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1-Aminoindanes as novel motif with potential atypical antipsychotic properties

James M. Graham,* Linda L. Coughenour, Bridget M. Barr, David L. Rock and Sham S. Nikam

Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, USA

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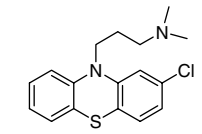
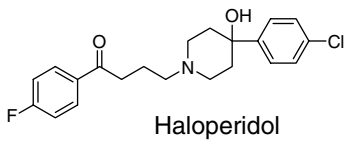
Abstract—As part of an on-going effort to investigate the chemical space requirements for D_2/5-HT_{2A} receptor antagonists as atypical antipsychotics, new 1-aminoindanes were synthesized. The replacement of the heterocycle (oxindole) in ziprasidone with a carbocycle (indane) was well tolerated and was found to retain binding affinities for dopamine D_2, serotonin 5-HT_{2A}, and serotonin 5-HT_{1A}. Such compounds hold promise as a new chemical motif with atypical antipsychotic properties for the treatment of schizophrenia and related disorders.

Schizophrenia is a chronic, debilitating disorder afflicting more than 24 million people worldwide[1] and is generally characterized by positive symptoms (hallucinations, delusions, etc.) and negative symptoms (cognitive deficits, social withdrawal, suicidality, etc.).[2] It is thought that excess dopamine in the brain underlies the positive symptoms of schizophrenia and that blockade of dopamine receptors is a requisite property for antipsychotic activity.[3] Older standards of treatment such as chlorpromazine and haloperidol are potent D_2 receptor antagonists, however, these treatment regimens have neglected negative symptoms, produced motor deficits (extra-pyramidal side effects (EPS)), and are implicated in the development of tardive dyskinesia, a long-term movement disorder.[4]

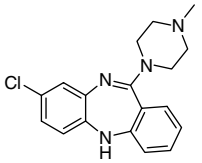
The second generation antipsychotics are referred to as atypical antipsychotics due to their lower propensity to elicit EPS and their moderate efficacy toward negative symptoms. Such compounds have potent activity at several serotonin (5-HT) receptor subtypes that are thought to lead to their improved efficacy and reduced liability for motor side effects. This rich pharmacological profile has led to the D_2/5-HT_{2A} hypothesis.[5] It is thought that potent 5-HT_{2A} antagonism together with relatively weaker dopamine antagonism are principal features that differentiate the side-effect profile of atypical antipsychotics like clozapine from the first generation of treatments such as haloperidol.[5] Although the newer atypical antipsychotics, exemplified by clozapine and olanzapine, have brought improvements in treatment of negative symptomology, chronic treatment with these medicines can still lead to substantial weight gain, blood dyscrasias, and some motor dysfunctions such as EPS.[6] With a high refractive treatment incidence and low compliance due to tolerability, the search continues for new atypical antipsychotics that have a better balance between efficacy and side-effect profile to treat this complex disease.



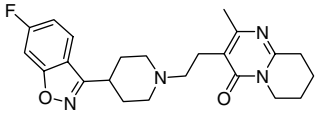
Chlorpromazine



Haloperidol



Clozapine



Risperidone

Keywords: Atypical antipsychotic; D_2 antagonism; 5HT antagonism; hERG; Indane.
* Corresponding author. Tel.: +1 734 649 8971; e-mail: jamesgraha@gmail.com

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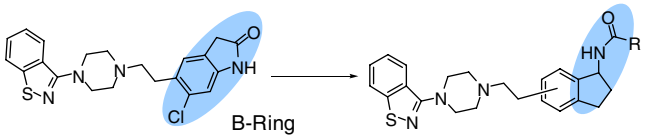
In this paper, we describe our recent efforts to discover novel templates for potential use as treatments of schizophrenia expanding on the D_2/5-HT_{2A} hypothesis and understanding how minor modifications in structure can lead to significant changes in pharmacological profile.[7,8] In addition to the D_2/5-HT_{2A} receptor antagonism, we wanted to retain affinity for serotonin 5-HT_{1A} receptors, an additional efficacy driver for superior treatment of cognitive and affective symptoms of the disorder. Clinical trials have shown that addition of tandospirone, a partial agonist at 5-HT_{1A} receptors, to a first generation antipsychotic produced an improvement in cognitive performance in schizophrenics.[9]

