Drugs of the Future 1998, 23(9): 955-965

CCC: 0377-8282/98

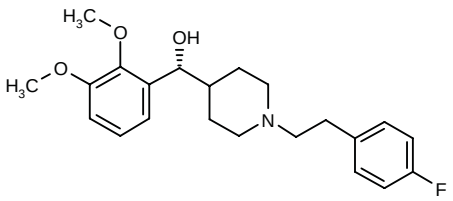
MDL-100907

5-HT$_{2A}$ Antagonist
Antipsychotic

M-100907

(+)-(*R*)-1-[1-[2-(4-Fluorophenyl)ethyl]piperidin-4-yl]-1-(2,3-dimethoxyphenyl)methanol

(+)-(*R*)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol



$C_{22}H_{28}FNO_3$ Mol wt: 373.4720

CAS: 139290-65-6
CAS: 139290-69-0 (as racemic)

EN: 179327

Synthesis

MDL-100907 can be obtained by several different ways:

1) The condensation of piperidine-4-carboxamide (I) with 2-(4-fluorophenyl)ethyl bromide (II) by means of K_2CO_3 in hot DMF gives 1-[2-(4-fluorophenyl)ethyl]piperidine-4-carboxamide (III), which by reaction with refluxing $POCl_3$ is converted into the nitrile (IV). The reduction of (IV) with diisobutyl aluminum hydride (DIBAL) in THF affords the aldehyde (V), which by condensation with 1,2-dimethoxybenzene (veratrole) (VI) by means of BuLi in THF affords racemic MDL-100907 (VII). The esterification of (VII) with (*S*)-2-methoxy-2-phenylacetic acid (VIII) by means of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) in refluxing $CHCl_3$ affords a mixture of diastereomers that is submitted to column chromatography over silica gel to afford the pure diastereomer (IX). Finally, (IX) is saponified with K_2CO_3 in methanol/water (1). Scheme 1.

2) Racemic MDL-100907 (VII) can also be obtained by reaction of piperidine-4-carboxylic acid (X) with di-*tert*-butyl dicarbonate (XI) by means of NaOH in *tert*-butanol/water, giving piperidine-1,4-dicarboxylic acid 1-mono-*tert*-butyl ester (XII), which is treated with *N*,*O*-dimethylhydroxylamine (XIII) and carbonyldiimidazole (CDI) in dichloromethane to afford the methoxy(methyl)amide (XIV). The condensation of (XIV) with veratrole (VI) by means of BuLi in THF gives 4-(2,3-dimethoxybenzoyl)-piperidine-1-carboxylic acid *tert*-butyl ester (XV), which is decarboxylated by means of trifluoroacetic acid, yielding ketone (XVI). The condensation of (XVI) with 2-(4-fluorophenyl)ethyl bromide (II) by means of K_2CO_3 in DMF affords 1-(2,3-dimethoxyphenyl)-1-[1-[2-(4-fluorophenyl)-ethyl]piperidin-4-yl]methanone (XVII). Finally, this compound is reduced with $NaBH_4$ in methanol (1). Scheme 2.

3) Racemic MDL-100907 (VII) can also be obtained as follows: The reaction of piperidine-4-carboxylic acid ethyl ester (XVIII) with the already mentioned bromide (II) by means of K_2CO_3 as before gives 1-[2-(4-fluorophenyl)ethyl]piperidine-4-carboxylic acid ethyl ester (XIX), which is treated with *N*,*O*-dimethylhydroxylamine (XIII) to afford carboxamide (XX). The condensation of (XX) with veratrole (VI) by means of BuLi as before yields the ketonic precursor (XVII), which is finally reduced as before (2). Scheme 3.

4) [^{11}C]-Radiolabelled MDL-100907 can be obtained as follows: Racemic MDL-100907 (VII) is treated with L-Selectride in THF, yielding racemic 1-[1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl]-1-(3-hydroxy-2-methoxyphenyl)methanol (*rac*-XXI), which is submitted to semipreparative HPLC separation over Chiracel OD, affording pure (*R*-XXI). Finally, this compound is methylated with [^{11}C]-methyl iodide and KOH in HMPA (2). Scheme 3.

If this methylation is performed with nonlabeled methyl iodide, MDL-100907 is obtained.

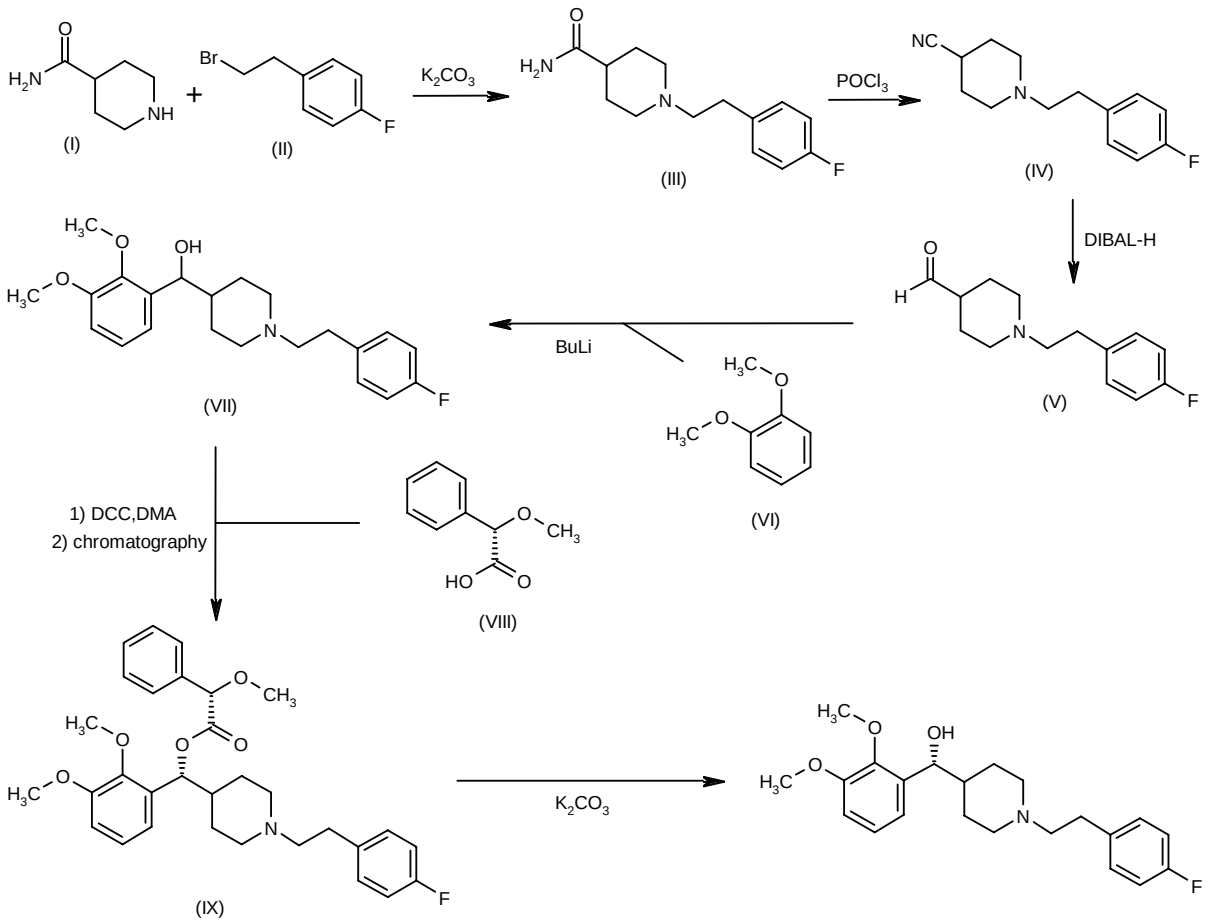
5) The radiolabeling of phenol (*R*-XXI) can also be performed with better yields using [^{11}C]-methyl trifluoromethanesulfonate (XXII) as methylating agent. Triflate (XXII) is obtained by reaction of silver triflate with [^{11}C]-methyl iodide (3). Scheme 3.

Description

Crystals, m.p. 112-3 °C.

