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Novel, Highly Potent, Selective 5-HT_{2A}/D_2 Receptor Antagonists as Potential Atypical Antipsychotics

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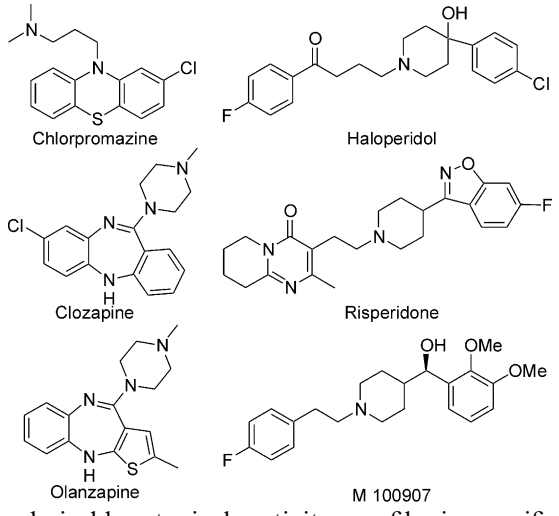
Abstract—The discovery of *N*-substituted-pyridoindolines and their binding affinities at the 5-HT_{2A}, 5-HT_{2C} and D_2 receptors, and in vivo efficacy as 5-HT_{2A} antagonists is described. The structure–activity relationship of a series of core tetracyclic derivatives with varying butyrophenone sidechains is also discussed. This study has led to the identification of potent, orally bioavailable 5-HT_{2A}/D_2 receptor dual antagonists as potential atypical antipsychotics.

Schizophrenia is a psychiatric disorder affecting approximately 1% of the general population.[1] Its common features are often categorized into positive symptoms, such as hallucinations, delusions and irrational fears and negative symptoms, including social withdrawal, flattened affect and impoverished speech.[2] Although the pathophysiology of schizophrenia has not been fully elucidated, dysfunction of the dopamine (DA) neurotransmitter systems within the brain is believed to play a key role in symptom expression and neuropsychologic dysfunction of the illness.[3]

Classical (typical) neuroleptics such as chlorpromazine and haloperidol are potent D_2 receptor antagonists that provide clear efficacy against positive symptoms.[4] These therapies are relatively ineffective in the treatment of negative symptoms, however, and chronic administration of these drugs is frequently associated with serious side effects such as extrapyramidal syndrome (EPS).[5] Since both their antipsychotic efficacy and induction of EPS originate from blockade of DA receptors, this side effect is largely unavoidable for the classical antipsychotics.[6]

The atypical antipsychotics represent a new class of therapeutic agents, and they demonstrate clinical efficacy against both positive and negative symptoms with reduced propensity to induce EPS.[7] These drugs, such as clozapine, olanzapine and risperidone, exhibit potent antagonism at multiple receptor subtypes including serotonin and DA receptors.



The desirable atypical activity profile is specifically derived from their actions on the serotonin and DA systems.[8] It has been suggested that blockade of 5-HT_{2A} receptors is responsible for both enhancing efficacy against negative symptoms and reducing EPS.[9] In fact, highly potent and selective 5-HT_{2A} receptor antagonist

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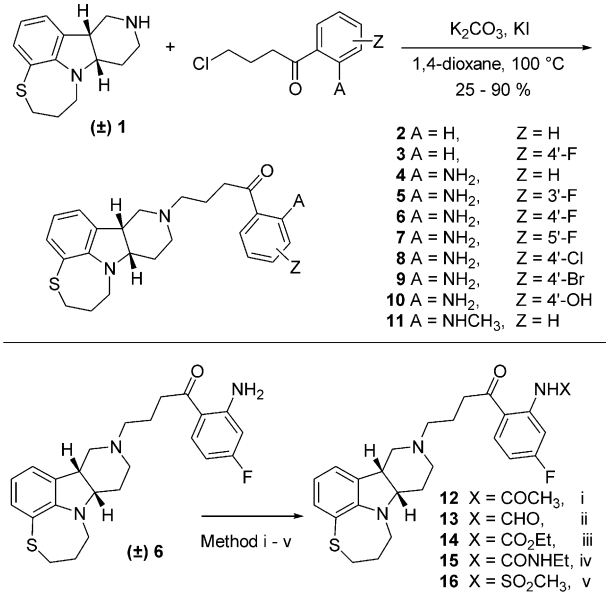
M100907[10] showed improvement in negative symptoms without EPS in a phase II clinical trial for schizophrenia.[11] However, development of this agent was discontinued in a phase III clinical trial[12] due to lack of efficacy for positive symptoms in an acute paradigm, suggesting a certain level of DA D_2 blockade may be necessary for robust efficacy. A higher degree of 5-HT_{2A} receptor occupancy (85–95%) is achieved compared to D_2 receptors (~40%) at clinically effective doses of clozapine,[13] suggesting that dual 5-HT_{2A}/D_2 antagonism, specifically preferential blockade of 5-HT_{2A} versus D_2 receptors, is required to retain the atypical antipsychotic profile of potential drug candidates.[14] To date however, it is not clear what optimal 5-HT_{2A}/D_2 ratio is required for antipsychotic efficacy. Clozapine is the most efficacious atypical antipsychotic[15] but is associated with the induction of agranulocytosis and seizure.[17] The newer antipsychotic agents also exhibit a variety of other side effects, which are most likely linked to their significant affinity for many other receptors.[17] Accordingly, the development of new agents, which are more efficacious and have fewer side effects than current treatments, remains a major challenge. In this paper, we describe our recent efforts in the area of selective dual 5-HT_{2A}/D_2 antagonists for potential use as atypical antipsychotics.

