. 45	+	Asymmetric compartments and rears	Costall *et al.*, 1989b
								BKW mice (20–30g)	0.00001–0.001	i.p. 45	+	Asymmetric compartments	Costall *et al.*, 1989a
								Gerbils	0.1 2	p.o. during 12–16 days (x1)	+	Asymmetric compartments	Cutler, 1990
								BKW mice (30–35g)	0.001–0.1	i.p. 45	+	Asymmetric compartments	Barnes *et al.*, 1992a
							Social interaction	Lister rats (250g)	0.1–1	p.o. 60	o		File and Johnston, 1989
								Rats	0.1–1	p.o. 60	o	HLU and LLF	File, 1990
								Wistar rats (210–280g)	0.00001–0.001	Amygdala 5	o	LLF	Higgins *et al.*, 1991
								Rats	1	p.o. 60	+	HLU	Johnston and File, 1988
								Lister rats (200–250g)	0.1–10	p.o.	+	HLU	Piper *et al.*, 1988
								Lister rats (200–250g)	0.0001–0.1	p.o. 45	+	HLU	Costall *et al.*, 1989c
								Rats	0.0001–0.01	p.o. 45	+	HLU	Tyers, 1989
								Gerbils	0.1 2	p.o. during 3 weeks (x1)	+	HLU and LLF	Cutler, 1990
								Gerbils	0.0015–0.15	p.o. during 11 days (x1)	+	HLU	Cutler and Piper, 1990
								Male and female DBA/2 mice (24–36g)	0.01	p.o. during 5–10 days (x1)	+	HLU	Cutler, 1991a
								Male and female DBA/2 mice	0.01	p.o. during 7–10 days (in drinking fluid)	+		Cutler, 1991b
								Wistar rats (210–280g)	0.00001–0.0001	Amygdala, 5	+	HLU	Higgins *et al.*, 1991
							Human threat	Marmoset	0.000001–0.1		+		Costall *et al.*, 1988a
								Marmoset *Callithrix jacchus* (295–335g)	0.001–0.1	s.c. 45	+		Costall *et al.*, 1989a
							Free observation	Cynomolgus monkeys	0.01–0.1	p.o.	+	Weak effect	Piper *et al.*, 1988
							Stress-induced colonic motor alterations	Wistar rats (250–300g)	0.1–1	i.p. 30	o		Gué *et al.*, 1993

GR68755 (selective antagonist) pK_i[11]:	<4	5.2	<4	9.8	Light/dark test	BKW mice	0.0000001–1	i.p.	+	Asymmetric compartments	Costall *et al.*, 1991b
					Social interaction	Lister rats	0.0001–5	p.o.	+	HLU	Hagan *et al.* , 1991
ICS 205-930 (selective antagonist)	>10000[a]	>10000[a]	>10000[a]	17000[a2]	>10000[a]	0.81[a4]	Geller–Seifter conflict test	Rats	0.01	s.c.	o	Modified Geller–Seifter test	Thiébot *et al.*, 1990
					Vogel's conflict test	Wistar rats (300–350g)	1–10	i.p. 30	o		Dunn *et al.*, 1991
						Wistar rats (210–280g)	0.00001–0.001	Amygdala, 5	o	Modified Vogel's test	Higgins *et al.*, 1991
						Rats		Accumbens	+		Plaznik *et al.*, 1991
						Wistar rats (180–220g)	0.0001–0.01	i.p. 60	+	Modified Vogel's test	Stefanski *et al.*, 1992a
						Rats	0.001–0.01		+		Stefanski *et al.*, 1992b
						Wistar rats	0.000005–0.00001	Hippocampus Nucleus	+		Stefanski *et al.*, 1993b
							0.00001	accumbens septi	+		
					Conflict test	White Carneau pigeons	0.001–0.3	i.m. 5	+	Weak effect	Gleeson *et al.*, 1989
					Elevated-plus maze	Rats	0.1	p.o. 60	+		Johnston and File, 1988
						Wistar rats (200–250g)	10.25–0.5	i.p. 30	+		Dunn *et al.*, 1991
					Light/dark test	BKW mice (25–30g)	0.00000001	Median raphé	o	Asymmetric compartments	Costall *et al.*, 1989c
							0.00001				
						Gerbils	0.1 2	p.o. during 12–16 days (x1)	o	Asymmetric compartments	Cutler, 1990
						Mice	0.0001–0.01	i.p.	+	Asymmetric compartments and rears	Costall *et al.*, 1987b
						Mice	0.00001–0.01	i.p.	+	Asymmetric compartments	Tyers *et al.*, 1987
						Mice	0.00001–0.01	i.p.	+	Asymmetric compartments	Costall *et al.*, 1988b
						BKW mice (25–30g)	0.00000001–0.00001	Dorsal raphé or Amygdala	+	Asymmetric compartments	Costall *et al.*, 1989c
						BKW mice (25–30g)	0.0001–0.1	i.p. 45	+	Asymmetric compartments	Costall *et al.*, 1989a
						C57Bl/6J mice (18–20g)	0.001 ng/kg – 1	i.p. 30	+		Kilfoil *et al.*, 1989
						BKW mice (20–30g)	0.00001–0.001	i.p. 45	+	Asymmetric compartments and rears	Costall *et al.*, 1989b
						ICR mice (20–35g)	0.001–1	i.p. 30	+	Transitions and Asymmetric compartments	Onaivi and Martin, 1989
						Female T/O mice (22–30g)	0.01	s.c. 30	+	Asymmetric compartments	Bill *et al.*, 1992
					Open-field	Wistar rats (250–270g)	0.187–20	i.p. 60	o		Papp and Przegalinski, 1989
						Wistar rats	0.000001–0.0001	Hippocampus	o		Stefanski *et al.*, 1993b
						Rats		Accumbens	+		Plaznik *et al.*, 1991
						Wistar rats (180–220g)	0.0001–0.01	i.p. 60	+	65 dB noise	Stefanski *et al.*, 1992a
						Rats	0.001–0.1		+		Stefanski *et al.*, 1992b
						Wistar rats	0.000001–0.00001	Nucleus	+ +	+5,7-DHT	Stefanski *et al.*, 1993b
							0.000005	accumbens septi			
					Social interaction	Rats	0.01–1	p.o. 60	o	HLU	Johnston and File, 1988
						Sprague–Dawley rats (200–250g)	0.05–1	s.c. 40	o		Kennett *et al.*, 1989
						Wistar rats (210–280g)	0.0001–0.001	Amygdala,	o	LLF	Higgins *et al.*, 1991
							0.00005–0.005	Dorsal raphé 5		HLU	
						Rats	0.0001–0.01	i.p.	+		Costall *et al.*, 1987a

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Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								Rats	0.00001–0.001	p.o. 45	+	HLU	Tyers *et al.*, 1987
								Lister rats (200–250g)	0.00001–0.1	p.o. 45	+	HLU	Costall *et al.*, 1989a
								Mice	0.00001–0.1	i.p. 45	+	Observations during 7min	Cutler and Dixon, 1989
								Gerbils	0.12	p.o. during 3 weeks (x1)	+	HLU and LLF	Cutler, 1990
								Wistar rats (250–300g)	1	i.p. 30	+		Dunn *et al.*, 1991
								Wistar rats (210–280g)	0.0001–0.001	Amygdala, 5	+	HLU	Higgins *et al.*, 1991
							Novelty-suppressed feeding	Sprague–Dawley rats (270–320g)	0.01–1	s.c. 30	o		Fletcher and Davies, 1990
								Rats	0.001		+		Rex *et al.*, 1991
							Marble burying test	Female MF1 mice (23–35g)	0.1–10	i.p. 30	o		Njung'e and Handley, 1991b
							Human threat	Marmoset *Callithrix jacchus* (350–400g)	0.0001–0.01	i.p.	+		Tyers *et al.*, 1987
								Marmoset	0.0001–0.001		+		Costall *et al.*, 1988b
								Marmoset *Callithrix jacchus* (295–335g)	0.1–1	s.c. 45	+		Costall *et al.*, 1989a
							Conditioned place aversion	Wistar rats (250–270g)	0.125–1	i.p. 60	+		Papp, 1988
							Passive-avoidance test	Wistar rats (250–270g)	0.0937–0.1875	i.p. 60	+		Papp and Przegalinski, 1989
							DPAG-Stimulation	Wistar rats (370–450g)	0.01–10	i.p. 35	o		Jenck *et al.*, 1989a
MDL 72222 (selective antagonist)	>1000[a25]	>1000[a25]	>1000[a6]	>10000[a25]	>1000[a25]	6.3[a4]	Geller–Seifter	Rats conflict test	10		o		Dunn *et al.*, 1990
								Rats	0.5–8		o	FR8	Hascoët *et al.*, 1992
							Vogel's conflict test	Wistar rats (300–350g)	5–20	i.p. 30	o	Modified Vogel's test	Dunn *et al.*, 1991
							Conflict test	White Carneau pigeons	0.01–3	i.m. 5	+	Weak effect	Gleeson *et al.*, 1989
							Elevated-plus maze	Rats	10		+		Dunn *et al.*, 1990
								Wistar rats (200–250g)	10	i.p. 30	+		Dunn *et al.*, 1991
								Wistar rats (150–220g)	1	i.p. 30	+		Griebel, 1993
							Light/dark test	BKW mice (20–30g)	10	i.p. 45	–	Asymmetric compartments and rears	Costall *et al.*, 1989b
									1		+		
								Female T/O mice (24–35g)	0.3–3	s.c. 30	+	Asymmetric compartments	Bill *et al.*, 1991
								ICR mice (20–35g)	0.001–1	i.p. 30	+	Transitions and Asymmetric compartments	Onaivi and Martin, 1989
							Social interaction	Lister rats (210–280g)	0.0010.01	Amygdala 5	o	LLF HLU	Higgins *et al.*, 1991
									0.00005–0.005	Dorsal raphé 5			
								Rats	0.001–0.1	p.o. 45	+	HLU	Tyers *et al.*, 1987
								Rats	10		+		Dunn *et al.*, 1990
								Wistar rats (250–300g)	20	i.p. 30	+		Dunn *et al.*, 1991
								Lister rats (210–280g)	0.001–0.01	Amygdala 5	+		Higgins *et al.*, 1991
							DPAG-Stimulation	Wistar rats (370–450g)	0.1–22	i.p. 35	o		Jenck *et al.*, 1989a