An on-going challenge in developing molecules with this structural and pharmacological profile is to maintain a favorable profile around cardiovascular risk. We achieved this by monitoring affinity for the hERG K^+ channel and adrenergic α_{1A} receptors. Potent α_{1A} receptor antagonism is an indication of potential cardiovascular liability, mainly orthostatic hypotension. However there is evidence that this pharmacology may add to the efficacy of antipsychotics by playing a sympathetic role in attenuating dopamine levels in the brain.[10] Therefore, the impact of the SAR studies on α_{1A} was monitored using radioligand receptor binding. Blockade of the hERG (I_{kr}) K^+ channel has been shown to produce drug-induced QTc prolongation, an activity that has been associated with Torsade de point and cardiac arrest.[11] hERG channel affinity was assessed by measurement of the ability to inhibit binding of dofetilide (DOF), a class III anti-arrhythmic, to recombinant hERG channels. Dofetilide is a potent, selective inhibitor of the potassium (I_{kr}) channel mainly responsible for cardiac repolarization[12,13] and has been correlated with hERG functional activity.[13] The high throughput DOF binding assay was a useful early discovery indicator of hERG activity for this series of compounds.



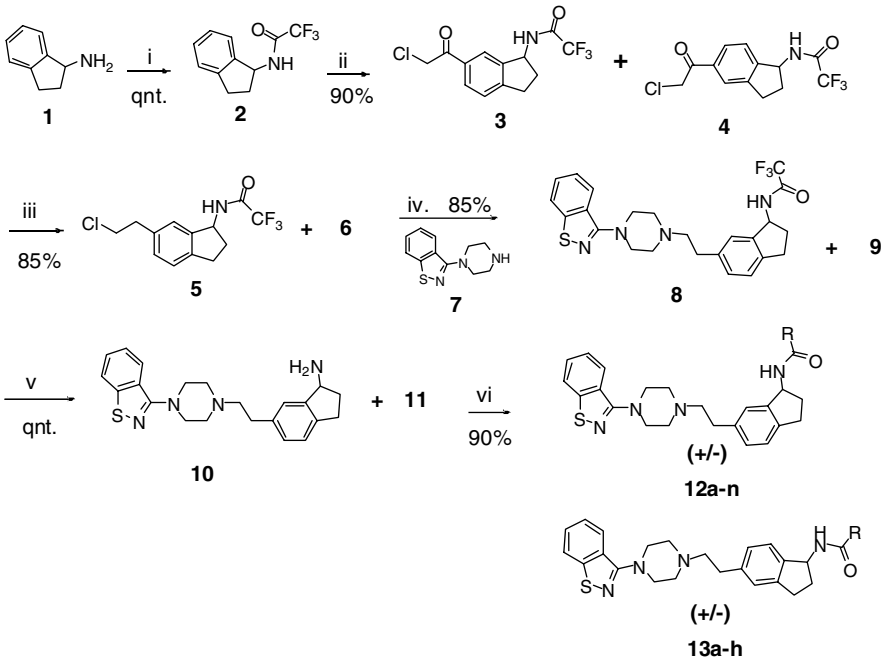
Ziprasidone

Assay	K_i, nM
D_2	5
5-HT_{2A}	0.08
5-HT_{1A}	4
α_{1A}	0.5
DOF	NA

Figure 1. Ziprasidone structure and binding affinities at relevant receptors. Binding data for DOF are not available. Proposed structure changes primarily in the B-ring.

The overall strategy was to use the structure of ziprasidone as a starting point, and replace the heterocyclic B-ring with a carbocycle having an exocyclic amide (Fig. 1) hoping to achieve compounds with low α_{1A} and DOF affinity.

The compounds made in this program include unique 5- and 6-linked 1-aminoindane scaffolds (Scheme 1). The chemistry was amenable to rapid diversification from aminoindanes **10** and **11**. Acylation of commercially available (+/−) 1-aminoindane with trifluoroacetic anhydride proceeded smoothly under common conditions. The trifluoro acetate functionality serves as a robust protecting group that stands up nicely to strongly acidic conditions in subsequent steps. The trifluoroacetamide compound **2** was acylated under standard Friedel–Crafts conditions in high yield to give a 55:45



Scheme 1. Reagents and conditions: (i) TFAA, Et_3N, THF; (ii) chloroacetyl chloride, $AlCl_3$, CH_2Cl_2; (iii) Et_3SiH, TFA; (iv) MeCN, K_2CO_3, μλ 150 °C; (v) K_2CO_3, MeOH/H_2O; (vi) acylating agent, Et_3N, THF.

mixture of isomers that were easily separated by flash chromatography into racemic regioisomers **3** and **4**. Independently, chloroketones **3** and **4** were reduced with triethylsilane in TFA to give chloroethyl compounds **5** and **6**, respectively, providing coupling substrates for the benzisothiazole piperazine **7**.

