Discovery of New Tetracyclic Tetrahydrofuran Derivatives as Potential Broad-Spectrum Psychotropic Agents

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Abstract: A series of novel tetracyclic tetrahydrofuran derivatives was prepared and evaluated for its potential psychotropic properties. In vitro affinities for multiple dopaminergic, serotonergic, α-adrenergic, and histamine receptors and for the norepinephrine transporter as well as the ED_{50} values obtained in some in vivo assays for antipsychotic, anxiolytic, and antidepressant potential are reported. Compounds (−)-**1**, (−)-**8d,** and (+)-**8d** have been identified as potential broad-spectrum psychotropic agents.

Activation of central dopaminergic systems is generally considered to be the most important factor in the etiology of schizophrenia.[1,2] Until mid 1980s, haloperidol[3] was thought to be the prototype antipsychotic.[4] The compound is very effective in reducing the positive symptomatology (hallucinations, delusional thinking, severe excitement, and unusual behavior). Like all neuroleptics, however, haloperidol has the disadvantages of extrapyramidal side effects (EPS) and of a limited effect on the negative symptoms of schizophrenia, such as anergy, apathy, lack of drive, social withdrawal, and depressive mood.[5] Nowadays it is thought that concomitant 5-HT_{2A} antagonism may overcome the drawbacks of central D_2 receptor blockade.[6,7] This concept is corroborated by the clinical results obtained with the second generation antipsychotics, all having the common property of central D_2 antagonism with predominant 5-HT_{2A} antagonism (Chart 1: clozapine, risperidone, olanzapine, quetiapine) and all claimed to be atypical in having extended effects on negative symptoms and reduced EPS liability.[8,9] This second generation of antipsychotics has the ability to simultaneously interact with different monoaminergic systems such as the dopaminergic-, serotonergic-, muscarinic-, α-adrenergic-, and histamine H_1-sites. This rich pharmacological profile may explain that more than 70% of prescriptions for atypical antipsychotic medications are being used for other conditions than schizophrenia.[10]

The same concept of "rich pharmacological profile" has been exploited in depression with the development of mianserin and mirtazapine (Chart 2). Both compounds show their antidepressant activity by interaction with several receptors, enhancing multiple monoaminergic system activities in parallel, thus broadening their potential application to different depressive conditions.[11]

Furthermore, the same approach has been successfully explored by combination of two different compounds (Olanzapine/Fluoxetine, Symbyax)[12] for the treatment of depressive episodes associated with bipolar disorder, another complex psychiatric illness. Along the same line, Olanzapine was recently approved by the US FDA for the treatment of acute mania and the prevention of relapse in bipolar disorders.[13]

Some years ago we started a program at Johnson & Johnson Pharmaceutical Research and Development searching for potent and centrally active 5-$HT_{2A/2C}$ receptor antagonists as potential anxiolytic/antidepressant agents. As a result of our synthesis program, we have recently described series of tetracyclic tetrahydrofuran derivatives having 5-$HT_{2A/2C}$ antagonism.[14,15] One of those compounds, (−)-**1** (Chart 3), was a potent *m*-chlorophenylpiperazine (mCPP) antagonist as shown in our in vivo mCPP challenge test and which might

Chart 1. Set of Marketed Second Generation Antipsychotics

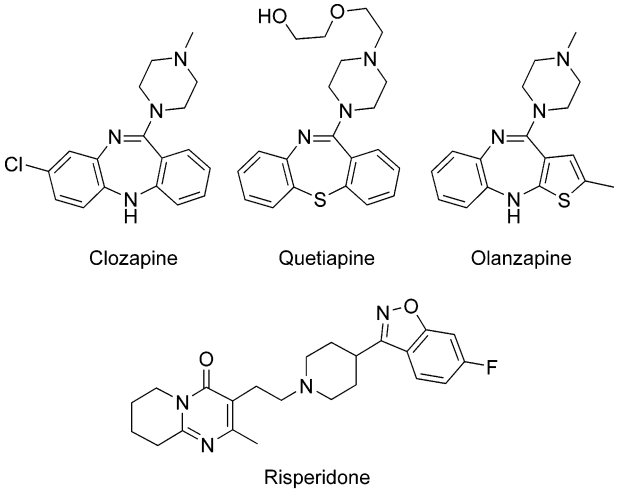


Chart 2. Set of Marketed Tetracyclic Antidepressants

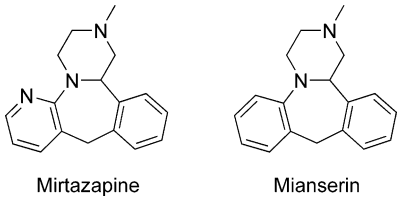
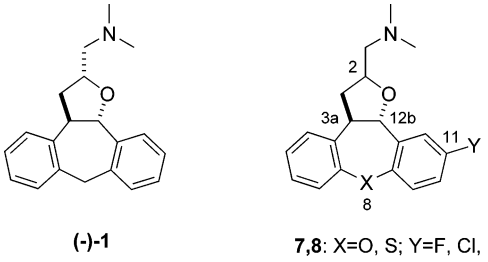