Ondansetron (selective antagonist)	>10000[a]	3700[a]	>10000[a]	>10000[a]	5000[a]	13.5[a4]	Geller–Seifter	Lister rats (200–250g) conflict test	0.0005–5	p.o.	o		Piper *et al.*, 1988
								Rats	0.01–0.1		o		Dunn *et al.*, 1990
							Vogel's conflict test	Rats	0.0005–1.6	i.p.	o		Jones *et al.*, 1987
								Lister rats	0.01–0.1	i.p. 30	o		Jones *et al.*, 1988
								Lister rats (200–250g)	0.0005–5	p.o.	o		Piper *et al.*, 1988
								Wistar rats (300–350g)	0.05–0.3	i.p. 30	o	Modified Vogel's test	Dunn *et al.*, 1991
								Lister rats (210–280g)	0.0001–0.01	Amygdala 5	o	Modified Vogel's test	Higgins *et al.*, 1991
								Wistar rats	0.00001–0.015	Nucleus accumbens septi	o		Stefanski *et al.*, 1993b
								Rats		Accumbens	+		Cutler, 1991a
								Wistar rats (180–220g)	0.1–1.5	i.p. 30	+	Modified Vogel's test	Stefanski *et al.*, 1992a
								Rats	1.5		+		Stefanski *et al.*, 1992b
								Wistar rats	0.001–0.0025	Hippocampus	+		Stefanski *et al.*, 1993b
							Conflict test	White Carneau pigeons	0.001–1	i.m. 5	−		Gleeson *et al.*, 1989
								Cynomolgus monkeys	0.01–0.1	p.o.	+		Jones *et al.*, 1987
							Elevated-plus maze	Rats	0.01–1	p.o. 60	o		Johnston and File, 1988
								Wistar rats (150–200g)	0.1	30	o		Kshama *et al.*, 1990
								Lister rats (200–270g)	0.01–1	i.p. 30	o		Wright *et al.*, 1992a
								Wistar rats	0.0075–0.015	s.c. 25 or 45	o		Borsini *et al.*, 1993
								Rats	0.01–0.1		+		Dunn *et al.*, 1990
								Wistar rats (200–250g)	0.05–0.1	i.p. 30	+		Dunn *et al.*, 1991
								Wistar CFY rats (250–300g)	0.0001–0.1	p.o. 30	+		Upton and Blackburn, 1991
								Lister rats (200–270g)	0.01	i.p. during 2 weeks (x2)	+		Wright *et al.*, 1992a
								Long–Evans Rats (240–260g)	0.04	i.p. 60	+		Prather *et al.*, 1993
								Female rats (160–180g)	0.01	i.p. 30	+		Vasar *et al.*, 1993
							Zero-maze	Sprague–Dawley rats	0.01	s.c. 30	+		Grewal *et al.*, 1993
							Light/dark test	Wistar rats (21 days)	0.001–1	i.p. 50	o		Morinan, 1989
								DAP mice	0.001–10	p.o. 30	o	Asymmetric compartments	Mos *et al.*, 1989
								Wistar rats (150–200g)	0.1	30	o	Asymmetric compartments	Kshama *et al.*, 1990
								Mice	0.00005–0.01	i.p.	+	Asymmetric compartments and rears	Costall *et al.*, 1987a
								Mice	0.00005–0.01	i.p.	+	Asymmetric compartments	Tyers *et al.*, 1987
								Mice	0.00005–0.01	i.p.	+	Asymmetric compartments	Costall *et al.*, 1988b
								BKW mice	0.00005–0.01	i.p. 45	+	Asymmetric compartments	Jones *et al.*, 1988
								Mice	0.0001–1	i.p.	+		Young and Johnson, 1988
								BKW mice (25–30g)	0.0000001–0.00001	Dorsal raphé or Amygdala	+	Asymmetric compartments	Costall *et al.*, 1989c
									0.0001	Median raphé	+	Weak effect	
								BKW mice	0.5–5	i.p. 45	+	Asymmetric compartments and rears	Costall *et al.*, 1989b
								BKW mice (25–30g)	0.00005–1	i.p. 45	+	Asymmetric compartments	Costall *et al.*, 1989a

Continued

Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								DAP mice	0.1	s.c. 30	+	Asymmetric compartments	Mos *et al.*, 1989
								Mice	0.00005–0.01	i.p. 30	+	Asymmetric compartments	Costall and Naylor, 1991
								Female ICR–DUB mice (17–35g)	0.01–0.1	i.p. 30	+	Asymmetric compartments	Young and Johnson, 1991c
								BKW mice (30–35g)	0.00001–0.1	i.p. 45	+	Asymmetric compartments	Barnes *et al.*, 1992a
								Female T/O mice (22–30g)	0.001–01	s.c. 30	+	Asymmetric compartments	Bill *et al.*, 1992
								C57 mice	0.001–3	p.o. 30	+	Asymmetric compartments	Fontana *et al.*, 1992
								CD-1 mice (20–22 g)	0.001	i.p. 45	+	Asymmetric compartments	Borsini *et al.*, 1993
							Holeboard	Wistar rats (150–200g)	0.1	30	o		Kshama *et al.*, 1990
							Open-field	Wistar rats (250–270g)	0.25–20	i.p. 60	o		Papp and Przegalinski, 1989
								Wistar rats	0.0005–0.005	Hippocampus	o		Stefanski *et al.*, 1993b
								Rats		Accumbens	+		Plaznik *et al.*, 1991
								Wistar rats (180–220g)	0.1–1.5	i.p. 30	+	65 dB noise	Stefanski *et al.*, 1992a
								Rats	0.001–0.1		+		Stefanski *et al.*, 1992b
								Wistar rats	0.001–0.0025	Nucleus accumbens septi	+		Stefanski *et al.*, 1993b
							Social interaction	Rats	0.01–1	p.o. 60	o	HLU	Johnston and File, 1988
								Lister rats (250g)	0.1–1	p.o. 60	o		File and Johnston, 1989
								Rats	0.1–1	p.o. 60	o	HLU and LLF	File, 1990
								Lister rats (210–280g)	0.0001–0.001 0.00005–0.005	Amygdala, 5 Dorsal raphé, 5	o	LLF HLU	Higgins *et al.*, 1991
								Rats	0.00005–0.01	i.p.	+		Costall *et al.*, 1987a
								Lister rats (180–230g)	0.0005–0.1	p.o. 45	+	HLU	Jones *et al.*, 1987
								Rats	0.0005–0.1	p.o. 45	+	HLU	Tyers *et al.*, 1987
								Lister rats (200–250g)	0.001–1	p.o. 45	+		Jones *et al.*, 1988
								Lister rats (200–250g)	0.1–10	p.o.	+	HLU	Piper *et al.*, 1988
								Lister rats (200–250g)	0.0005–0.1	p.o. 45	+	HLU	Costall *et al.*, 1989a
								Rats	0.01–1		+		Dunn *et al.*, 1990
								Rats	0.01–1	i.p. 45	+		Costall and Naylor, 1991
								Wistar rats (250–300g)	0.05	i.p. 30	+		Dunn *et al.*, 1991
								Lister rats (210–280g)	0.0000001–0.0001	Amygdala, 5	+	HLU	Higgins *et al.*, 1991
							Defense test battery	Male and female Long–Evans rats (154–253g)	0.001–0.1	i.p. 45	o		Shepherd *et al.*, 1993
							Fear-potentiated startle reflex	Lister rats (375–415g)	0.01–0.1	i.p. 45	+		Glenn and Green, 1989
							Novelty-suppressed feeding	Rats	0.001		+		Rex *et al.*, 1991
							Ultrasonic 'distress' vocalization	Rats	0.001 1	i.p. 30	o		Mos *et al.*, 1989