The syntheses of the tetracyclic butyrophenones and related analogues are shown in the following schemes. The *cis*-(8a,12a)-6,7,8a,9,10,11,12,12a-octahydro-5H-pyrido[4,3-*b*][1,4]thiazepino[2,3,4-*hi*]indole core (±)-**1** was synthesized as described previously.[18] 1-(2′-Amino-phenyl)-4-chloro-butan-1-one derivatives were prepared by Friedel–Crafts acylation of 4-chloro-butyronitrile to the corresponding anilines using a modification of Schwarcz's procedure.[19] Alkylation of the 2°-amine of compound (±)-**1** with substituted 4-chloro-butyrophenones using K_2CO_3 and KI at 100 °C gave the tetracyclic butyrophenones **2**–**11** in moderate to good yields, as shown in Scheme 1.

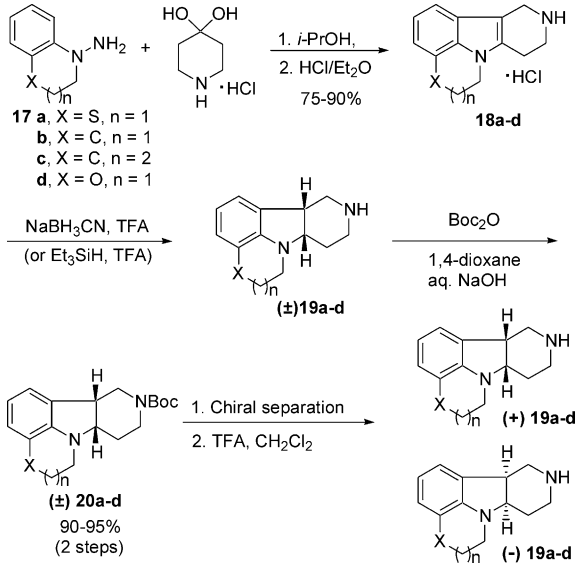


Scheme 1. (i) $(CH_3CO)_2O$, CH_2Cl_2, pyridine (91%); (ii) CH_3CO_2CHO, neat (76%); (iii) $ClCO_2Et$, pyridine (15%); (iv) EtNCO neat (81%); (v) CH_3SO_2Cl, Et_3N, CH_2Cl_2 (99%).

The 2′-amino group of compound (±)-**6** was further elaborated by a variety of methods to afford the functionalized derivatives **12**–**16**.

The synthetic approach to the optically pure alternate core tetracycles **19a**–**d** is detailed in Scheme 2. In general, Fischer indole cyclization of the bicyclic hydrazines **17a**–**d** with 4-piperidone hydrochloride in refluxing *i*-PrOH produced the corresponding tetracyclic indoles **18a**–**d** in excellent yields. Subsequent *cis*-reductions of **18a**–**d** with either $NaCNBH_3$ or Et_3SiH in TFA, followed by treatment with $(Boc)_2O$ afforded the *cis*-*N*-Boc-indolines (±)-**20a**–**d**. The separation of the enantiomers of (±)-**20a**–**d** was efficiently performed (>99% e.e.) by chiral chromatography as previously described for the preparation of optically pure (+), (−)-**1**.[18] Removal of the Boc protecting group of the resultant enantiomers was effected by standard treatment with TFA in CH_2Cl_2 to afford the corresponding secondary amines **19a**–**d**. The absolute configurations of (+), (−) **19a**–**d** were deduced on the basis of their optical rotations according to the Lowe–Brewster rule[20] coupled with their in vitro binding affinity data at the 5-HT_{2A} receptor. The absolute stereochemistry of the more potent enantiomer (+)-**1** at the 5-HT_{2A} receptor was determined to be 8a-(*S*), 12a-(*R*) by single crystal X-ray crystallography of the HCl salt. These optically pure tetracyclic secondary amines were then converted to the corresponding butyrophenones via the general coupling procedure outlined in Scheme 1.