Chart 3



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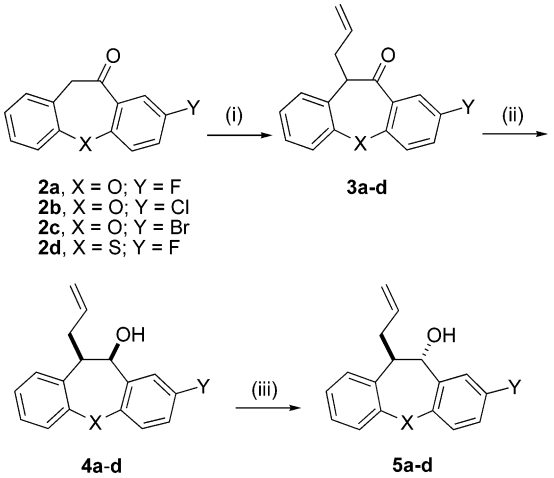
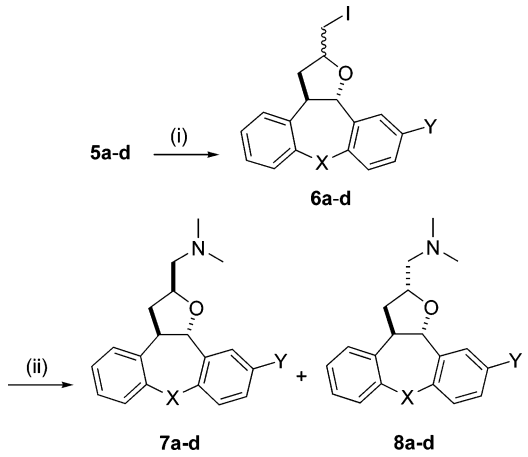
Scheme 1[a] Synthesis of the Trans β-Allylic Alcohols **5**



[a] Reagents and conditions: (i) NaH, THF, 0 °C, 2 h then allyl bromide, 0 °C to room temperature, overnight, (40−90%); (ii) L-selectride, THF, −30 °C to room temperature, 6 h, (90−97%); (iii) *p*-nitrobenzoic acid, DIAD, PPh_3, THF, 0 °C to room temperature 12 h, then LiOH, rt, overnight, (70−83%).

Scheme 2[a] Synthesis of Tetracyclic Tetrahydrofurans **7**, **8**



[a] Reagents and conditions: (i) IPy_2BF_4, CH_2Cl_2, 10 min, rt, (85−94%); (ii) dimethylamine, CaO, THF, 120 °C, overnight, (77−86%).

correspond to anxiolytic activity.[15,16] We report herein the preliminary results of our efforts in the chemical improvement of this scaffold (Chart 3, analogues **7** and **8**) that have led to the discovery of a family of potent broad-spectrum psychotropic compounds **8**. The in vitro binding affinities for various CNS receptors, as well as the ED_{50} values in some in vivo behavioral animal models for the most interesting compounds within this series are reported in this communication.

The synthesis of the target compounds **7a**−**d** and **8a**−**d** was achieved by the general method shown in Schemes 1 and 2.[14,15] First, the reaction of the corresponding tricyclic ketones **2a**−**d**[17,18] with sodium hydride, followed by addition of allyl bromide afforded the α-allylated ketones **3a**−**d** in good to moderate yields (40−90%, Scheme 1). The reduction of ketones **3a**−**d** with L-selectride at −30 °C in THF gave the expected cis alcohols **4a**−**d** with complete diastereoselectivity and excellent yields (90−97%), as it is shown in Scheme 1. The required trans β-allylic alcohols **5a**−**d** were prepared by Mitsunobu inversion reaction of the cis alcohols **4a**−**d** with *p*-nitrobenzoic acid, followed by ester hydrolysis, in good overall yields (70−83%). The construction of the tetrahydrofuran ring was performed by iodocyclization of the corresponding alcohols **5a**−**d** with IPy_2BF_4 [bis(pyridine)iodonium(I) tetrafluoroborate; Barluenga's reagent],[19] as it is shown in Scheme 2. The tetracyclic iodo derivatives **6a**−**d** were obtained in excellent yields (85−94%) as nearly equimolecular mixtures of diastereoisomers. Finally, the displacement of the iodine atom of **6a**−**d** by dimethylamine afforded the corresponding target compounds **7** and **8** as mixtures of diastereoisomers, that were separated by HPLC chromatography.