						Wistar rats (9–11 days)	0.3–3	30	o	Warm condition	Mos and Olivier, 1989
									o	Cold condition	
						AP mice (4–6 days)	2.5–5	30	+		Nastiti *et al.*, 1991
					Marble burying test	Female MF1 mice (23–35g)	0.01–1	i.p. 30	o		Njung'e and Handley, 1991b
					Stress-induced hyperthermia	Swiss mice (25–30g)	0.0001–0.1	i.p. 45	o		Lecci *et al.*, 1990
						Mice CD-1	0.01–0.1	i.p. 30	o		Borsini *et al.*, 1993
					Four hot-plates	Female DAP mice	0.001–10 0.001	p.o. 30 s.c. 30	o +		Mos *et al.*, 1989
					Free observation	Cynomolgus monkeys (3.1–5.4 kg)	0.01–0.1	p.o.	+		Tyers *et al.*, 1987
							0.01–0.1	p.o.	+		Jones *et al.*, 1988
							0.01–0.1	p.o.	+	Weak effect	Piper *et al.*, 1988
					Aggression-provoked	Cynomolgus monkeys	0.1	p.o. during 5 hr	+		Borsini *et al.*, 1993
					Human threat	Marmoset *Callithrix jacchus* (350–400g)	0.0001–0.01	s.c. 45	+		Jones *et al.*, 1988
							0.001	i.p.	+		Tyers *et al.*, 1987
						Marmoset	0.0001–0.001		+		Costall *et al.*, 1988b
						Marmoset *Callithrix jacchus* (295–335g)	0.1–1	s.c. 45	+		Costall *et al.*, 1989a
						Cynomolgus monkeys	0.01–0.1	p.o. during 15 days (x1)	+		Piper *et al.*, 1992
					Passive-avoidance test	Wistar rats (250–270g)	0.125–1	i.p. 60	+		Papp and Przegalinski, 1989
						Wistar rats (220–240g)	0.0625–0.5	i.p. 30	+	Weak effect	Sanger and Joly, 1989–1990
					DPAG-Stimulation	Wistar rats (370–450g)	0.1–10	i.p. 35	o		Jenck *et al.*, 1989a
RS-42359-197				0.12[a25]	Elevated-plus maze	Lister rats (295–335g)	0.0000001–0.0001	i.p. 40	+		Costall *et al.*, 1993
(5-HT$_3$ antagonist)					Light/dark test	C57 mice	0.000003–3	p.o. 30	+	Asymmetric compartments	Fontana *et al.*, 1992
						Mice	0.000001–10	p.o. i.p. 40	+	Asymmetric compartments	Costall *et al.*, 1993
					Social interaction	Lister rats (295–335g)	0.000001–1	i.p. 40	+		Costall *et al.*, 1993
					Human threat	Marmoset	0.00001–0.001	s.c. 40	+		Costall *et al.*, 1993
(R)-RS-56812					Vogel's conflict test	Rats	0.003–1	i.p.	o		Fontana *et al.*, 1993
(selective antagonist)					Light/dark test	Mice	0.0000003–30	i.p.	o		Fontana *et al.*, 1993
(S)-RS-56812					Vogel's conflict test	Rats	0.003–1	i.p.	o		Fontana *et al.*, 1993
(selective antagonist)					Light/dark test	Mice	0.0000003–30	i.p.	+		Fontana *et al.*, 1993
WAY100289					Light/dark test	Female T/O mice (22–30g)	0.1–10	p.o. 45 s.c. 30	+	Asymmetric	Bill *et al.*, 1992
(selective antagonist)											
pK$_i$:	< 5	< 5	< 5[q]	< 5	8.8[a7]	Fear-potentiated startle reflex	Lister rats (250–285g)	0.03–0.3	s.c. 30	+		Bill *et al.*, 1992
Y-25,130						Stress-induced	ddY mice antinociception	0.03–0.1 (18–20g)	i.p. 30	+		Tokuyama *et al.*, 1993
(5-HT$_3$ antagonist)												
Zacopride	> 10000[a]	> 10000[a]	> 10000[a]	3600[a]	2600[a]	0.32[a4]	Vogel's conflict test	Wistar rats (300–350g)	1–10	i.p. 30	o	Modified Vogel's test	Dunn *et al.*, 1991
(selective antagonist)							Elevated-plus maze	Lister rats (250g)	0.01–1	i.p. p.o. 60	o		File and Johnston, 1989
								Wistar rats (150–200g)	2	30	o		Kshama *et al.*, 1990
								Wistar rats (200–250g)	0.1–0.3	i.p. 30	+		Dunn *et al.*, 1991
							Light/dark test	Wistar rats (150–200g)	2	30	o	Asymmetric compartments	Kshama *et al.*, 1990

Continued

Table 1. *Continued*

Compounds	Affinities (*Ki*, nM) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$	Models	Animals	Efficient doses or doses tested (mg/kg)	Routes administration, latency (min)	Effects	Comments	References
								BKW mice (30–35g)	0.0001–10	i.p. 45	+	Asymmetric compartments	Costall *et al.*, 1988a
								Mice	0.0001–17.8	i.p.	+		Young and Johnson, 1988
									0.001–100	p.o.	+		
								BKW mice (20–30g)	0.001–0.05	i.p. 45	+	Asymmetric compartments and rears	Costall *et al.*, 1989b
								Female ICR–DUB mice (17–35g)	0.0001–17.8	i.p. 30	+	Asymmetric compartments	Young and Johnson, 1991b
								BKW mice (30–35g)	0.01–0.1	i.p. 45	+	Asymmetric compartments	Barnes *et al.*, 1992b
								Female T/O mice (22–30g)	0.001–1	s.c. 30	+	Asymmetric compartments	Bill *et al.*, 1992
								Swiss mice (10 weeks)	0.001–0.01	p.o. 30	+		Griebel, 1993
							Holeboard	Wistar rats (150–200g)	2	30	o		Kshama *et al.*, 1990
							Social interaction	Lister rats (250g)	0.01–1	i.p. 60	o		File and Johnston, 1989
								Sprague–Dawley rats (225–275g)	0.001–10	i.p. 45	+		Costall *et al.*, 1989a
								Wistar rats (250–300g)	0.3–1	i.p. 30	+		Dunn *et al.*, 1991
							Human threat	Marmoset *Callithrix jacchus* (350–400g)	0.0001–0.001	s.c. 45	+		Costall *et al.*, 1989b
(−)Zacopride (selective antagonist)						0.33[a8]	Elevated-plus maze	Lister rats (250g)	0.001–1	i.p. 30	o	Chronic vehicle treated rats (14 days)	File and Andrews, 1993
							Light/dark test	BKW mice (30–35g)	0.000001–10	i.p. 45	o	Asymmetric compartments	Barnes *et al.*, 1992b
								BKW mice (30–35g)	0.00001–0.01	i.p. 45	o	Asymmetric compartments	Barnes *et al.*, 1992b
								Female ICR–DUB mice (17–35g)	0.01–1	i.p. 60	+	Asymmetric compartments	Young and Johnson, 1991a
							Social interaction	Lister rats (250–300g)	0.00001–1	i.p. 45	−		Barnes *et al.*, 1992b
(+)Zacopride (selective antagonist)						2.29[a8]	Elevated-plus maze	Lister rats (250g)	0.001–1	i.p. 30	o	Chronic vehicle treated rats (14 days)	File and Andrews, 1993
							Light/dark test	Female ICR–DUB mice (17–35g)	0.00001–10	i.p. 60	+	Asymmetric compartments	Young and Johnson, 1991a
								BKW mice (30–35g)	0.000001–10	i.p. 45	+	Asymmetric compartments	Barnes *et al.*, 1992b
								BKW mice (30–35g)	0.0001–0.1	i.p. 45	+	Asymmetric compartments	Barnes *et al.*, 1992a
								Mice	0.01	i.p.	+	Asymmetric compartments	Cheng *et al.*, 1992
							Social interaction	Lister rats (250–300g)	0.00001–1	i.p. 45	+		Barnes *et al.*, 1992b