L.A. Sorbera, J. Silvestre, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of MDL-100907



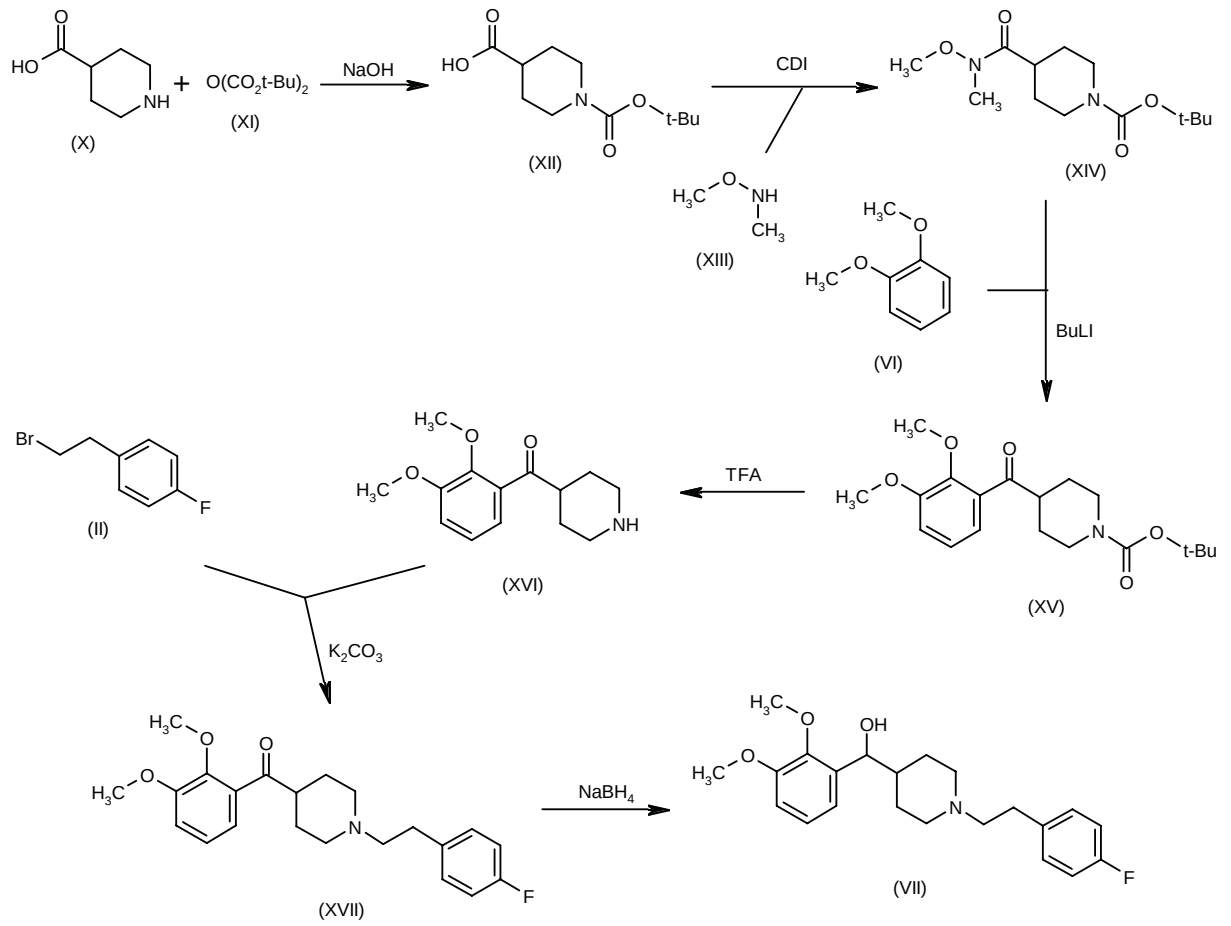
Introduction

The serotonergic system is believed to be involved in a range of CNS disorders (*e.g.*, depression, anxiety, sleep), feeding disorders and drug abuse (4). Since it was observed that lysergic acid diethylamide (LSD) could induce schizophrenia-like effects in humans, an involvement of the serotonergic system in the pathophysiology of schizophrenia was already suggested in the 1950s (5). Physiological responses to serotonin (5-HT) are known to be mediated by 5-HT receptors which have been classified into seven distinct families or classes according to structural diversity and particular transduction mechanisms with multiple receptor subtypes comprising some of the classes (6, 7). One such receptor, 5-HT_{2A}, is widely distributed in the CNS and has been proposed to be a putative target for atypical antipsychotic drugs (8-10).

It is widely accepted that schizophrenia is due to excessive dopaminergic activity in the CNS and major pharmacological tools against schizophrenia, e.g., the typical antipsychotic haloperidol, act by blocking central dopamine D_2 receptors. These compounds have been shown to be effective in the treatment of positive symptoms of schizophrenia. However, dopamine D_2 blockade is generally ineffective for treating negative symptoms and has been associated with extrapyramidal side effects (EPS) observed with the use of these compounds. Dopaminergic and serotonergic systems are closely connected and functionally highly interactive (11, 12) and there is considerable evidence suggesting that 5-HT can interact with the dopaminergic system of the midbrain.

Atypical antipsychotics are compounds shown to be effective in treating a number of psychotic disorders, including schizophrenia, with an improved efficacy for negative symptoms and a low liability for EPS. Such compounds act on a wide range of neurotransmitter receptors other than dopamine D_2, such as serotonin 5-HT_2, α-adrenergic, muscarinic, histamine and dopamine D_4 receptors (13, 14), but it is thought that their "atypical" profile (low EPS liability and efficacy against negative

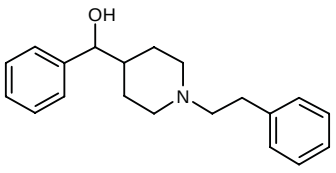
Scheme 2: Synthesis of the Intermediate (VII) (racemic MDL-100907)



(X) (XI) (XII) (XIII) (XIV) (VI) (II) (XVI) (XV) (XVII) (VII)