The relative stereochemistry of each pure diastereoisomer **7a**−**d** and **8a**−**d** was assigned by means of 2D-NOESY experiments. Compound **8d** was separated into its corresponding pair of enantiomers (+)-**8d**/(−)-**8d** by chiral HPLC chromatography.

The binding affinities of (−)-**1** and the new compounds **7** and **8** for the dopaminergic (D_1, D_2, D_3), serotonergic (5-HT_{2A}, 5-HT_{2C}, 5-HT_7), α-adrenergic (α_1, α_{2A}, α_{2C}), and H_1 receptors and the norepinephrine (NET) transporter are shown in Table 1. Binding data obtained for haloperidol and several marketed psychotropics under the same experimental conditions are also shown.

Structure−activity relationships were first studied to determine the optimal relative configuration of the new halo-substituted tetracyclic tetrahydrofuran derivatives **7**, **8**. As can be deduced from the data presented in Table 1, compounds **8a**−**d**, presenting the same relative stereochemistry around the tetrahydrofuran ring as in (−)-**1**, were clearly superior to their corresponding pairs (epimers at position 2, Chart 3) **7a**−**d**. The analogues with a sulfur (**7d** and **8d**) spacer between the two aromatic rings maintained a similar receptor profile to that of (−)-**1**, showing nanomolar activities for the whole panel of CNS receptors studied. In general, the dibenzoxepin derivatives (X = O) showed lower affinities than (−)-**1** and the sulfur analogues (**7d**, **8d**) for most of the receptors, **8b** (X = O; Y = Cl) being an exception. The high affinity for the 5-HT_{2C} and H_1 receptors was a constant for the whole series. Also remarkable was that the presence of a halogen atom at C11 position (Chart 3) resulted in a marked increase in D_2 binding affinity. This effect was clearly pronounced for compounds **8b** and **8d** when compared with compound (−)-**1**. These rich binding profiles encouraged us to resolve chromatographically the racemate **8d** and study in detail the enantiomerically pure analogues (−)-**8d** and (+)-**8d**. Additionally a broader pharmacological characterization of (−)-**1** was also considered.

The K_i values for the enantiomers (−)-**1**, (−)-**8d**, and (+)-**8d** were compared with those obtained for haloperidol and the broad-spectrum psychotropics clozapine, olanzapine, risperidone, mirtazapine, and mianserin in Table 1.

(−)-**1** was selected as the lead compound of the series. The compound, in addition to the reported high affinities for 5-HT_{2A}, 5-HT_{2C}, and H_1 receptors,[15] was found to be a potent norepinephrine reuptake inhibitor (NET, K_i = 7.8) with high affinity for 5-HT_7 receptors as well. Additionally it showed moderate affinities for dopaminergic and α-adrenergic receptors. Compound (−)-**8d** possessed higher affinities for each of the receptors tested than its corresponding enantiomeric pair (+)-**8d**,

Table 1. Binding Affinities for D_1, D_2, D_3, 5-HT_{2A}, 5-HT_{2C}, 5-HT_7, H_1, α_1, α_{2A}, α_{2C} Receptors and NET Transporter for Compounds (−)-**1**, **7a**−**d**, **8a**−**d**, and a Set of Reference Compounds