+ = anxiolysis; o = inactive; − = anxiogenesis; i.c.v. = intracerebroventricular injection; i.t. = intrathecal injection; DPAG = Dorsal periaqueductal gray; VI = Variable Interval; FI = Fixed Interval; FR = Fixed Ratio schedule; CRF = Continuous Reinforcement Schedule; LLF = Low Light Familiar; HLU = High Light Unfamiliar; LED = Lower Effective Dose; [a]Olivier *et al.*, 1992; [b]Hoyer and Schoeffter, 1991; [c]Peroutka, 1986; [d]Lyon and Titeler, 1988; [e]Nelson *et al.*, 1989; [f]Leysen *et al.*, 1982; [g]Schmidt and Peroutka, 1990; [h]Gozlan *et al.*, 1983; [i]Sanders-Bush, 1988; [j]VanWijngaarden *et al.*, 1990; [k]Kilpatrick *et al.*, 1990a; [l]Nelson and Thomas, 1989; [m]Hoyer *et al.*, 1985; [n]Engel *et al.*, 1986; [o]Schlicker *et al.*, 1989; [p]Thomas *et al.*, 1987; [q]Rhodes *et al.*, 1993; [r]Malgouris *et al.*, 1993; [s]Yagaloff and Hartig, 1985; [t]Kilpatrick *et al.*, 1989; [u]Ybema *et al.*, 1992; [v]Conn and Sanders-Bush, 1986; [w]Kidd *et al.*, 1993; [x]Takao *et al.*, 1992; [y]Hoyer, 1991; [z]Moreau *et al.*, 1992; [a1]Schoeffter and Hoyer, 1989; [a2]Peroutka *et al.*, 1988; [a3]Kennett, 1992; [a4]Hoyer and Neijt, 1988; [a5]Doble *et al.*, 1990; [a6]Heuring *et al.*, 1987; [a7]Bill *et al.*, 1992; [a8]Bolanos *et al.*, 1990; [a9]Blackburn *et al.*, 1993; [a10]De Vry *et al.*, 1991; [a11]Kilpatrick *et al.*, 1991; [a12]Costall *et al.*, 1991a; [a13]Andersson *et al.*, 1992; [a14]Bruinvels *et al.*, 1991; [a15]Barnes *et al.*, 1991; [a16]Barrett and Zhang, 1991; [a17]Colpaert *et al.*, 1992; [a18]Metzenauer *et al.*, 1992; [a19]Levy and van de Kar, 1992; [a20]Major *et al.*, 1991; [a21]Fletcher *et al.*, 1991; [a22]Maitre, 1992; [a23]Hyttel, 1977; [a24]Berendsen and Broekkamp, 1990; [a25]Wong *et al.*, 1992; [a26]Kilpatrick *et al.*, 1990b; [a27]Millan *et al.*, 1991; [a28]Miyauchi *et al.*, 1993; [a29]Egawa *et al.*, 1993; [a30]Da Prada *et al.*, 1982; [a31]Brown *et al.*, 1989; [a32]Audinot *et al.*, 1993.

of the central 5-HT system in the regulation of anxiety- or fear-related responses is only evident in particular experimental procedures.

2. ANIMAL MODELS OF ANXIETY DISORDERS: ATTEMPTS AT CLASSIFICATION

A survey of current animal models of anxiety reveals a bewildering diversity of procedures (for reviews, see Treit, 1985; Lister, 1990; Sanger, 1991). There are more than 30 animal behavior paradigms that claim to model anxiety (Fig. 1). Most of them involved exposure of animals to external (e.g. cues previously paired with footshock) or internal (e.g. drug states) stimuli that are assumed to be capable of inducing anxiety in humans. The first category can be grouped into two subclasses: the first includes ethologically based paradigms and involves animals' spontaneous or natural reactions to stress stimuli that do not explicitly involve pain or discomfort (e.g. exposure to a novel test chamber); the second involves animals' conditioned responses to stressful and often painful events (e.g. exposure to electric footshock). Some authors have attempted to classify anxiety models more precisely into three, four or more categories. For instance, Treit (1985) further divided the models based on conditioned reactions into two subgroups; models based on traditional learning paradigms (e.g. Geller–Seifter conflict test) and those involving phylogenetically prepared forms of aversive learning (e.g. conditioned taste aversion, conditioned defensive burying). More recently, Handley (1991) proposed a classification based on the nature of the aversive stimulus and on the response elicited, suggesting that the neuronal control of anxiety may differ according to whether the interpretation of a signal as aversive is innate or learned (Gray, 1982) and whether it causes the emission of a response or conversely inhibits an ongoing, rewarded behavior. Hence, Handley distinguished three main types of animal models of aversive behavior, namely, passive avoidance tests, active avoidance tests and conflict tests.

For the sake of convenience, anxiety models in the present review are placed into one of the following two categories: (a) tests based on unconditioned responses and (b) models based on conditioned reactions (Fig. 1). The first category can be further divided into four subgroups: (a1) models based on exploratory behavior in rodents (e.g. elevated plus-maze; light/dark test); (a2) models based on rodent and monkey social behavior (e.g. social interaction test; human threat in monkeys); (a3) situations based on somatic stress reactions (e.g. stress-induced hyperthermia), and in the last group, we can find some miscellaneous models that do not fit easily into the other subgroups, such as the marble burying test or the anxiety/fear test battery. In the second category, the traditional conflict paradigms (e.g. Geller–Seifter and Vogel conflict tests) are distinguished from a number of other models involving conditioned responses, including the fear-potentiated startle reflex or the conditioned emotional response (CER) test.

3. BEHAVIORAL EFFECTS OF DRUGS MODULATING 5-HYDROXYTRYPTAMINE NEUROTRANSMISSION IN ANIMAL MODELS OF ANXIETY

3.1. Behavioral Actions of Central Application of 5-Hydroxytryptamine and Peripheral Administration of 5-Hydroxytryptamine Indirect Ligands

3.1.1. 5-*Hydroxytryptamine*

As shown by Fig. 2a, a direct application of 5-HT in brain structures has been found to produce an anxiogenic-like profile in several studies. These results seem consistent with the observation that intraventricularly administered 5-HT is accumulated (with a half-life of about 4–5 hr) in several brain regions, including the periaqueductal gray area of the midbrain, the septum and the amygdala (Aghajanian and Bloom, 1967), regions frequently associated with punished and aversive behavior (Adams, 1979; Olds and Olds, 1962). Furthermore, they fit well with the 5-HT hypothesis of anxiety, as the increased availability of 5-HT in the brain may have potentiated emotional reactivity in the animals. However, as also illustrated by Fig. 2a, a similar treatment often reduces anxious responses. This inconsistency from one study to another probably is due to a number of factors. For example,

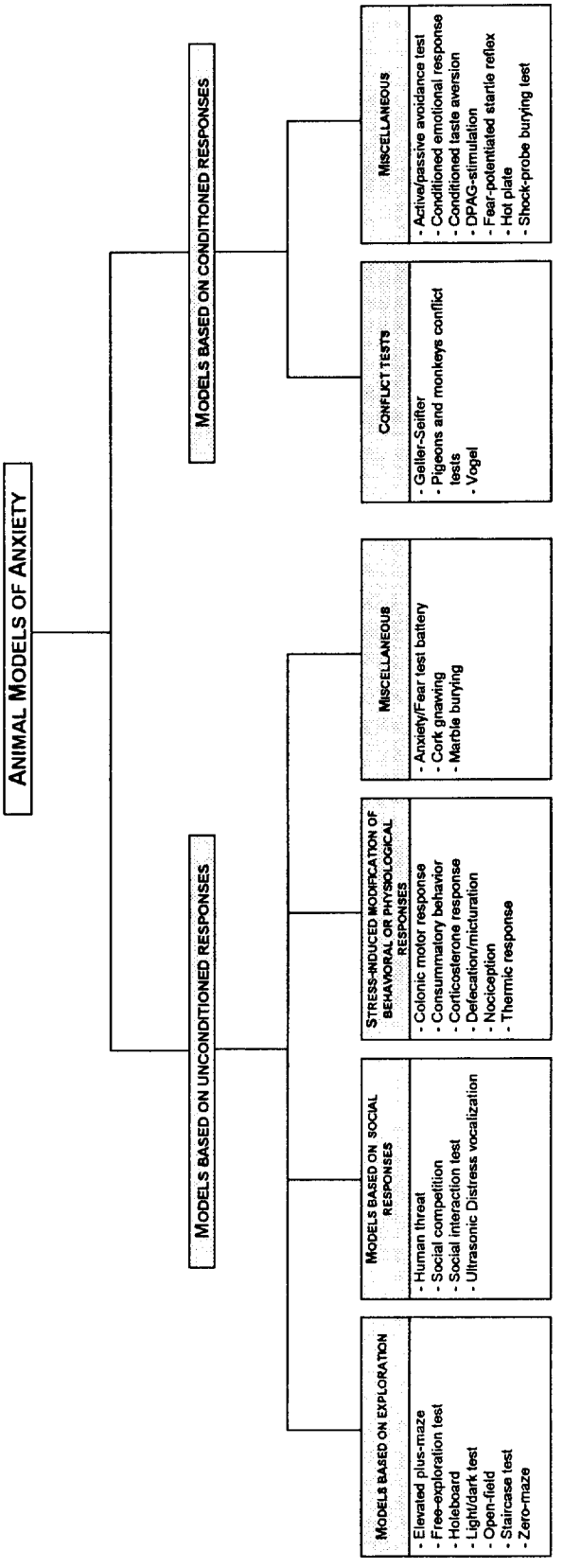

Fig. 1. Classification of the existing animal models of anxiety disorders.

it is obvious that the target site into which the injection was performed explains, at least in part, this variability. Several authors who found an anxiolytic-like action of 5-HT (Thiébot *et al.*, 1982, 1984; Higgins *et al.*, 1991) injected the neurotransmitter directly into the dorsal raphé. Yet, it is clearly established that this area contains a great density of 5-HT_{1A} receptors, which are localized on the cell bodies. The activation of these binding sites provides an inhibitory control on ascending serotonergic activity. Therefore, the anti-anxiety effect of such injections probably involves reduced 5-HT function. This variability could also be attributed to the use of different experimental paradigms. As is made clear by Fig. 3a, the anxiolytic-like actions of 5-HT have been found more often in conditioned procedures (64%) than in models based on spontaneous responses (20%). Thus, ethologically based tests may provide results more consistent with the classic 5-HT hypothesis of anxiety.