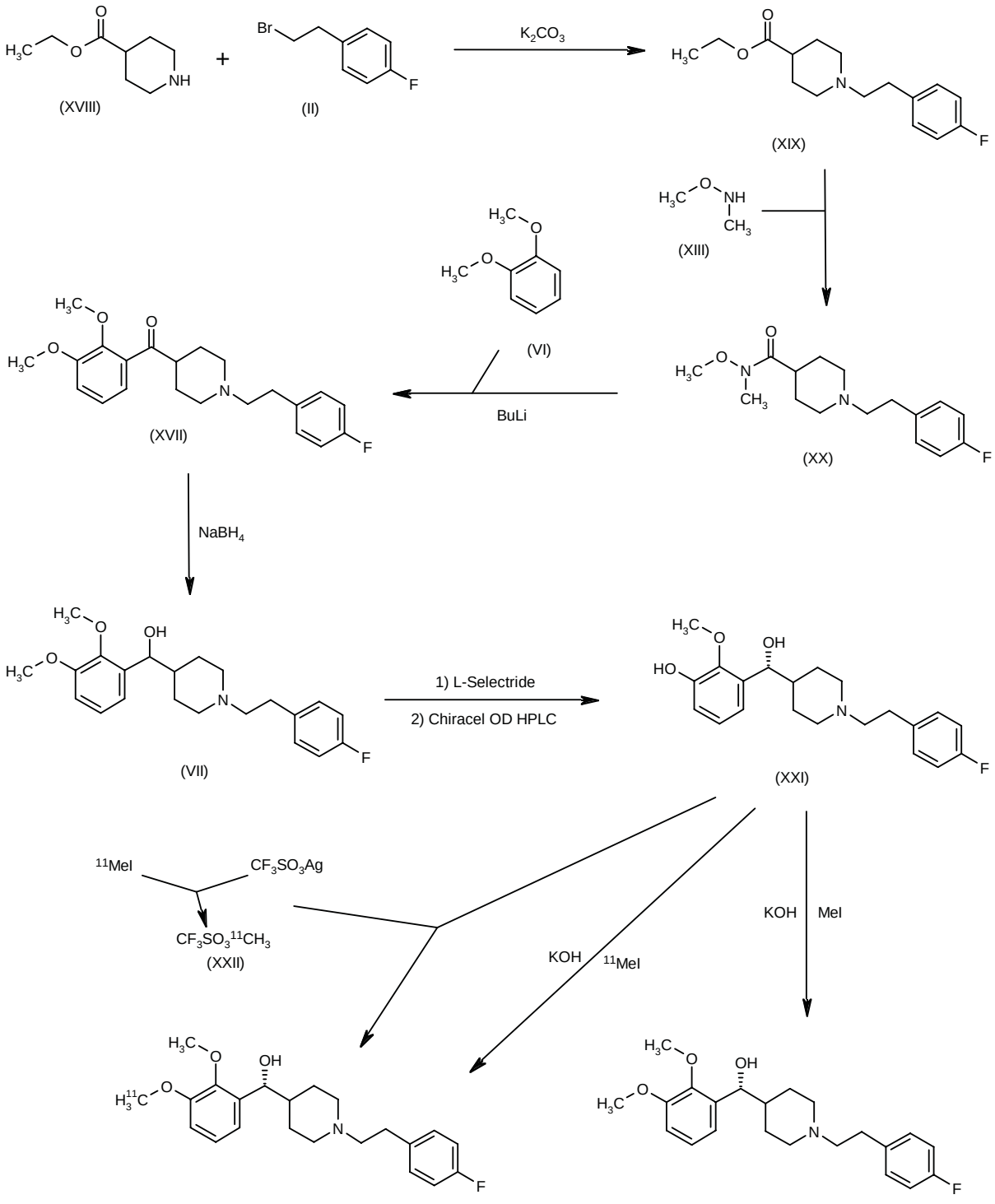
symptoms) is a consequence of their ability to act preferentially through the 5-HT_2 and not the D_2 receptor (15). Since atypical antipsychotics appear to act mainly through the serotonergic system, it is thought that the 5-HT_2 receptor plays a role in schizophrenia by modulating dopaminergic neurotransmission. Thus, 5-HT_2 receptor antagonism may be a critical factor in the "atypical" profile of these antipsychotics (15). Indeed, clinical data indicates that 5-HT_2 antagonism is associated with low EPS liability and improvement in negative symptoms of schizophrenia (16). Atypical antipsychotics preferentially acting via 5-HT_2 receptors would have low EPS liability, in part due to the reduction in abnormally increased dopamine synthesis and release associated with schizophrenia. There are a number of putative antipsychotic drugs (*e.g.*, risperidone, olanzapine, quetiapine) that act mainly through 5-HT_{2A} receptors. Hence, considerable attention has been focused on combining 5-HT_{2A}/D_2 antagonistic effects, with preferential 5-HT_{2A} antagonism, in the development of new antipsychotics.

Scientists at Hoechst Marion Roussel concentrated their efforts on modifying haloperidol in order to increase the distance between the 4-piperdinyl-phenyl ring and the piperidine nitrogen to a distance similar to that found in clozapine. A series of structural modifications led to the synthesis of the first selective 5-HT_{2A} antagonist, MDL-11939 [I] (glemanserin) (17). Further resolution of the chiral center of MDL-11939 and determination of the preferred aryl substituents led to the rationale for synthesis of a potent, selective 5-HT_{2A} receptor antagonist, MDL-100907 (18).



[I]

Scheme 3: Synthesis of MDL-100907 and [^{11}C]-MDL-100907



Pharmacological Actions

MDL-100907 is a highly selective 5-HT$_{2A}$ receptor antagonist (19-21) which has been shown to have a pattern of neurochemical, electrophysiological and behavioral effects consistent with atypical antipsychotic activity (19, 20, 22-25). MDL-100907 has the highest affinity for the 5-HT$_{2A}$ receptor as compared to other receptor sites.

Table I: Receptor binding profile of MDL-100907.

Receptor	Ligand	Tissue	K_i(nM)	Reference
α_1-Adrenergic	[^{3}H]prazosin	rat cortex	128	25
α_2-Adrenergic	[^{3}H]rauwolscine	rat cortex	>1000*	25
β-Adrenergic	[^{3}H]dihydroalprenolol	rat cortex	>10,000*	25
Benzodiazepine	[^{3}H]flunitrazepam	bovine cortex	>10,000*	25
Dopamine D_1	[^{3}H]SCH-23390	human cloned receptor	5300	25
Dopamine D_2	[^{3}H]spiperone	human cloned receptor	2250	25
	[^{3}H]spiperone	rat striatum	4265	58
Dopamine D_3	[^{3}H]spiperone	rat cloned receptor	6700	25
Dopamine D_4	[^{3}H]spiperone	human cloned receptor	540	25
Dopamine D_5	[^{3}H]SCH-23390	human cloned receptor	10000	25
$GABA_A$	[^{3}H]muscimol	rat cortex	>100,000*	25
Glycine	[^{3}H]strychnine	rat brainstem	>100,000*	25
Histamine H_1	[^{3}H]pyrilamine	rat cortex	>1000*	25
Serotonin 5-HT_{1A}	[^{3}H]8-OH-DPAT	rat cortex	>10,000*	25
Serotonin 5-HT_{1D}	[^{3}H]5-HT	cow striatum	>1000*	25
Serotonin 5-HT_{1F}	[^{125}I]LSD	rat cloned receptor	>1000*	25
Serotonin 5-HT_{2A}	[^{3}H]ketanserin	human cloned receptor	1.5	25
	[^{3}H]ketanserin	rat cortex	1.37	25
	[^{3}H]ketanserin	rat frontal cortex	0.59	50
	[^{3}H]ketanserin	rat frontal cortex	0.7	51
	[^{125}I]LSD	cloned receptor	0.34	25
	[^{3}H]ketanserin	monkey cortex	0.36	25
	[^{3}H]ketanserin	transfected fibroblast cell line	0.66	25
	[^{3}H]MDL-100907	rat frontal cortex	1.0	51
Serotonin 5-HT_{2C}	[^{3}H]mesulergine	transfected fibroblast cell line	88.0	25
	[^{3}H]mesulergine	pig choroid plexus	107	50
Serotonin 5-HT_3	[^{3}H]GR65630	NG108-15 cell membranes	>10000 *	25
Serotonin 5-HT_4	[^{3}H]GR-113808	rat striatum	>100,000*	25
Serotonin 5-$HT_{5A\&B}$	[^{125}I]LSD	rat cloned receptor	>1000*	25
Serotonin 5-HT6	[^{3}H]LSD	cloned receptor	>5000	52
Serotonin 5-HT7	[^{125}I]LSD	rat cloned receptor	226	25
L-type calcium channel	[^{3}H]nitrendipine	rat heart	>10,000*	25
Muscarinic (unselective)	[^{3}H]quinuclidinyl benzylate	rat brain	>10,000*	25
Muscarinic M_2	[^{3}H]N-methyl-scopolamine	human	>10,000*	25
Muscarinic M_3	[^{3}H]N-methyl-scopolamine	human	>10,000*	25
Opiate	[^{3}H]naloxone	rat cortex	>10,000*	25
σ	[^{3}H]PPP	rat brain	87.0	25
Tachykinin NK_1	[^{125}I]Bolton-Hunter Subs. P	guinea pig lung	>10000*	25

*IC_{50}(nM). Source: Prous Science MFLine database.

The affinities of MDL-100907 for a number of neurotransmitter receptors are shown in Table I.