The SAR optimization of the side chain was initially investigated by introducing a variety of substituents to the phenylbutyrophenone moiety while keeping the core tetracyclic amine unit constant. The binding affinities of the core pyrido[4,3-*b*][1,4]thiazepino[2,3,4-*hi*]indole derivatives (±)-**2**–**16** at the 5-HT_{2A}, 5-HT_{2C}, and DA D_2 receptors are summarized in Table 1.[21] In general, all



Scheme 2. Syntheses of optically pure tetracyclic indolines.

Table 1. Butyrophenone sidechain SAR

Compd	K_i (nM)[a]			D2/5-HT_{2A}
	5-HT_{2A}[b]	DAD_2[c]	5-HT_{2C}[b]	
2	2.7	17	417	6.3
3	2.5	8.8	609	3.5
4	2.1	6.0	200	2.9
5	7.6	14	672	1.8
6	0.7	4.1	106	5.9
7	15	15	258	1.0
8	70	2.3	754	0.03
9	79	4.7	112	0.06
10	90	50	259	0.56
11	62	31	253	0.5
12	0.8	3.4	222	4.3
13	90	7.7	259	0.09
14	51	15.1	349	0.29
15	11	26	48	2.3
16	7.5	18	639	2.4

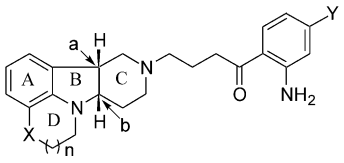
[a]Values are means of three experiment, standard deviation is <0.3.
[b][^{125}I] DOI was used for the 5-HT_{2A} and 5-HT_{2C} assay.[21]
[c][^{3}H] *N*-methylspiperone was used for the D_2 receptor assay.[21]

butyrophenone analogues were determined to be antagonists, as measured by a compound's ability to stimulate the accumulation of [^{3}H]-inositol phosphates (IP_3) in HEK-293e cells expressing the desired receptor,[21] and exhibited potent affinity for the 5-HT_{2A} receptor with varying levels of selectivity for the DA D_2 and 5-HT_{2C} receptors. In addition, functional antagonism at the 5-HT_{2A} receptor was measured as a compound's ability to block the stimulation of IP_3 accumulation induced by 5-HT (300 nM).[21] The parent, completely unsubstituted phenylbutyrophenone derivative **2**, shows the value of this class of compounds as selective 5-HT_{2A} antagonists. The 4′-F analogue **3** exhibits maintained 5-HT_{2A} affinity with modest changes to the selectivity profile. Installation of a 2′-amino group (**4** and **6**) enhances binding affinity at all three receptors relative to their corresponding parent derivatives. However, moving the fluorine to the 3′ or 5′-position (**5** and **7**) caused a modest reduction of binding affinities for both the 5-HT_{2A} and DA D_2 receptors. Introduction of bulkier halide substituents at the 4′-position of the buyrophenone (**8** and **9**) afforded greatly improved affinity for the DA D_2 receptor while lowering 5-HT_{2A} affinity by ~35-fold. As a result, these derivatives display reversed receptor selectivity profile (potent D_2 relative to 5-HT_{2A} affinity) similar to classical neuroleptics.

Further investigation of the SAR was undertaken by functionalizatoin of the 2′-amino group of **6**. Derivatives **12**–**16** demonstrate the sensitivity of the 2′-amino moiety towards affinity for the target receptors. With the exception of the *N*-acetyl analogue **12**, these compounds were roughly 10- to 100-fold less potent at the 5-HT_{2A} receptor than the parent aniline **6**. Corresponding affinities for the D_2 receptor varied and the trend here was less obvious.

To further explore the selectivity profile of these derivatives, the two optimized side chains, portrayed by derivatives **4** and **6**, were then introduced to each optically pure alternate core system **19a**–**d** described in Scheme 2. These derivatives, summarized in Table 2, examine the diversity of the D-ring subunits as well as the stereochemistry of the B–C ring junction.