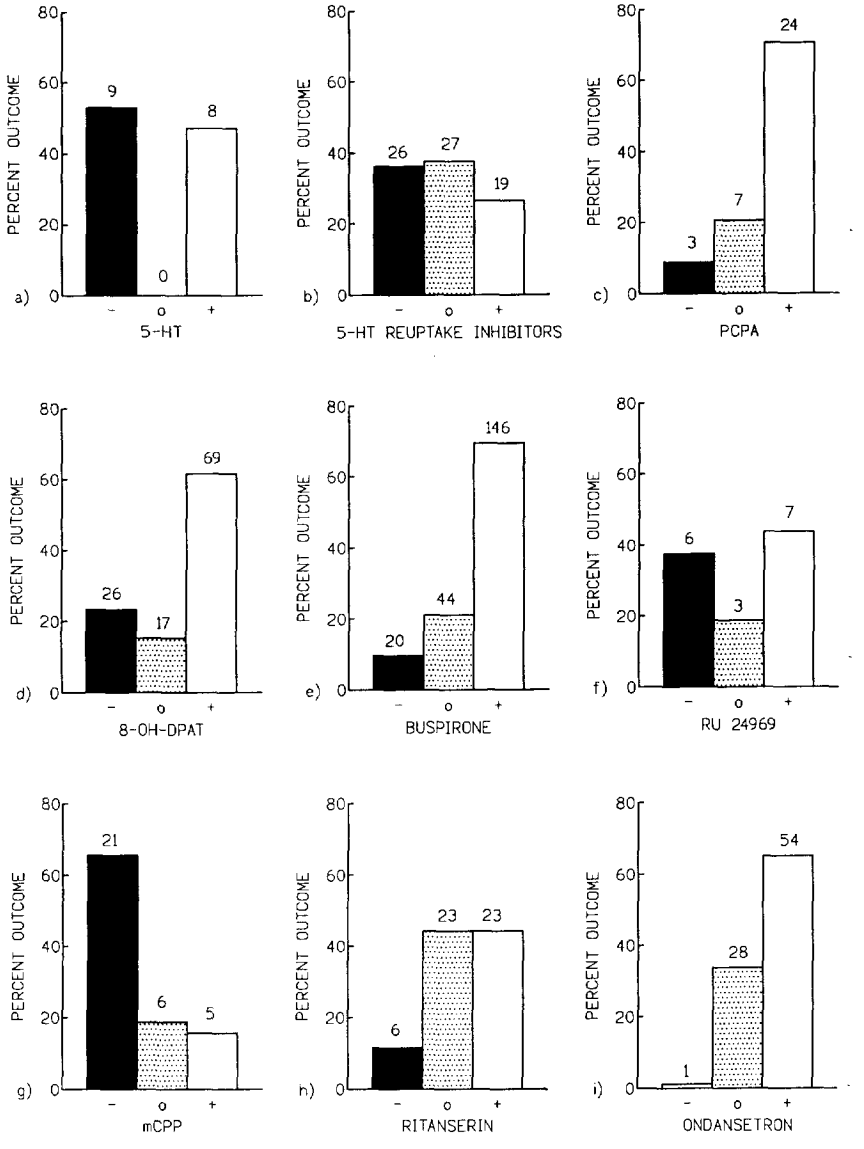

Fig. 2. Illustration of the outcomes of the most studied compounds modulating 5-HT neurotransmission after a single acute dose in animal models of anxiety disorders. −, anxiogenic; +, anxiolytic; o, inactive.

3.1.2. 5-*Hydroxytryptamine Reuptake Inhibitors (SRIs)*

Several lines of evidence indicate that extracellular 5-HT concentration is increased by SRIs (e.g. Auerbach *et al.*, 1989; Rutter and Auerbach, 1993). Various functional measures also indicate that serotonergic function is increased acutely after SRIs are given (Fuller *et al.*, 1991). Consequently, we can expect that the administration of these compounds may modulate fear-related behaviors in animal models of anxiety.

Single acute doses of these agents have been investigated largely in animal models of anxiety. More than 70 experiments have been carried out with SRIs. Incontestably, the most studied agent in this group is imipramine. The initial work of Cook and Davidson (1973) suggested that imipramine was inactive in the Geller–Seifter conflict procedure. However, more recently, authors using either unconditioned models or learning paradigms demonstrated a modification of the animals' emotional reactivity after a single acute dose of imipramine. Anxiogenic-like effects have been recorded in the Geller–Seifter (Sanger, 1992) and Vogel's (McCown *et al.*, 1983; Fontana and Commissaris, 1988) conflict tests, but also in the CER (Sanger, 1990). However, contradictory evidence has also been reported. Indeed, imipramine was found to be anxiolytic by a number of groups (Meert and Colpaert, 1986a; Craft *et al.*, 1988 in the shock–probe burying test in rats; Young and Johnson, 1991c in the light/dark test in mice). Variable effects have also been reported for other SRIs (e.g. amitriptyline, citalopram, fluoxetine). Nearly 38% of the studies failed to detect effects of these compounds, while the same percentage revealed an increase in the anxious responses of the animals (Fig. 2b). Finally, 26% of the investigations found some evidence for an anxiolytic-like action of SRIs. The suggestion that the behavioral effects of these compounds, which are all potential antidepressant drugs, cannot be detected in anxiety models, should be tempered by a number of clinical studies showing a potentiation in anxious symptoms early in the treatment, especially in patients suffering from panic attacks (Gorman *et al.*, 1987; van Praag, 1988; Westenberg and den Boer, 1988; Humble *et al.*, 1989; Giesecke, 1990; Westenberg, 1992).

Analysis of the different experimental procedures used provides evidence that some models are more sensitive than others to the behavioral action of SRIs. As summarized in Fig. 3b, tests based on spontaneous responses more often revealed a modification in the behavioral responses of baselines (70%) than did conditioned paradigms (48%). In addition, results from ethologically based models seem more consistent with the 'classic' hypothesis of 5-HT function in anxiety, as 45% of the experiments revealed an anxiogenic-like profile of SRIs, whereas only 20% of the investigations using conditioned paradigms showed such an activity. It must be emphasized, however, that several models from the first group revealed anxiolytic-like effects of SRIs. Such an action is notably observed with the marble burying test (Njung'e and Handley, 1991b) and the ultrasonic distress vocalization model (Mos and Olivier, 1989; Winslow and Insel, 1991b). Nevertheless, the results from these models must be considered with caution. For example, it is striking that the marble burying test was unable to reveal any anxiogenic-like action of compounds known to possess such an effect, such as yohimbine or β-CCE (Njung'e and Handley, 1991a). Furthermore, the ultrasonic distress vocalization test could not detect the anxiolytic effect of meprobamate (Benton and Nastiti, 1988) and revealed an 'anxiolytic' profile of morphine (Carden and Hoffer, 1990).

3.1.3. p-*Chlorophenylalanine (PCPA)*

Koe and Weissman (1966) and Jequier *et al.* (1967) were the first to show that the administration of PCPA depletes in a specific manner the synthesis of 5-HT by inhibiting the release of tryptophan-hydroxylase, which is involved in the formation of 5-HTP. More recently, Chaput *et al.* (1990) reported that 350 mg/kg of PCPA (during 2 days, with a daily injection) reduced the dorsal hippocampal 5-HT concentration by about 95%.