The safety and functional selectivity of MDL-100907 for the 5-HT_{2A} receptor have been extensively examined in several preclinical trials. MDL-100907 was found to bind with high affinity to the 5-HT_{2A} receptor in several tissue and cell types, including rat cortical membranes, monkey frontal cortex, several cell lines and cells transfected with the human cloned receptor. MDL-100907 reversed the 5-HT-stimulated inositol phosphate accumulation in fibroblast cells (NIH 3T3) expressing either the rat 5-HT_{2A} or 5-HT_{2C} receptor with IC_{50}s of 0.6 nM and 770 nM, respectively, thus demonstrating the functional 5-HT_{2A} antagonism and selectivity of the compound (25). Functional 5-HT_{2A} antagonism was further demonstrated when the ability of MDL-100907 to antagonize the discriminative effects of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOI), a 5-$HT_{2A/2C}$ receptor agonist capable of inducing some psychotic symptoms, was investigated. Rats trained to discriminate DOI (0.63 mg/kg i.p.) from saline with a standard two-level food reinforced operant procedure in a drug discriminant paradigm were pretreated 45 min before testing with the antagonists. MDL-100907 was found to potently inhibit the DOI-discriminant effect with an ED_{50} of 0.0006 mg/kg. These results demonstrate that the effects of DOI are mediated through 5-HT_{2A} receptors and suggest that antagonism of 5-HT_{2A} receptors may be involved in the actions of atypical psychotics (26). In addition, electrophysiological studies have shown that exposure of rat interneurons from piriform cortex slices to MDL-100907 (1-10 nM) results in a reversible parallel shift to the right of the 5-HT dose

Table II: Serotonin 5-HT$_{2A}$ receptor affinity, selectivity and specificity ratios of K_i (nM) for typical and atypical antipsychotics with respect to those receptors suggested to be associated with psychotic disorders.

Compound	5-HT$_{2A}$	5-HT$_{2A}$/5-HT$_{2C}$	5-HT$_{2A}$/D$_2$	5-HT$_{2A}$/D$_4$	5-HT$_{2A}$/σ	Ref.
MDL-100907	0.70	0.008	0.0003	0.0013	0.008	25, 51
Risperidone	0.65	0.025	0.17	0.09	ND	53, 54
Ritanserin	7.84	1.13	0.16	ND	ND	55
Ketanserin	2.83	0.052	0.0058	0.00098	ND	55, 56
Amperozide	16	0.014	0.03	0.028	0.0085	57
Clozapine	14.9	1.86	0.28	0.41	0.00047*	53, 54, 58-62
Haloperidol	54.2	0.017	37.4	7.69	3.0*	53, 54, 58-62
S-16924	4.47	0.55	0.61	0.54	ND	53, 60, 61

*Ratio obtained from IC_{50} (nM) values. Source: Prous Science MFLine database.

response curve (K_d = 1.17). These results further demonstrate that the 5-HT$_{2A}$, and not the 5-HT$_{2C}$, receptor is responsible for 5-HT-induced excitation (27).

MDL-100907 is one of the most specific and selective compounds acting on the 5-HT$_{2A}$ receptor. Table II shows both selectivity and specificity ratios for MDL-100907, 5-HT$_{2A}$ antagonists and other typical and atypical antipsychotic compounds for those receptors thought to be closely involved in schizophrenia. MDL-100907 was shown to have a 60- to 300-fold higher affinity for 5-HT$_{2A}$ receptors than 5-HT$_{2C}$ receptors.

The low EPS liability of MDL-100907, as well as its potential clozapine-like antipsychotic activity, have been demonstrated by neurochemical studies in rats and mice. Acute administration of MDL-100907 (1.0 mg/kg i.p.) or clozapine (20 mg/kg i.p.) 20 min prior to insertion of the recording electrode suppressed amphetamine-induced slowing of ventral tegmental A10 region dopaminergic neurons and slightly increased the number of active A9 and A10 dopamine neurons. Chronic administration of either agent for 21 days resulted in a reduction in the number of spontaneously active A9 and A10 dopamine neurons, while haloperidol treatment (0.5 mg/kg/day i.p.) decreased activity in both regions. Moreover, dopamine metabolism in the striatum or nucleus accumbens was not increased by acute or chronic MDL-100907 treatment. Administration of a dopamine releaser/uptake blocker (amfonelic acid; 2.5 mg/kg s.c.) 5 min prior to haloperidol treatment (1.0 mg/kg i.p.) increased dopamine metabolism, demonstrating a characteristic effect of typical antipsychotics. In contrast, this increase was not observed when MDL-100907 (1.0 mg/kg i.p.) or clozapine (25 mg/kg i.p.) were given after amfonelic acid treatment (20).

An electrophysiological study, describing a potential model for screening atypical antipsychotic drugs involving the glutamatergic system, demonstrated that 15-min pretreatment with MDL-100907 (20 and 100 nM) effectively abolished phencyclidine (PCP)-induced suppression of NMDA responses in rat medial prefrontal cortex pyramidal neurons. Treatment with clozapine at a concentration of 100 nM resulted in only a 50% reduction in NMDA responses, while haloperidol or raclopride were ineffective. These results further support that MDL-100907 may be an effective agent in inhibiting those PCP-induced psychotomimetic conditions mediated by NMDA receptor blockade in addition to schizophrenic symptoms (28).

In vivo studies using MDL-100907 were performed to examine the mechanism of regulation of dopamine release induced by indirect agonists such as amphetamines. Administration of MDL-100907 (1 mg/kg s.c.) to rats resulted in a significant 46% reduction in the increase of extracellular levels of striatal dopamine induced by an amphetamine analog, MDMA (20 mg/kg s.c.) without altering basal dopamine release. When MDL-100907 was infused (0.1 and 1.0 μM) into the striatum with a dialysis probe, a dose-dependent decrease in MDMA-induced dopamine efflux was observed. However, superfusion of MDL-100907 (1 μM) striatal slices had no effect on MDMA-induced efflux of preloaded [^{3}H]-dopamine. Thus, 5-HT$_2$ receptors may be involved in the mediation of MDMA-induced increases in dopaminergic activity (29).

The effects of MDL-100907 on basal and MK-801-induced changes in regional dopaminergic activity have also been reported. MDL-100907 (1 mg/kg i.p.) was found to inhibit MK-801 (2 mg/kg i.p.)-induced dopamine efflux in the nucleus accumbens without affecting basal release. However, MDL-100907 increased dopamine release in medial prefrontal cortex even when infused directly (1 μM), indicating possible involvement of local receptors. Moreover, the effects of MDL-100907 were inhibited when 5-HT stores were depleted in the medial prefrontal cortex by treatment with a synthesis blocker, p-chlorophenylalanine. From these results, the authors concluded that MDL-100907 antagonizes MK-801-induced effects through interference of mesolimbic dopamine release and enhancement of serotonergic action (30).

Recently, it has been proposed from the results of a preclinical study that the antipsychotic efficacy exerted by 5-HT$_{2A}$ receptor blockade is dependent on increased serotonergic tone. Results demonstrated that MDL-100907 (0.01-1.0 mg/kg) inhibited MK-801-induced hyperlocomotion in mice, an effect which was suppressed in mice pretreated with PCPA and dose-dependently restored by 5-hydroxytrytophan administration to replace the depleted endogenous 5-HT. Similar but less potent effects were detected in animals treated with nonselective atypical antipsychotic such as clozapine or olanzapine and no effect was observed in animals receiving dopamine antagonists (31).

Table III: Comparative in vivo potencies in mice (ED_{50} mg/kg) of MDL-100907 and other compounds with proven antipsychotic properties.

Compound	Head-twitches	Hyperactivity	Climbing	Sedation	Ref.
MDL-100907	0.03[a]	0.08[a]	>32[a]	7.2[a]	25
Risperidone	0.03[b]	0.045[a]	0.13a	0.5[a]	25, 63-66
	0.007[a]	0.81[b]			
Ritanserin	0.82[a]	0.44[a]	17.8[a]	>16[a]	25
Amperozide	20.6[a]	0.26[a]	7.5[a]	6.7[a]	25
Clozapine	1.8[a]	0.57[a]	6.8[c]	2.5[a]	25, 63-69
	6.6[b]	3.13[b]	16.0[a]	11.3[b]	
			20.5[b]		
Haloperidol	4.0[b]	0.09[a]	0.041[c]	0.63[b]	25, 64-72
	4.3[a]	0.14[b]	0.542[a]	0.70[a]	
			0.595[b]		

Head twitches = MeODMT-induced inhibition; hyperactivity = AMPH-induced locomotor activity inhibition; climbing = APO-induced inhibition; sedation = spontaneous locomotor activity inhibition. [a]i.p., [b]p.o., [c]s.c. administration. Source: Prous Science MFLine database.