			K_i (nM)[a]										
compound	X	Y	D_1	D_2	D_3	5-HT_{2A}	5-HT_7	5-HT_{2C}	NET	H_1	α_1	α_{2A}	α_{2C}
7a	O	F	nt[b]	191	293	>5454	57	7.6	20	33	338	251	219
8a	O	F	nt[b]	32	31	>5454	80	4.3	3.6	7.5	71	269	200
7b	O	Cl	250	68	45	22	92	3.7	88	14	228	302	677
8b	O	Cl	83	5.9	251	6.0	251	2.4	9.4	4.3	35	10	26
7c	O	Br	nt[b]	369	nt[b]	38	nt[b]	17	>5454	nt[b]	nt[b]	nt[b]	nt[c]
8c	O	Br	154	66	95	15	35	8.9	382	42	234	407	742
7d	S	F	19	12	8.6	13	34	0.65	2.7	1.2	32	72	78
8d	S	F	5.2	2.3	1.1	0.56	6.6	<0.42	1.6	0.52	8.8	66	59
(−)-**8d**	S	F	3.0	1.7	19	0.24	6.2	0.21	2.0	0.60	7.5	79	73
(+)-**8d**	S	F	22	12	15	1.6	6.5	1.5	40	1.4	41	156	93
(−)-**1**	-	-	63	61	84	2.5	13	0.93	7.8	0.43	108	126	69
haloperidol	-	-	359[c]	2.5	4.4	435	1123	>5454	>5454	1199	26	473	256
clozapine	-	-	539[c]	144	242	6.3	48	21	697	1.1	22	24	2.9
olanzapine	-	-	118[c]	78	43	2.3	365	14	958	1.2	88	192	82
risperidone	-	-	147[c]	6.4	16	0.81	4.3	12	>5454	33	2.5	10	3.2
mirtazapine	-	-	4167[c]	>5454	5723	69	265	39	1640	1.6	608	20	18
mianserin	-	-	1420[c]	2197	2841	4.3	56	4.4	101	1.7	74	4.8	3.8

[a] The activity of compounds was confirmed in an independent experiment. Only differences in pIC_{50} up to 0.6 (SD < 0.5) were considered as reproducible and were maintained. The K_i values represent the concentration giving half-maximal inhibition of [^{3}H]SCH23390 (D_1), [^{3}H]spiperone (D_2), [^{125}I]iodosulpride, (D_3), [^{125}I]R91150 (5-HT_{2A}), [^{3}H]mesulergine (5-HT_{2C}), [^{3}H]5-HT (5-HT_7), [^{3}H]nisoxetine (NET), [^{3}H]pyrilamine (H_1), [^{3}H]prazosin (α_1), and [^{3}H]rauwolscine (α_{1A}, α_{2C}) binding to cloned human receptors or (for NET and α_1) to rat tissue. [b] Not tested. [c] The K_i values represent the concentration giving half-maximal inhibition of [^{3}H]SCH23390 (D_1) binding to rat tissue.

Table 2. In Vivo Pharmacological Profile of Compounds (−)-**1**, (−)-**8d**, (+)-**8d** Haloperidol and a Set of Broad-spectrum Psychotropics[a]

	apomorphine[b]	tryptamine cyanosis[c]	tryptamine convulsions[d]	tryptamine back. locomotion[e]	mCPP[f]	RO-4-1284 [g]
(−) **1**	2.0 (0.92−4.4)	0.020 (0.011−0.035)	0.020 (0.011−0.035)	1.2(0.72−2.2)	0.18 (0.081−0.41)	0.20 (0.070−0.57)
(−)-**8d**	0.13 (0.058−0.27)	0.013 (0.0057−0.027)	0.0079 (0.0036−0.017)	0.32 (0.18−0.55)	> 0.63[h]	0.025 (0.012−0.052)
(+)-**8d**	1.2 (0.72−2.2)	0.050 (0.023−0.11)	0.080 (0.046−0.14)	> 2.5[h]	> 2.5[h]	2.0 (0.92−4.4)
haloperidol	0.032 (0.024−0.044)	≥ 10[h]	0.29 (0.15−0.56)	> 10[h]	nt[i]	> 10[h]
clozapine	8.2 (6.0−11)	0.26 (0.16−0.41)	0.22 (0.14−0.36)	5.4 (3.4−8.7)	>2.5[h]	>80[h]
olanzapine	0.26 (0.17−0.38)	0.032 (0.026−0.040)	0.086 (0.057−0.13)	2.4 (1.6−3.5)	0.44 (- − -)	> 10[h]
risperidone	0.17 (0.12−0.31)	0.0020 (0.0015−0.0028)	0.037 (0.027−0.050)	> 10[h]	> 0.31[h]	> 10[h]
mirtazapine	> 10[h]	0.80 (0.37−1.74)	0.32 (0.18−0.55)	0.50 (0.23−1.10)	0.10 (0.028−0.38)	> 40[h]
mianserine	> 10[h]	0.18 (0.10−0.34)	0.24 (0.11−0.54)	0.55 (0.30−1.01)	1.26 (0.38−4.17)	> 40[h]