The evidence that pretreatment (during 3 days, with a daily injection in most cases) with PCPA may modulate animals' emotional reactivity first arose from the study of Tenen (1967), who demonstrated the efficacy of this 5-HT depletor in counteracting the disruption of drinking induced by stress. Since this initial experiment, more than 30 studies have investigated the behavioral effect of PCPA in anxiety models (Fig. 2c). Seventy per cent of these studies revealed an anxiolytic-like action of PCPA, whereas only 9% showed the opposite effect. Although some learning paradigms

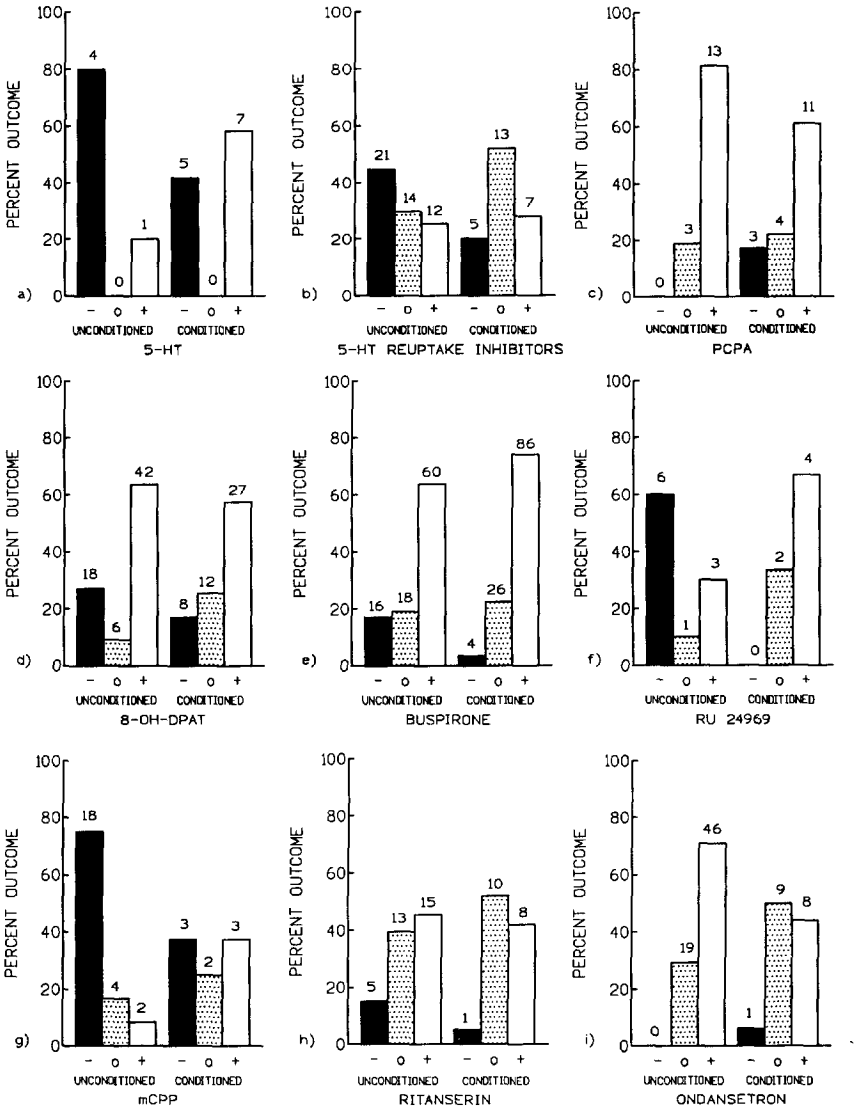

Fig. 3. Illustration of the outcomes of the most studied compounds modulating 5-HT neurotransmission after a single acute dose in animal models of anxiety disorders subdivided into unconditioned procedures and conditioned tests.

(e.g. dorsal periaqueductal gray (DPAG) stimulation) showed PCPA potentiation of anxiety, more than 60% of the experiments using such procedures provided evidence for an anti-anxiety action of this compound (Fig. 3c). It appears, therefore, that most anxiety models can reveal an anxiolytic-like profile of PCPA. Such an effect is consistent with the classic hypothesis of 5-HT in anxiety.

3.2. Behavioral Effects of Direct-acting 5-Hydroxytryptamine Ligands

The focus on the involvement of 5-HT in modulating anxiety disorders coincided with the identification of various 5-HT binding sites in the brain (Hamon *et al.*, 1990). Molecular biological data concerning 5-HT receptor subtypes are increasing exponentially. At the present time, the 5-HT receptor family can be split into seven groups: 5-HT_1-like, 5-HT_2-like, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7. Within the 5-HT_1 family, five subtypes have been described, i.e. 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}. The 5-HT_2 group can be further divided into 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} (Hoyer *et al.*, 1994). Of these, at least the 5-HT_{1A}, 5-HT_{1B}, 5-$HT_{2A,2C}$ and 5-HT_3 receptors have been implicated in anxiety.

3.2.1. 5-*Hydroxytryptamine$_{1A}$ Receptor Ligands*

5-HT$_{1A}$ receptors are located both presynaptically (somatodendritic autoreceptors) on the 5-HT cell bodies in the raphé nuclei of the brainstem, which innervate the forebrain, and postsynaptically, in particular in limbic structures, such as the hippocampus and the amygdala. Activation of presynaptic 5-HT$_{1A}$ receptors results in an inhibition of cell firing and, hence, a decrease in 5-HT neurotransmission, while the activation of postsynaptic 5-HT$_{1A}$ receptors leads to a neuronal inhibition in some limbic structures (e.g. hippocampus, septum). Both of these actions provide a rationale for studying 5-HT$_{1A}$ receptor ligands in animal models of anxiety.

The amount of data that has been accumulated on the effects of 5-HT$_{1A}$ receptor ligands in the various anxiety procedures is vast. The most widely studied agents in this group are the pyrimidinylpiperazine partial agonist buspirone and the aminotetralin full agonist 8-OH-DPAT. Within the past 12 years, the behavioral effects of buspirone have been investigated in about 200 experiments, while more than 100 studies have involved 8-OH-DPAT. Anxiolytic-like properties of buspirone and 8-OH-DPAT have been shown in 71 and 61% of the experiments, respectively (Fig. 2d,e). Reports of an opposite effect have also been found, while several studies could not reveal any modification of baseline levels after the administration of buspirone or 8-OH-DPAT. Numerous previous and recent reviews have discussed extensively the variability in the effects of 5-HT$_{1A}$ ligands, in particular, those observed with the two drugs mentioned above (e.g. de Vry *et al.*, 1991; Handley, 1991; Treit, 1991; Oakley and Tyers, 1992; Barrett and Vanover, 1993; Handley and McBlane, 1993a,b,c). Some authors (Treit, 1991; Oakley and Tyers, 1992) have suggested that pharmacological variables, such as the route of administration or the doses used, may account for some of this variation. For example, Treit (1991) suggested that the outcome of an administration of 5-HT$_{1A}$ receptor agonists into the central nervous system is more reliable than peripheral application. However, detailed examination of the literature indicates that neither route of administration or drug dose can satisfactorily explain these inconsistencies. For instance, both anxiolytic- and anxiogenic-like properties of 8-OH-DPAT have been revealed in a large dose-range (0.001–5 mg/kg).

To explain this variability, most authors have focused on the procedures used and/or the experimental conditions. A common opinion is that traditional conflict paradigms are less sensitive to the action of 5-HT$_{1A}$ agonists than unconditioned models. However, as is made clear by Fig. 3d,e, both types are equal in revealing anxiolytic-like effects of these compounds. A more reliable explanation involves the experimental and/or the environmental conditions used by each laboratory. For instance, the evidence for both anxiolytic and anxiogenic effects of 5-HT$_{1A}$ ligands in the elevated plus-maze is extensive. Handley and McBlane (1993b) recently investigated the possibility of obtaining either effect at will in one laboratory by altering the conditions of the experiments. They showed that increasing illumination from 170 to 785 lux reversed the effect of 8-OH-DPAT from anxiogenic to anxiolytic. Moreover, they demonstrated that these differences cannot be accounted for by any simple differences in strain, maze construction protocol or control baseline. Furthermore, a series of experiments in conflict-type procedures (Costello *et al.*, 1991a; Sanger, 1990, 1992; Wojnicki and Barrett, 1993) has shown that there are conditions under which it is possible to obtain increases in suppressed responding of rats or pigeons with buspirone. For example, Sanger (1990) demonstrated that when responding was suppressed in the presence of a stimulus correlated with *response-independent shock*, buspirone produced a similar behavioral pattern to that seen with benzodiazepines. In contrast, when responding was suppressed by *response-dependent shock*, buspirone did not produce an increase in punished responding of rats. It is obvious from these studies that the behavioral effects of 5-HT$_{1A}$ ligands easily can switch from 'anxiolytic' to 'inactive' or even 'anxiogenic' when small alterations are made in the procedure used. However, further studies with other 5-HT$_{1A}$ ligands are needed in order to establish the generality of the effects of such procedural variations on the behavior change associated with this class of compounds.

3.2.2. 5-*Hydroxytryptamine$_{1B}$ Receptor Agonists*

5-HT$_{1B}$ sites are both presynaptic terminal autoreceptors and postsynaptic receptors. They also exist as heteroceptors on cholinergic neurons (Hoyer and Middlemiss, 1989; Middlemiss and Hutson,

1990; Palacios *et al.*, 1992). Contrary to recent theories based on species variations in pharmacological measurements (Heuring *et al.*, 1987; Hoyer and Middlemiss, 1989), molecular biological data have demonstrated that 5-HT_{1B} receptors exist in numerous species, including humans (Jin *et al.*, 1992).