The antipsychotic effects of MDL-100907 may be partially explained by the results of a study which illustrated that 5-HT_{2A} receptors exert some degree of basal control over extrapyramidal and limbic neurotensin systems. Rats were administered either MDL-100907 (1 mg/kg), clozapine (20 mg/kg), haloperidol (0.5 mg/kg) or the vehicle 1, 2, 4 and 5 times with a 4-h interval between i.p. injections. MDL-100907 and clozapine had similar effects on neurotensin-like immunoreactivity in anterior caudate structures in contrast to the 2-3 times greater increase in levels observed in haloperidol-treated animals. Similarly, haloperidol was much more potent in posterior caudate structures; however, all three agents had similar actions in the nucleus accumbens. MDL-100907 and clozapine did not alter neurotensin-like immunoreactivity in other extrapyramidal and limbic-associated brain structures while haloperidol increased levels after 1-2 and 4 administrations in extrapyramidal and limbic regions, respectively (32).

MDL-100907 has been used to investigate the involvement of the 5-HT_{2A} receptor in a wide variety of physiological events. One such study, in which rat cortical brain slices were perfused with MDL-100907 (1 or 10 mcM), ketanserin (1, 10 or 100 μM) and ritanserin (10 μM) under K^+-evoked release conditions, demonstrated that GABA release was inhibited by 12-31% in the presence of these receptor antagonists, suggesting that 5-HT via the 5-HT_{2A} receptors facilitates GABA release in the brain (33).

It is also worth noting that in vitro studies using MDL-100907 have shown that 5-HT_{2A} receptors may be involved in the mobilization of polyunsaturated fatty acids such as arachidonic acid (AA; 20:4n6) and docosahexaenoic acid (DHA; 22:6n3). Rat C6 glioma cells expressing 5-HT_{2A} receptors were prelabeled with [^{3}H]-AA and [^{14}C]-DHA and treated with MDL-100907 or ketanserin tartate (1 μM) and challenged 15 min later with 5-HT or DOI. MDL-100907 reduced agonist-stimulated mobilization of both AA and DHA, indicating a possible mechanism by which astroglia provide neurons with fatty acids (34).

The atypical antipsychotic profile of MDL-100907 has been further demonstrated in dopamine-, 5-HT- and glutamate-based animal models of psychosis. Table III summarizes the activities of MDL-100907 and other typical and atypical antipsychotics on a selection of psychotic symptoms and sedation in mice.

MDL-100907 is capable of inhibiting amphetamine-induced locomotion (ED_{50} = 0.3 mg/kg) without affecting baseline activity or apomorphine-induced stereotypy in mice. In contrast, in addition to reducing amphetamine-induced locomotion, haloperidol (0.01-0.5 mg/kg), clozapine (0.25-8.0 mg/kg) and amperozide (0.06-2.0 mg/kg) all resulted in sedative effects due to significant reductions in baseline locomotor activity. Furthermore, neither MDL-100907 nor clozapine (1, 10 or 50 mg/kg) caused catalepsy when administered to rats. Taken together, these results indicated that MDL-100907 had antipsychotic properties with low EPS liability (20).

MDL-100907 also inhibited 5-MeODMT- or 5-hydroxytryptophan-induced head twitches in mice and rats, respectively. Moreover, higher CNS safety scores were achieved with MDL-100907 as opposed to treatment with haloperidol, clozapine, risperidone, ritanserin or amperozide when ataxia, α_1-adrenergic, muscle relaxation, depressant effect and striatal D_2 receptor activities were measured in mice (25).

The efficacy of MDL-100907 was also examined in primates. Amphetamine (1 mg/kg i.m.)-treated adult macaques were nasogastrically administered one dose of MDL-100907 (0.1-5.0 mg/kg) 2 days/week. Behavior was observed for 2 x 60-min periods at 30 and 90 min postadministration of MDL-100907. Amphetamine-induced submissive gestures were dose-dependently reduced and amphetamine-stimulated visual screening and social withdrawal were also decreased. MDL-100907 treatment did not affect amphetamine-induced stereotypy or cause movement disturbances. The reversal of amphetamine-induced behavioral changes in these primates further indicates that MDL-100907 may be an effective antipsychotic agent (35).

An *in vivo* study in mice demonstrated that atypical and typical antipsychotics such as MDL-100907, clozapine and risperidone blocked PCP- and amphetamine-stimulated locomotion in a similar manner. Moreover,

haloperidol suppressed amphetamine-stimulated locomotion more potently than PCP-stimulated movement. These results suggest that while PCP-induced locomotion is more sensitive to 5-HT_2 antagonism, amphetamine-stimulated locomotion is influenced more by dopaminergic antagonism, further demonstrating the atypical profile of the compound (36). These results were corroborated in another study investigating the roles of dopaminergic and serotonergic receptors in the modulation of PCP- *vs.* amphetamine-stimulated locomotion in rats. Rats were pretreated (s.c.) with MDL-100907 and other antipsychotics such as clozapine, raclopride, risperidone and haloperidol and administered PCP (20 mg/g s.c.) or amphetamine (2.5 mg/kg i.p.) 30 min later. The atypical antipsychotics clozapine and MDL-100907 more potently inhibited PCP-stimulated locomotion as opposed to amphetamine-stimulated locomotion when compared to the effects of haloperidol and raclopride. Antagonists of 5-HT_{2C} (SB-200646; 20 mg/kg p.o.) and α_1-and α_2-adrenergic (prazosin or RX-821002, respectively; 0.63 mg/kg s.c.) receptors did not significantly affect either amphetamine- or PCP-stimulated locomotion (37). The results from this study provide further evidence for a functional relationship between 5-HT_{2A} receptors and treatment of psychotic disorders.

A study proposing a potential model for characterizing atypical antipsychotic agents has demonstrated that 5-HT via 5-HT_{2A} receptors are responsible for MDMA-stimulated locomotion. Rats were administered MDMA (1, 2, 4, 10, 20 or 40 mg/kg s.c.) 30 min after injection of MDL-100907 (1 mg/kg i.p.). MDL-100907 pretreatment significantly reduced MDMA-stimulated locomotion without affecting basal levels. Treatment with other 5-HT_{2A} antagonists such as ritanserin, clozapine, MDL-28133A and methiothepin, in addition to 5-HT_{1A} (propranolol) and D_2 or D_1 receptor antagonism (haloperidol and SCH-23390, respectively), resulted in reductions in MDMA-stimulated locomotion. Moreover, intraventricular administration of 5,7-dihydroxytryptamine resulted in regional decreases in 5-HT in addition to decreasing MDMA-stimulated locomotion. These results indicated involvement of 5-HT_{1A}, D_1 and D_2, as well as 5-HT_{2A} receptors in MDMA-stimulated locomotion (38).

Evaluation of the involvement of dopamine and serotonin in psychostimulant-induced facilitation of brain stimulation reward was examined in a study in which rats, trained to self-stimulate, were injected i.p. with amphetamine, cocaine, eticlopride (dopamine D_2 antagonist), MDL-100907 or a combination of both antagonists with cocaine or amphetamine. It was shown that while eticlopride reduced the rewarding effects of both psychostimulants, MDL-100907 did not significantly influence cocaine or amphetamine-induced effects when administered alone or in combination with eticlopride, suggesting that 5-HT, at least via 5-HT_{2A} receptors, does not modulate the euphoric effects associated with psychostimulants (39).

Investigation of the effects of MDL-100907 and therefore the 5-HT_{2A} receptor involvement in anxiety and learning has demonstrated that the compound possesses some slight anxiolytic-like properties with no disruptional activity on learning (40-42).

Suppression of 5-HT_{2A} receptor activity with MDL-100907 treatment had no effect on the incidence of anxiety when investigated using rat (Vogel drinking conflict and elevated plus-maze test) and mouse (defense test battery and light/dark choice test) models of anxiety. Animals were injected i.p. with either MDL-100907, a nonselective 5-HT_2 antagonist (mianserin; 10 mg/kg) or a selective 5-$HT_{2B/2C}$ antagonist (SB-206553; 3-10 mg/kg) 30 min prior to anxiety testing. SB-206553 and mianserin treatment resulted in anxiolytic-like actions including increased punished responding in the Vogel drinking test and increased entries into open arms in the elevated plus-maze, in contrast to MDL-100907 treatment which had no effect (40). However, when MDL-100907 treatment was examined in the rat Geller-Seifter model of anxiety, some anxiolytic effects were observed but only with high doses of 2 and 10 mg/kg (41).