Table 2. Tetracyclic indoline core SAR



Compd	X	Y	*n*	Stereo chem. a,b	K_i (nM)[a]			D_2/5-HT_{2A}
					5-HT_{2a}[b]	DAD_2[c]	5-HT_{2C}[b]	
(+)-**21**	S	H	1	***S,R***	0.8	41	417	51
(+)-**22**		F		***S,R***	0.3	4.0	90	13
(−)-**21**		H		*R,S*	6.6	19	237	2.9
(−)-**22**		F		*R,S*	1.5	14	184	9.3
(+)-**4**	S	H	2	***S,R***	0.6	15	172	25
(+)-**6**		F		***S,R***	0.4	2.7	82	6.8
(−)-**4**		H		*R,S*	10.4	5.9	320	0.57
(−)-**6**		F		*R,S*	4.2	4.7	452	1.1
(+)-**23**	C	H	1	***S,R***	0.8	68	106	85
(+)-**24**		F		***S,R***	0.5	5.2	53	10.2
(−)-**23**		H		*R,S*	3.7	63	94	17
(−)-**24**		F		*R,S*	1.2	29	71	24
(+)-**25**	C	H	2	***S,R***	0.7	11	106	16
(+)-**26**		F		***S,R***	0.6	3.5	136	5.8
(−)-**25**		H		*R,S*	3.1	20	148	6.5
(−)-**26**		F		*R,S*	0.9	19	136	21
(+)-**27**	O	H	1	***S,R***	1.6	23	335	14
(+)-**28**		F		***S,R***	0.2	2.3	128	12
(−)-**27**		H		*R,S*	11.9	60	501	5.0
(−)-**28**		F		*R,S*	2.8	16	664	5.7

[a]Values are means of three experiment, standard deviation is <0.3.
[b][^{125}I] DOI was used for the 5-HT_{2A} and 5-HT_{2C} assay.[21]
[c][^{3}H] *N*-methylspiperone was used for the D_2 receptor assay.[21]

In general, all examples in this series show excellent potency for the 5-HT_{2A} receptor with good selectivity over the 5-HT_{2C} receptor. In all core series, the (+)-enantiomers, bearing the a-(*S*), b-(*R*) configuration at the B/C ring junction, exhibit superior affinity relative to the corresponding (−)-series compounds for the 5-HT_{2A} receptor. This, however, is not the case with the corresponding DA D_2 affinity, thus affording variant levels of 5-HT_{2A}/D_2 receptor selectivity for these enantiomeric pairs. As can be seen with each initial entry for a core series [(+)-**21**, (+)-**4**, (+)-**23**, (+)-**25**, (+)-**27**] the affinities for the 5-HT_{2A} receptor are nearly equipotent. However, the corresponding D_2 affinities vary significantly even though the butyrophenone side chains are unchanged. Substitution of the 4′-F butyrophenone side chain in the core series [see (+)-**22**, (+)-**6**, (+)-**24**, (+)-**26**, (+)-**28**] affords a slight increase in 5-HT_{2A} affinity with a somewhat diminished range of target receptor selectivity.

Upon close examination of the SAR of the core variants, it is apparent that the derivatives containing 7-membered D-rings are generally more potent at the D_2 receptor than their corresponding six-membered

Table 3. In vivo efficacy of tetracyclic butyrophenones

Compd	Inh. of quipazine induced head twitching[22] ED_{50} (mg/kg) po[a]
(+)-**3**	0.86
(+)-**6**	0.52
(−)-**24**	1.40
(−)-**28**	0.03

[a]Animals were dosed with a 0.25% aqueous Methocell suspension of the test compound orally by gavage.

D-ring congeners [see e.g., (+)-**21** and (+)-**4**, (+)-**23** and (+)-**25**]. However, the effective differences in affinity at the 5-HT_{2A} receptor for these corresponding six-/seven-membered D-ring pairs is insignificant. The overall result is a series of closely related derivatives, varying in both core and side chain substitution, with profiles for the target 5-HT_{2A} and D_2 receptors that allow for a spectrum of selectivity ranging from 1- to 85- fold.

The in vivo efficacy of four representative compounds were determined in a classical rat behavioral assay measuring 5-HT_{2A} antagonism.[22] The data, summarized in Table 3, shows these compounds to be orally bioavailable and highly efficacious as 5-HT_{2A} antagonists in rats. Further studies to examine the viability of these derivatives as potent antipsychotics are planned and the results will be published in due course.

In summary, a series of tetracyclic indoline butyrophenone analogues as 5-HT_{2A}/DA D_2 dual antagonists were prepared and examined for affinity, selectivity, and functional efficacy. The SAR focused on substitutions of the butyrophenone sidechains, composition and size of the D-rings and chirality of the core tetracycles. Selected examples demonstrated excellent oral bioavailability and efficacy as 5-HT_{2A} antagonists in a classical rat behavioral model. The varying affinity ratio of this series at the D_2 and 5-HT_{2A} receptors could be tailored by manipulating the sidechain, D-ring size and composition and absolute stereochemistry of the core tetracycles.

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