Owing to the lack of selective ligands, the evidence for the involvement of 5-HT_{1B} sites in anxiety states is limited. A recent preliminary study using mutant mice showed, however, that this receptor plays a determinant role in the modulation of emotional responses (Hen *et al.*, 1993). These authors generated, by homologous recombination, mutant mice lacking the gene encoding 5-HT_{1B} receptor and showed that this binding site is totally absent in the homozygous mutant mice. They further demonstrated a lack of anxiogenic-like responses to RU 24969 (a mixed 5-HT_{1A}/5-HT_{1B} agonist) in mice that do not possess the 5-HT_{1B} receptor subtype. Experiments with RU 24969 using normal mice or rats have shown anxiogenic- as well as anxiolytic-like effects; and, in some studies, the drug was found to be inactive (Fig. 2f). A more detailed analysis of the data indicates that in ethologically based procedures, RU 24969 produced an anxiogenic effect in 60% of the experiments, whereas it was inactive or even showed an anxiolytic-like profile in 10 and 30% of the studies, respectively. In contrast, authors using conditioned paradigms reported an anxiolytic-like action of the compound in 60% of the investigations, or could not reveal any effect in 40% of the experiments. In the first category, studies using the ultrasonic distress vocalization paradigm (Gardner, 1985c; Mos and Olivier, 1989) and the marble burying test (Njung'e and Handley, 1991a) revealed an opposite effect (anxiolytic) of RU 24969 compared with the other tests of this group (elevated plus-maze and social interaction test). Thus, results of both tests should be approached with caution. Data obtained with RU 24969 in traditional conflict procedures are also inconsistent: it was found anxiolytic in the Vogel's conflict test in rat (Korneyev and Seredenin, 1993) and in pigeons (Gleeson *et al.*, 1989) and inactive in the Geller–Seifter paradigm in rats (Deacon and Gardner, 1986) and in monkeys (Gleeson and Barrett, 1990). This variability might be due, at least in part, to the use of various types of schedules in conflict procedures or to species differences (particularly in the '5-HT_{1B}-like' receptors).

3.2.3. 5-*Hydroxytryptamine*$_{2A}$ *and* 5-*Hydroxytryptamine*$_{2C}$ *Receptors*

5-HT_{2A} (previous name: 5-HT_2) receptors are located postsynaptically in many areas of the cortex, the claustrum, some components of the limbic system and parts of the basal ganglia (Hoyer *et al.*, 1986). 5-HT_{2C} (previous name: 5-HT_{1C}) sites are found predominantly in the choroid plexus, as well as the limbic and basal ganglia areas (Pazos *et al.*, 1984). In general, compounds claimed to be 5-HT_{2A} receptor selective show similar affinity for 5-HT_{2C} receptors (Hoyer, 1988, Hoyer *et al.*, 1989), which is not surprising, given the very close structural similarity of these two receptors (Hartig, 1989; Julius *et al.*, 1988). For that reason, the study into their specific roles in anxiety states is limited.

3.2.3.1. 5-*Hydroxytryptamine*$_{2A/2C}$ *receptor agonists*. The most studied drugs of this group are TFMPP and mCPP, two mixed 5-$HT_{2A/2C}$ receptor agonists. The latter has been assessed in more than 30 studies using anxiety models. Most of them described anxiogenic-like effects of mCPP (Fig. 2g). These results are in accordance with clinical data that demonstrated that mCPP had anxiogenic effects in healthy subjects and potentiated anxious reactions in agoraphobic, obsessive–compulsive disorder and panic disorder patients (e.g. Klein *et al.*, 1991; Germine *et al.*, 1992; Pigott *et al.*, 1993). As shown in Fig. 3g, unconditioned paradigms seem particularly sensitive to the anxiogenic effects of mCPP, as 75% of the studies observed a potentiation in the anxious responses in animals. Again, the marble burying test (Njung'e and Handley, 1991b) and the ultrasonic distress vocalization test (Winslow and Insel, 1991a) revealed an opposite effect. The result of the latter study is surprising, as the same authors found an anxiogenic-like action of TFMPP, a compound pharmacologically closed to mCPP. Only eight studies have investigated the effect of mCPP in conditioned procedures (compared with 24 in unconditioned models). Some of these found an anxiogenic-like effect (Kilts *et al.*, 1982 in the Vogel's conflict test; Mansbach and Geyer, 1988 in the fear-potentiated startle reflex test; Martin, 1993 in the shuttle box), while others reported an anxiolytic-like profile (Davis *et al.*, 1986 in the fear-potentiated startle reflex test; Jenck *et al.*, 1989a in the DPAG-stimulation paradigm; Meert, 1989 in the shock–probe burying test) or no effect at all (Davis *et al.*, 1986 in the fear-potentiated startle reflex test; Rocha *et al.*, 1993a in the conditioned taste aversion). Differences in procedures

or methodology might explain some of these discrepancies in the results obtained with these latter tests. Thus, studies using the rat fear-potentiated startle reflex paradigm, in which mCPP was variously found to be anxiolytic, inactive or anxiogenic, used four different administration routes: subcutaneous (anxiogenesis), intrathecal (inactive), intraperitoneal (anxiolysis) and intracerebroventricular (anxiolysis). Results obtained with unconditioned procedures are closer to the clinical results, and this must be taken into account in future investigations of such agents.

3.2.3.2. *5-Hydroxytryptamine$_{2A/2C}$ receptor antagonists*. As with ligands for other 5-HT receptors, studies with 5-HT$_{2A/2C}$ receptor antagonists have produced equivocal results. Figure 2h shows results obtained with ritanserin, the most studied compound in this category. To date, 50 experiments have investigated the behavioral effects of ritanserin in animal models of anxiety. The drug has been found to produce anxiolytic-like effects in more than 40% of the studies, while 12% of them reported evidence for increasing anxiety. Finally, 44% of the reports indicated a lack of activity of the drug in these tests. There is no evidence for a greater sensitivity for one or the other category of models (Fig. 3h). Thus, ritanserin has been reported to have disinhibitory effects, anxiogenic-like effects and/or even no effect in the traditional conflict procedures (Geller–Seifter and Vogel), as well as in exploration tests, such as the elevated plus-maze, the light/dark test or the open-field. It must be emphasized, however, that in one of the models (pigeon conflict paradigm), ritanserin produced reliable and reproducible anti-conflict activity, although the magnitude of the effects is less than those observed in this particular model with benzodiazepines (Gleeson *et al.*, 1989; Brocco *et al.*, 1990).

A similar behavioral profile is seen with other mixed 5-HT$_{2A/2C}$ receptor antagonists, such as ketanserin, cinanserin, ICI 169369, mianserin or the more recently synthesized compound LY 53857. Clinical studies with ritanserin also reported a variety of effects. Thus, it was found to be effective in generalized anxiety disorders (Ceulemans *et al.*, 1985; Arriaga *et al.*, 1986; da Roza Davis *et al.*, 1992), agoraphobia (Humble *et al.*, 1986) and aversive classical conditioning in healthy volunteers (Hensman *et al.*, 1991), but these effects have not been confirmed systematically (Ceulemans, 1985) and do not appear to extend to panic disorder. Indeed, panic may even be exacerbated by ritanserin (Den Boer and Westenberg, 1990). The reasons for this apparent difference in anxiety-modulating action of ritanserin and related compounds remain to be determined. Perhaps the evaluation of the behavioral effects of more selective ligands for either the 5-HT$_{2A}$ or the 5-HT$_{2C}$ site now available (e.g. SR 46349B for the 5-HT$_{2A}$ subtype) could shed light on the differential involvement of these receptors in the modulation of emotional responses.

3.2.4. *5-Hydroxytryptamine$_3$ Receptor Antagonists*

The identification and characterization of 5-HT$_3$ binding sites in brain tissue, in particular in limbic areas such as the amygdala (Kilpatrick *et al.*, 1987; Barnes *et al.*, 1988; Peroutka and Hamik, 1988), and the synthesis of highly selective ligands for these receptors, have been the starting point of numerous studies that investigated the behavioral action of 5-HT$_3$ receptor antagonists in animal models of anxiety.

A number of 5-HT$_3$ receptor antagonists has been examined for potential anxiolytic-like activity in animals: anpirtoline, DAU 6215, GR 68755, granisetron (BRL 43694), MDL 72222, ondansetron (GR 38032F), RS-42359-197, tropisetron (ICS 205-930), WAY 100289, Y-25,130 and zacopride. Among these compounds, ondansetron has been the most studied. More than 75 experiments have investigated the modulatory action of ondansetron on anxiety-related responses in animals. As shown in Fig. 2i, 66% of the results provided evidence for an anxiolytic-like action of this compound, while 33% of them did not observe any modification in the animals' responses. Only one study reported an anxiogenic action of ondansetron (Gleeson *et al.*, 1989). This is surprising in view of the outcomes of the other drugs mentioned in Sections 3.1.1–3.2.3, which all reported clear evidence for both anxiolytic- and anxiogenic-like effects. More precisely, authors using ethologically based tests reported an anxiolytic-like effect in 72% of the cases (Fig. 3i). Interestingly, most of these studies revealed a positive effect over a wide dose range, with minimum dose levels in the nano/picogram range. Furthermore, ondansetron mimics the anxiolytic activity seen with benzodiazepines. However, they differ from the latter as they lack the sedative and muscle relaxant effects of benzodiazepines and fail to antagonise electric shock and leptazol-induced convulsions (Costall *et al.*,

1988e). In addition, unlike benzodiazepines, ondansetron and 5-HT_3 receptor antagonists, in general, have been found to enhance performance in tests of cognition (Costall *et al.*, 1992b).