Furthermore, the effects of MDL-100907 on the autoshaping learning task were investigated. Following autoshaping training sessions, rats were administered i.p. either MDL-100907 (0.1, 1.0 or 3.0 mg/kg), a 5-$HT_{1A/1B/1D}$ receptor antagonist (GR-46611; 1 or 10 mg/kg), a 5-$HT_{1B/1D}$ receptor antagonist (GR-127935; 0.1, 1 or 10 mg/kg) or the vehicle and tested 24 h later. Other animals received a combination of the antagonists and TFMPP, mCPP, fluoxetine, DOI, 1-NP, mesulergine, ketanserin or PCA. Rats treated with GR-46611 displayed a decrease in learning consolidation as opposed to an increase observed in GR-127935 (10 mg/kg)-treated rats. MDL-100907 had no effect when administered alone, indicating that suppression of 5-HT_{2A} receptors has no effect on learning. However, the increases in learning observed with DOI, ketanserin and TFMPP treatment were blocked by MDL-100907 and a reduction in the learning enhancing effects of mCPP, 1-NP and mesulergine were also observed in these animals. The results of this study demonstrate that stimulation of 5-$HT_{1B/1D}$ receptors reduces consolidation of learning as opposed to increased learning resulting from stimulation of 5-HT_{2A}/5-HT_{2C} receptors (42).

Pharmacokinetics and Metabolism

Pharmacokinetic studies in rats and dogs have demonstrated that MDL-100907 is well absorbed and undergoes extensive first-pass metabolism to MDL-105725, an active metabolite. However, the parent compound was found to be the predominant species in the brain when *in vivo* microdialysis sampling was performed in rats following administration of MDL-100907 (5 mg/kg i.v. or 50 mg/kg p.o.) or MDL-105725. Permeability of MDL-100907 through the blood-brain barrier was 4 times greater than that of MDL-105725 and metabolism of the parent compound was found to be minimal in the brain (43).

Clinical Studies

In order to determine the proper doses required for treatment of schizophrenic patients, the time course of 5-HT_2 receptor occupancy in the human frontal cerebral cortex was determined in 9 healthy subjects who underwent positron emission tomography (PET). PET used [^{11}C]-*N*-methylspiperone (NMSP) as a tracer which binds to both D_2 receptors in the basal ganglia and to 5-HT_2 receptors in cortical regions. Following a single dose of MDL-100907 (10 or 20 mg p.o.), 5-HT_2 occupancy was found to be 70-90%. When compared to 8 h postdosing with 10 mg, receptor occupancy significantly decreased by 18-21% at 24 h, which was 17% lower than that observed with 20 mg at 24 h (44, 45). In addition, several studies have described the development of a PET emitting [^{11}C]-MDL-100907 tracer for the distinct labeling of 5-HT_{2A} receptors in the human brain (46, 47).

Results from early clinical trials have corroborated the findings from preclinical studies suggesting an efficacy of MDL-100907 against both positive and negative symptoms of schizophrenia with a significantly reduced side effect profile (48). Finally, the clinical efficacy of MDL-100907 has been recently reported in which schizophrenic patients treated with fixed doses of MDL-100907 displayed significant improvement of symptoms. In addition, MDL-100907 treatment was shown to possess an excellent tolerability profile (49).

Manufacturer

Hoechst Marion Roussel, Inc. (US).

References

1. Carr, A.A., Kane, J.M., Hay, D.A. (Merrell Dow Pharm., Inc.). *(+)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol.* EP 531410, JP 93507482, US 5134149, WO 9118602.

2. Mathis, C.A., Mahmood, K., Huang, Y., Simpson, N.R., Gerdes, J.M., Price, J.C. *Synthesis and preliminary in vivo evaluation of [^{11}C]MDL 100907: A potent and selective radioligand for the 5-HT_{2A} receptor system.* Med Chem Res 1996, 6: 1-10.

3. Lundkvist, C., Sandell, J., Nagren, K., Pike, V.W., Swahn, C.-G., Wikström, H., Halldin, C. *Improved synthesis of [^{11}C]FLB 457, [^{11}C]WAY 100635, [^{11}C]MDL 100907 and [^{11}C]β-CIT-FE by use of [^{11}C]methyl triflate.* J Label Compounds Radiopharm 1997, 40: 583-5.

4. Saxena, P.R. *Serotonin receptors: Subtypes, functional responses and therapeutic relevance.* Pharmacol Ther 1995, 66: 339-68.

5. Wooley, D.W., Shaw, E. *A biochemical and pharmacological suggestion about certain mental disorders.* Proc Natl Acad Sci USA 1954, 40: 228-31.

6. Hoyer, D., Clarke, D.E., Fozard, J.R., Hartig, P.R., Martin, G.R., Mylecharane, E.J., Saxena, P.R., Humphrey, P.P. *VII. International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin).* Pharmacol Rev 1994, 46: 157-203.

7. Hoyer, D., Martin, G. *5-HT receptor classification and nomenclature: Towards a harmonization with the human genome.* Neuropharmacology 1997, 36: 419-28.

8. Geriach, J. *New antipsychotics: Classification, efficacy, and adverse effects.* Schizophr Bull 1991, 17: 289-309.

9. Joyce, J.N., Shane, A., Lexow, N., Winokur, A., Casanova, M.F., Kleinman, J.E. *Serotonin uptake sites and serotonin receptors are altered in the limbic system of schizophrenics.* Neuropsychopharmacology 1993, 8: 315-36.

10. Lieberman, J.A. *Understanding the mechanism of action of atypical antipsychotic drugs.* Brit J Psychiatry 1993, 163: 7-18.

11. Kelland, M.D., Freeman, A.S., Chiodo, L.A. *Serotonergic afferent regulation on the basic physiology and pharmacological responsiveness of nigrostriatal dopamine neurons.* J Pharmacol Exp Ther 1990, 253: 803-11.

12. Törk, I. *Anatomy of the serotonergic system.* Ann NY Acad Sci 1991, 600: 9-34.

13. Kusumi, I., Matsubara, S., Takahashi, Y., Ishikane, T., Koyama, T. *Characterization of [^{3}H]clozapine binding sites in rat brain.* J Neural Transm — Gen Sect 1995, 101: 51-64.

14. Bymaster, F.P., Calligaro, D.O., Falcone, J.F., Marsh, R.D., Moore, N.A., Tye, N.C., Seeman, P., Wong, D.T. *Radioreceptor binding profile of the atypical antipsychotic olanzapine.* Neuropsychopharmacology 1995, 14: 87-96.

15. Meltzer, H.Y., Matsubara, S., Lee, J.-C. *Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin 2 pK_i values.* J Pharmacol Exp Ther 1989, 251: 238-51.

16. Carpenter, W.T. Jr. *Serotonin-dopamine antagonists and treatment of negative symptoms.* J Clin Pharmacol 1995, 15(Suppl. 1): 30-5S.

17. Dudley, M.W., Weich, N.L., Miller, F.P. et al. *Pharmacological effects of MDL 11,939: A selective, centrally acting antagonist of 5-HT_2 receptors.* Drug Dev Res 1988, 13: 29-43.

18. Schmidt, C.J., Kehne, J.H., Carr, A.A. *MDL 100,907: A selective 5-HT_{2A} receptor antagonist for the treatment of schizophrenia.* CNS Drug Rev 1997, 3: 49-67.

19. Schmidt, C.J., Fadayel, G.M., Sullivan, C.K., Taylor, V.L. *5-HT_2 receptors exert a state-dependent regulation of dopaminergic function: Studies with MDL 100,907 and the amphetamine analogue, 3,4-methylenedioxymethamphetamine.* Eur J Pharmacol 1992, 223: 65-74.