[a] Results are expressed as ED_{50} values in mg/kg after subcutaneous administration of the tested compounds; 95% confidence limits are shown in parentheses. [b] Inhibition of apomorphine-induced agitation in rats. [c] Reversal of tryptamine-induced cyanosis in rats. [d] Inhibition of tryptamine-induced bilateral convulsions in rats. [e] Reversal of tryptamine-induced backward locomotion in rats. [f] Antagonism of *m*-chlorophenylpiperazine induced anxiety in rats. [g] Reversal of RO-4-1284 induced hypothermia in mice. [h] Highest tested dose expressed in mg/kg. [i] Not tested.

except for the D_3 receptor, for which both compounds showed equipotent activities. Compound (−)-**8d** showed higher or comparable K_i values for D_2, 5-HT_{2A} 5-HT_{2C}, and 5-HT_7 receptors than the marketed atypical antipsychotics clozapine, olanzapine, and risperidone and the antidepressants mirtazapine and mianserin, the affinity for the D_2 receptor being comparable to that of haloperidol, a classical D_2 blocker. Additionally, (−)-**1**, (+)-**8d**, and (−)-**8d** showed high affinities for the norepinephrine transporter, The enantiomerically pure compounds (−)-**1**, (−)-**8d**, and (+)-**8d** were tested in several of our in vivo animal behavioral models to further evaluate their therapeutic potential.

The compounds were studied in rats, after subcutaneous administration, for their ability to (1) inhibit apomorphine-induced agitation, which predicts central D_2 antagonism and therefore antipsychotic activity,[20] (2) reverse tryptamine-induced cyanosis and bilateral convulsions (predictable for peripheral and central 5-HT_{2A} antagonism),[20] (3) reverse tryptamine-induced backward locomotion[20] and *m*-chlorophenylpiperazine-induced anxiety,[16] thought to reflect central 5-HT_{2C} antagonism and anxiolytic properties. The potential antidepressant component of the compounds (due to their affinity for NET) were evaluated in mice by measuring their ability to reverse RO-4-1284-induced hypothermia.[21]

The results obtained from the in vivo studies for the compounds (−)-**1**, (−)-**8d**, and (+)-**8d** are shown in Table 2. The data obtained for some reference compounds (haloperidol, clozapine, olanzapine, risperidone, mirtazapine, mianserin) are also presented. Our lead compound, within the series of tetrahydrofuran derivatives, (−)-**1** showed activity in the six in vivo assays shown in Table 2, being especially active for reversal of the tryptamine-induced cyanosis and bilateral convulsions with an ED_{50} of 0.020 mg/kg in both tests. The compound also antagonized mCPP-induced anxiety with an ED_{50} of 0.18 mg/kg. These results are in concordance with the binding affinities shown in Table 1.

As it could be anticipated from the binding studies, the enantiomer (−)-**8d** was clearly superior to its corresponding pair (+)-**8d** and compound (−)-**1** in all the in vivo models with the exception of the mCPP test, where both compounds were inactive. It is noteworthy that these compounds showed relevant higher potency in the tryptamine tests, predictable for 5-HT_{2A} antagonism, than in the apomorphine assay, which predicts D_2 antagonism.

The activities shown by (−)-**1**, (+)-**8d**, and (−)-**8d** are comparable to those obtained with the second-generation antipsychotics (clozapine, olanzapine, and risperidone) in the tests related to the inhibition of apomor-

phine and tryptamine-induced effects (Table 2, see ED_{50} values for the first four tests). Furthermore, as it was previously disclosed,[15] (−)-**1** antagonized mCPP-induced anxiety in rats at similar doses as the marketed antidepressants mianserin and mirtazapine. A differentiating feature to any of the reference compounds shown in Table 2 is the ability of these tetracyclic tetrahydrofuran analogues to reverse RO-4-1284-induced hypothermia in mice at low doses, which could be predictive for an antidepressant component, that might indicate a potential application to the treatment of bipolar disorders.

As a conclusion, compounds (−)-**1**, (+)-**8d**, and (−)-**8d** stand for the most potent members of this new family of tetracyclic tetrahydrofuran derivatives. Our data show that these molecules present a wide profile of pharmacological activities with potential clinical interest. Clinical trials should prove to what extent these compounds have a real benefit over the current therapies for the treatment of psychoaffective disorders. These studies are in progress and will be reported in due course.

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Supporting Information Available: Data for all new compounds described in this paper include (1) LCMS and (2) elemental analysis (3) ^{1}H NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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