As shown in Fig. 3i, however, in some studies using these same models (28%), ondansetron has failed to show anxiolytic-like effects. Obviously, some methodological problems with procedures involving spontaneous behavior influence the data obtained. For example, negative results have been observed in the light/dark choice paradigm when rats were the experimental subjects (Morinan, 1989; Kshama *et al.*, 1990). Furthermore, ondansetron was found to be inactive in a few studies using the elevated-plus maze. As mentioned in the Introduction, these differences evidently are produced by a multitude of, perhaps small, methodological differences that do not necessarily become clear, even with the most detailed scrutiny of published reports. In addressing the problem raised by the plus-maze data, Handley and McBlane (1993b) recently questioned whether such differences could involve genetic variability in rats or even investigation, as minor stressors often affect positively motivated behavior.

When the reliance has been placed on conditioned procedures, the potential anti-anxiety actions of 5-HT_3 receptor antagonists have been observed in only a few studies. For instance, ondansetron was found to be anxiolytic in 44% of the investigations using conditioned procedures, whereas it was ineffective in 50% of such studies (Fig. 3i). Costall and Naylor (1991) recently have suggested that the models failing to show anxiolytic-like effects of 5-HT_3 receptor antagonists may be insensitive to novel pharmacological mechanisms involved in anxiety. Alternatively, Barrett and Vanover (1993) speculated that the specific conditions of the models revealing an anxiolytic-like action of these agents may be sensitive to a behavioral effect other than an anxiolytic effect. No matter what approach is used, only positive effects in clinical trials can help to decide which of the animal models are the best predictors of these effects. Even less is known, from a clinical point of view, about possible anxiolytic effects of 5-HT_3 receptor antagonists. Whilst a number of open and placebo-controlled studies have either been carried out or are under way since 1986 (Schweizer and Rickels, 1991), only one has been published so far. Lecrubier *et al.* (1993) recently reported that tropisetron is efficacious in the treatment of generalized anxiety disorder. However, no data from any other of these studies have been made available yet, apparently because 5-HT_3 receptor antagonists do not show significant treatment differences between drugs and placebo.

In conclusion, in the case of 5-HT_3 receptor antagonists, both types of animal models appear to have little problem finding an anxiolytic-like effect. Yet, this does not show up in the clinical tests. Insofar as this is true, it indicates that we can get good agreement (in the published literature at least) regarding a particular effect in animal models, yet not predict good clinical efficacy. This suggests (a very practical outcome) that more favorable attention be given to the publication of nonsignificant effects, and, second (of more scientific interest) that we continue and, in fact, enhance our efforts to understand why animal models sometimes predict and why they sometimes do not.

4. PERSPECTIVES AND SUMMARY

It is obvious from the data discussed above and summarized in the table that 5-HT-related drugs have equivocal anxiety-modulating properties in animal models. The reasons for this variability in drug effect remain in great part unknown, but certainly include some factors (such as species differences or sex of the animals), which have been widely assessed in many recent reviews (e.g. Barrett and Gleeson, 1991; Briley *et al.*, 1991; Costall and Naylor, 1991; de Vry *et al.*, 1991; Handley, 1991; Treit, 1991; Oakley and Tyers, 1992; Wettstein, 1992; Barrett and Vanover, 1993; Handley and McBlane, 1993a,b,c; Hughes, 1993; Schreiber and de Vry, 1993). Much of the current interest in this field is focussed on differential responsivity of various animal paradigms after 5-HT drug challenge. As reviewed in the present paper, agents triggering the release or increasing the availability of 5-HT, such as the neurotransmitter itself, 5-HT reuptake inhibitors, RU 24969 or mCPP usually promoted anxiety responses in ethologically based procedures, whereas they were inactive or even decreased emotional reactivity in traditional learning paradigms. Clearly, the results obtained in unconditioned models seem more consistent with the classic 5-HT hypothesis of anxiety, which assumes that 5-HT activity enhances anxiety. Hence, these results question the validity of conditioned paradigms, in particular conflict tests, in the investigation of the behavioral effects of drugs known

to possess anxiogenic properties, including compounds stimulating 5-HT neurotransmission. As mentioned by Treit (1985), one of the problems with conflict tests is that significant anticonflict effects have been produced by drugs that either produce or potentiate anxious responses in humans, such as amphetamine (Lehman and Ban, 1971; McMillan, 1973; Miczek, 1973; McKearney and Barrett, 1975), LSD (Commissaris and Rech, 1982), caffeine (Beer *et al.*, 1972), isoproterenol (Patel and Malick, 1980) or the β_2-adrenoceptor antagonists idazoxan and yohimbine (Sanger, 1991). Obviously, the data from these latter studies, as well as some that reported anxiolytic-like action of drugs stimulating the 5-HT system, confirm Treit's assumption (Treit, 1985) that conflict tests are not totally selective, and strongly suggest that these paradigms are 'only' animal models of 'anxiolytic' drugs. This is problematic when considering the behavioral studies of newly synthesized drugs, as we do not necessarily expect one or the other effect of these compounds. Thus, to detect false-positive effects in conflict procedures, authors should complete their studies by adding results obtained in models able to reveal both anxiolytic- and anxiogenic-like properties of drugs. This is less likely to happen, however, when it is required that conditioning task researchers should adopt ethological tasks, or vice versa.

In contrast, data showing anxiolytic-like effects with compounds interacting selectively with 5-HT_{1A} receptors, or even with drugs blocking 5-$HT_{2A/2C}$ binding sites, did not provide evidence that one particular category of models is involved in one particular effect. As with benzodiazepine receptor agonists, both conditioned and unconditioned tests revealed, in the majority of cases, an anxiolytic-like action of 5-HT_{1A} full or partial agonists, even if these effects were more variable and smaller in magnitude when compared with standard anxiolytics. As it has been assessed in previous reviews (see references above), these phenomena are not discussed in the present paper. Furthermore, Treit's assertion that only the light/dark choice paradigm, the social interaction test and the fear-potentiated startle model show "good sensitivity to both benzodiazepine and 5-HT_{1A} agonists" is unacceptable, as both 8-OH-DPAT and buspirone were found to have anxiolytic, anxiogenic or null effects in all three models (see Table 1). At this time, only the conflict procedure in pigeons revealed invariably an anxiolytic-like action of 5-HT_{1A} compounds, and this effect is comparable to that obtained with benzodiazepines (Barrett and Vanover, 1993). However, these results must be confirmed by laboratories other than that of Barrett's group, which investigated in great part the effects of these drugs in the pigeon's conflict test.

Anxiolytic-like effects of 5-HT_3 receptor antagonists have also been established only in selected test procedures. Consideration of the distinction between ethologically based tests, and 'conventional' testing procedures indicates that these effects only occur in the first mentioned models. In these, only the light/dark choice paradigm in mice constantly showed an anxiolytic-like action of these agents.

Variation in the effects of 5-HT drugs in animal models of anxiety could reflect differences in the degree to which the models themselves represent fear or anxiety (Treit, 1991). It is obvious that all models are not equivalent. Thus, models based on reactions to non-painful stressors or on spontaneous responses, in particular exploration procedures or the social interaction test, may reflect a type of anxiety linked with uncontrollable stress ('depressive anxiety'), as animals are exposed by force to a novel and/or aversive environment from which they cannot escape, while those based on conditioning and/or reactions to painful stressors, especially the Geller–Seifter and Vogel's conflict tests, may reflect a type of anxiety associated with controllable aversive events ('anticipatory anxiety') (Gardner, 1986; Soubrié and Thiébot, 1986). Thus, 5-HT modulation at 5-HT_3 target sites might be selectively involved in situations dealing with the so-called 'depressive anxiety', whereas 5-HT_{1A}, and perhaps 5-$HT_{2A/2C}$ receptors, may be involved in both types of anxiety-related responses. This view is akin to Gardner's, Handley's and McBlane's assumption of the existence of multiple 5-HT mechanisms in anxiety (Gardner, 1986; Handley, 1991; Handley and McBlane, 1991).

To shed light on the complex story concerning the involvement of 5-HT neurotransmission in the regulation of emotional reactivity, clinical investigations more and more hold the key. Several 5-HT-interacting compounds are now in various phases of clinical development, in particular, drugs acting selectively at 5-HT_{1A} sites (e.g. S20499, MDL 73005EF, WY-50,324). Information from clinical trials should permit future experimental research in this area to focus more precisely on the behavioral paradigms that are particularly sensitive to the effects of 5-HT drugs and on the 5-HT receptor subtypes that are specifically involved in the modulation of fear-related behaviors.

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