20. Sorensen, S.M., Kehne, J.H., Fadayel, G.M., Humphreys, T.M., Ketteler, H.J., Sullivan, C.K., Taylor, V.L., Schmidt, C.J. *Characterization of the 5-HT_2 receptor antagonist MDL 100907 as a putative atypical antipsychotic: Behavioral, electrophysiological and neurochemical studies.* J Pharmacol Exp Ther 1993, 266: 684-91.

21. Carlsson, M.L. *The selective 5-HT_{2A} receptor antagonist MDL 100,907 counteracts the psychomotor stimulation ensuing manipulations with monoaminergic, gutamatergic or muscarinic neurotransmission in the mouse — Implications for psychosis.* J Neural Trans — Gen Sect 1995, 100: 225-37.

22. Palfreyman, M.G., Schmidt, C.J., Sorensen, S.M. et al. *Electrophysiological, biochemical and behavioral evidence for 5-HT$_2$ and 5-HT$_3$ mediated control of dopaminergic function.* Psychopharmacology 1993, 112: 60-7.

23. Schmidt, C.J., Kehne, J.H., Carr, A.A. et al. *Contribution of serotonin neurotoxins to understanding psychiatric disorders: The role of 5-HT$_2$ receptors in schizophrenia and antipsychotic activity.* Int Clin Psychopharmacol 1993, 8(Suppl. 2): 25-32.

24. Schmidt, C.J., Fadayel, G.M. *The selective 5-HT$_{2A}$ receptor antagonist, MDL 100,907, increases dopamine efflux in the prefrontal cortex of the rat.* Eur J Pharmacol 1995, 273: 273-9.

25. Kehne, J.H., Baron, B.M., Carr, A.A. et al. *Preclinical characterization of the potential of the putative atypical antipsychotic MDL 100,907 as a potent 5-HT$_{2A}$ antagonist with a favorable CNS safety profile.* J Pharmacol Exp Ther 1996, 277: 968-81.

26. Schreiber, R., Brocco, M., Millan, M.J. *Blockade of the discriminative stimulus effects of DOI by MDL 100,907 and the "atypical" antipsychotics, clozapine and risperidone.* Eur J Pharmacol 1994, 264: 99-102.

27. Marek, G.J., Aghajanian, G.K. *Excitation of interneurons in piriform cortex by 5-hydroxytryptamine: Blockade by MDL 100,07, a highly selective 5-HT$_{2A}$ receptor antagonist.* Eur J Pharmacol 1994, 259: 137-41.

28. Wang, R.Y., Liang, X. *M100907 and clozapine, but not haloperidol or raclopride, prevent phencyclidine-induced blockade of NMDA responses in pyramidal neurons of the rat medial prefrontal cortical slice.* Neuropsychopharmacology 1998, 19: 74-85.

29. Schmidt, C.J., Sullivan, C.K., Taylor, V.L., Fadayel, G.M. *In vivo studies on the regulation of dopamine release by the 5-HT$_2$ receptor antagonist, MDL 100,907.* Soc Neurosci Abst 1992, 18(Part 2): Abst 580.3.

30. Schmidt, C.J., Fadayel, G.M., Ring, S.C., Taylor, V.L. *5-HT$_{2A}$ receptor-mediated regulation of cortical and subcortical dopaminergic systems: Studies with the selective antagonist, MDL 100907.* Schizophr Res 1995, 15: 164.

31. Martin, P., Waters, N., Schmidt, C.J., Carlsson, A., Carlsson, M.L. *Rodent data and general hypothesis: Antipsychotic action exerted through 5-HT$_{2A}$ receptor antagonism is dependent on increased serotonergic tone.* J Neural Transm 1998, 105: 365-96.

32. Hanson, G.R., Bush, L.G., Taylor, V.L., Gibb, J.W., Davis, K., Schmidt, C.J. *Comparison of neurotensin responses to MDL 100,07, a selective 5-HT$_{2A}$ antagonist, with clozapine and haloperidol.* Brain Res Bull 1997, 42: 211-9.

33. Cozzi, N.V., Nichols, D.E. *5-HT$_{2A}$ receptor antagonists inhibit potassium-stimulated γ-aminobutyric acid release in rat frontal cortex.* Eur J Pharmacol 1996, 309: 25-31.

34. Garcia, M.C., Kim, H.-Y. *Mobilization of arachidonate and docosahexanoate by stimulation of the 5-HT$_{2A}$ receptor in rat C6 glioma cells.* Brain Res 1997, 768: 43-8.

35. Shapiro, L.E., Schlemmer, R.F., Young, J.E., Fleming, C.K., Davis, J.M. *Antagonism of amphetamine-induced behavioral changes in selected members of a primate social colony by the selective 5-HT$_{2A}$ antagonist MDL 100,907.* Soc Neurosci Abst 1996, 22(Part 1): Abst 76.2.

36. Hitchcock, J.M., Grauffel, C.A. *Comparison of the 5-HT$_{2A}$ antagonist MDL 100,907 with typical and atypical antipsychotics in phencyclidine- and amphetamine-stimulated locomotion tests in mice.* Schizophr Res 1996, 18: Abst VI.A.7.

37. Maurel-Remy, S., Audinot, V., Lejeune, F., Bervoets, K., Millan, M.J. *Blockade of phencyclidine-induced hyperlocomotion in rats by clozapine, MDL 100,907 and other antipsychotics correlates with affinity at 5-HT$_{2A}$ receptors.* Brit J Pharmacol 1995, 114(Suppl.): Abst 154P.

38. Kehne, J.H., Ketteler, H.J., McCloskey, T.C., Sullivan, C.K., Dudley, M.W., Schmidt, C.J. *Effects of the selective 5-HT$_{2A}$ receptor antagonist MDL 100,907 on MDMA-induced locomotor stimulation in rats.* Neuropsychopharmacology 1996, 15: 116-24.

39. Griebel, G., Perrault, G., Sanger, D.J. *A comparative study of the effects of selective and non-selective 5-HT$_2$ receptor subtype antagonists in rat and mouse models of anxiety.* Neuropharmacology 1997, 36: 793-802.

41. Bright, F., Trail, B., Blackburn, T.P., Kennett, G.A. *Effects of clozapine and MDL 100,907 in the rat Geller-Seifter model of anxiety.* Brit J Pharmacol 1997, 120(Suppl.): Abst 244P.

42. Meneses, A., Terrón, J.A., Hong, E. *Effects of the 5-HT receptor antagonists GR127935 (5-HT$_{1B/1D}$) and MDL100907 (5-HT$_{2A}$) in the consolidation of learning.* Behav Brain Res 1997, 89: 217-23.

43. Scott, D.O., Heath, T.G. *Investigation of the CNS penetration of a potent 5-HT$_{2A}$ receptor antagonist (MDL 100,907) and an active metabolite (MDL 105,725) using in vivo microdialysis sampling in the rat.* J Pharm Biomed Anal 1998, 17: 17-25.

44. Grunder, G., Yokoi, F., Offord, S.J., Salzmann, J.K., Krasenbaum, D.N., Szymanski, S., Ravert, H.T., Dannals, R.F., Wong, D.F. *Human 5-HT$_{2A}$ receptor occupancy after a single dose of a putative atypical antipsychotic MDL 100,907.* J Nucl Med 1996, 37(5, Suppl.): Abst No. 439.

45. Gründer, G., Yokoi, F., Offord, S.J., Ravert, H.T., Dannals, R.F., Salzmann, J.K., Szymanski, S., Wilson, P.D., Howard, D.R., Wong, D.F. *Time course of 5-HT$_{2A}$ receptor occupancy in the human brain after a single oral dose of the putative antipsychotic drug MDL 100,907 measured by positron emission tomography.* Neuropsychopharmacology 1997, 17: 175-85.

46. Halldin, C., Lundkvist, C., Guinovart, N. et al. *[^{11}C]MDL 100,907, a radioligand for selective imaging of 5-HT$_{2A}$ receptors with PET.* J Nucl Med 1996, 37(5, Suppl.): Abst No. 424.

47. Wong, D.F., Grunder, G., Yokoi, F. et al. *Imaging human cerebral 5-HT$_{2A}$ receptors with C-11 MDL 100,907.* J Nucl Med 1996, 37(5, Suppl.): Abst 438.

48. Sorensen, S.M., Schmidt, C.J., Kehne, J.H., Wettstein, J.G., van Giersbergen, P., Huebert, N., Hitchcock, J.M. *Profile of the 5-HT$_{2A}$ antagonist M100907 in preclinical tests for efficacy against positive and negative symptoms of schizophrenia.* 21st CINP Cong (July 12-16, Glasgow) 1998, Abst PT10045.

49. Offord, S.J. *M100907, a highly selective 5-HT$_{2A}$ antagonist for treatment of schizophrenia: Early indication of safety and clinical activity in schizophrenic patients.* 21st CINP Cong (July 12-16, Glasgow) 1998, Abst PT10052.

50. Schreiber, R., Brocco, M., Audinot, V., Gobert, A., Veiga, S., Millan, M.J. *(1-(2,5-Dimethoxy-4 iodophenyl)-2-aminopropane)-induced head-twitches in the rat are mediated by 5-hydroxytriptamine (5-HT$_{2A}$) receptors: Modulation by novel 5-HT$_{2A/2C}$ antagonists, D$_1$ antagonists and 5-HT$_{1A}$ agonists.* J Pharmacol Exp Ther 1995, 273: 101-12.

51. Johnson, M.P., Siegel, B.W., Carr, A.A. *[^{3}H]MDL-100,907: A novel selective 5-HT$_{2A}$ receptor ligand.* Naunyn-Schmied Arch Pharmacol 1996, 354: 205-9.

52. Roth, B.L., Craigo, S.C., Choudhary, M.S., Uluer, A., Monsuma, F.J. Jr., Shen, Y., Meltzer, H.Y., Sibley, D.R. *Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors.* J Pharmacol Exp Ther 1994, 268: 1403-10.

53. Audinot, V., Canton, H., Newman-Tancredi, A., Jacques, V., Verrièle, L., Millan, M.J. *In vitro and ex vivo patterns of occupation of 5-HT2A and alpha1-adrenergic as compared to dopamine D2 receptors by novel antipsychotics.* Eur Neuropsychopharmacol 1995, 5: Abst P-4-12.

54. Bymaster, F.P., Calligaro, D.O., Falcone, J.F., Marsh, R.D., Moore, N.A., Tye, N.C., Seeman, P., Wong, D.T. *Radioreceptor binding profile of the atypical antipsychotic olanzapine.* Neuropsychopharmacology 1995, 14: 87-96.

55. Kleven, M.S., Assie, M.B., Koek, W. *Pharmacological characterization of in vivo properties of putative mixed 5-HT$_{1A}$ agonist/5-HT$_{2A/2C}$ antagonist anxiolytics. II. Drug discrimination and behavioral observation studies in rats.* J Pharmacol Exp Ther 1997, 282: 747-59.

56. Helmeste, D.M., Tang, S.W., Li, M., Fang, H. *Multiple [^{3}H]-nemonapride binding sites in calf brain.* Naunyn-Schmied Arch Pharmacol 1997, 356: 17-21.

57. Svartengen, J., Pettersson, E., Bjork, A. *Interactions of the novel antipsychotic drug amperozide and its metabolite FG5620 with central nervous system receptors and monoamine uptake sites: Relation to behavioral and clinical effects.* Biol Psychiatry 1997, 42: 247-59.

58. Schoemaker, H., Claustre, Y., Fage, D., Rouquier, L., Chergui, K., Curet, O., Oblin, A., Gonon, F., Carter, C., Benavides, J., Scatton, B. *Neurochemical characteristics of amisulpride, an atypical dopamine D$_2$/D$_3$ receptor antagonist with both presynaptic and limbic selectivity.* J Pharmacol Exp Ther 1997, 280: 83-97.

59. Durcan, M.J., Rigdon, G.C., Norman, M.H., Morgan, P.F. *Is clozapine selective for the dopamine D$_4$ receptors?* Life Sci 1995, 57: PL275-83.

60. Millan, M.J.S., Audinot, V., Brocco, M. et al. *S-16924: A pyrrolidine-substituted benzodioxane with higher affinity at 5-HT$_{1A/2A/2C}$ than D$_2$ receptors, and an "atypical" antipsychotic profile in the rat.* Brit J Pharmacol 1995, 114(Suppl.): Abst 156P.

61. Lavielle, G.S., Gobert, A., Audinot, V. et al. *S-16924, a novel potential antipsychotic with high activity at 5-HT$_{1A}$ and D$_4$ receptors: A comparison to haloperidol, clozapine and ziprasidone.* IBC 1st Int Symp Schizophr (May 8-9, Philadelphia) 1995.

62. Ravina, E., Fueyo, J., Masaguer, C.F. et al. *Synthesis and affinities for dopamine (D$_2$) and 5-hydroxytryptamine (5-HT$_{2A}$) receptors of 1-(benzoylpropyl)-4-(1-oxocycloalkyl-2-ethyl)-piperazines as cyclic butyrophenone derivatives.* Chem Pharm Bull 1996, 44: 534-41.

63. Norman, M.H., Navas, F. III, Thompson, J.B., Rigdon, G.C. *Synthesis and evaluation of heterocyclic carboamides as potential antipsychotic agents.* J Med Chem 1996, 39: 4692-703.

64. Codony, X., Ballarin, M., Carceller, A., Guitart, X., Laloya, M., Ruiz, M.T., Mercè, R., Farré, A.J. *Effects of E-5842, a novel σ compound, in preclinical antipsychotic tests.* Meth Find Exp Clin Pharmacol 1997, 19(Suppl. A): Abst PA-3.

65. Rigdon, G.C., Norman, M.H., Cooper, B.R., Howard, J.L., Boncek, V.M., Faison, W.L., Nanry, K.P., Pollard, G.T. *1192U90 in animal tests that predict antipsychotic efficacy, anxiolysis, and extrapyramidal side effects.* Neuropsychopharmacology 1996, 15: 231-42.

66. Bolos, J., Gubert, S., Anglada, L., Planas, J.M., Burgarolas, C., Castello, J.M., Sacristan, A., Ortiz, J.A. *7-[3-(1-Piperidinyl)-propoxyl]chromenones as potential atypical antipsychotics.* J Med Chem 1996, 39: 2962-70.

67. Norman, M.H., Rigdon, G.C., Hall, W.R., Navas, F. III. *Structure-activity relationships of a series of substituted benzamides: Potent D$_2$/5-HT$_2$ antagonists and 5-HT$_{1A}$ agonists as neuroleptic agents.* J Med Chem 1996, 39: 1172-88.

68. Ohmori, J., Maeno, K., Hidaka, K. Et al. *Dopamine D$_3$ and D4 receptor antagonists: Synthesis and structure-activity relationships of (S)-(+)-N-(1-benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (YM-43611) and related compounds.* J Med Chem 1996, 39: 2764-72.

69. Bristow, L.J., Flatman, K.L., Hutson, P.H., Kulagowski, J.J., Leeson, P.D., Young, L., Tricklebank, M.D. *The atypical neuroleptic profile of the glycine/N-methyl-D-aspartate receptor antagonist, L-701,324, in rodents.* J Pharmacol Exp Ther 1996, 277: 578-85.

70. Koshiya, K., Nakatoh, K., Hattori, H., Usuda, S. *Differential roles of D$_2$, D$_3$ and D$_4$ receptors in dopamine-related behaviors as assessed with a novel D$_3$/D$_4$ antagonist YM-43611.* Eur Neuropsychopharmacol 1996, 6(Suppl. 3): Abst P-9-6.

71. Griffon, N., Diaz, J., Levesque, D. et al. *Localization, regulation, and role of the dopamine D$_3$ receptor are distinct from those of the D$_2$ receptor.* Clin Neuropharmacol 1995, 18(Suppl. 1): S130-42.

72. Ishizumi, K., Kojima, A., Antoku, F., Saji, I., Yoshigi, M. *Succinimide derivatives. II. Synthesis and antipsychotic activity of N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2-cis-cyclohexanedicarboximide (SM-9018) and related compounds.* Chem Pharm Bull 1995, 43: 2139-51.