The conditions for the coupling reaction had to be optimized as under conventional conditions (reflux, 72 h) the piperazine alkylates in a variable 25–40%. Microwave conditions (MeCN, Et_3N, 150 °C) gave significantly improved and consistent yields (~85%) of piperazinyl derivatives **8** and **9** along with shorter reaction times (~15 min). Details of this procedure and method development will be described in a subsequent publication. Regioisomers **8** and **9** were efficiently deprotected under mild conditions to unveil the free amines **10** and **11**, respectively, which were used as convenient substrates for rapid analog preparation. From these common substrates, the appropriate acid chlorides were employed to yield 6-linked targets **12a**–**n** and 5-linked targets **13a**–**g** under standard conditions.

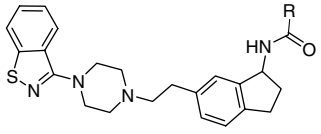
The affinities of target compounds were evaluated in in vitro binding assays using radiolabeled reference ligands [^{3}H]*N*-methylspiperone for D_2; [^{3}H]ketanserin for 5-HT_{2A}; [^{3}H]8-OH-DPAT for 5-HT_{1A}; [^{3}H]prazosin for adrenergic α_{1A}; and [^{3}H]dofetilide for dofetilide binding site in the hERG K^+ channel.[14]

The in vitro binding data for 6-linked 1-aminoindane amides, as well as the primary amine compound **10**, are detailed in Table 1. Overall, the binding affinities across D_2, 5-HT_{2A}, 5-HT_{1A}, and α_{1A} were in the desired range, however, dofetilide binding was high and ranged in affinity from 35 nM to 885 nM. Subtle differences were seen between aryl and alkyl amide motifs. Targets with aryl amides (**12f**–**n**) had up to 4- to 6-fold higher affinity for D_2 than the aliphatic amides **8**, **9**, and **12a**–**e**. These targets also show mixed 5-HT affinities with more than half having 5-HT_{2A} potencies of 1–5 nM giving rise to a less favorable D_2/5-HT_{2A} ratio, which is considered important to mitigating EPS. The aryl amides show a trend toward lower affinities for 5-HT_{1A} and α_{1A}. Aryl amides from this series are hampered by very potent dofetilide binding with compounds **12i** and **12m** having 78 nM and 35 nM binding affinities, respectively.

The alkyl amides **9** and **12a**–**e** have excellent D_2/5-HT_{2A} ratios, high affinities for 5-HT_{1A}, and a good α_{1A} profile relative to D_2, although DOF binding was generally quite potent. Of all the 6-linked targets compounds **9** and **12a** showed the best overall profile including reduced affinity for the dofetilide binding site with K_i values of 616 nM and 885 nM, respectively.

Table 2 shows the in vitro binding data for 5-substituted aminoindane amides **11** and **13a**–**g**. Changes in binding affinities at the D_2 receptor in this series are less subtle, with higher homologs and branched alkyl amides (**13b**–**e)** showing a pronounced lack of affinity for D_2 receptors while they retain higher binding affinities for 5-HT_{2A}, 5-HT_{1A}, and α_{1A}. Binding at α_{1A} is particularly high with several targets showing picomolar affinity. This series also retain the high potency at the dofetilide binding site also seen in the 6-linked isomers **12a**–**l**. Only compounds **13a**, **13f**, and **13g** from this series have reasonable overall binding profiles, although compounds **13f** and **13g** have potent interactions with the dofetilide site. Of the 5-substituted aminoindane amides, **13a** is distinguished as the superior compound with excellent potencies at

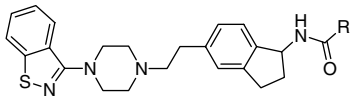
Table 1. 6-Linked 1-aminoindane amides



Compound	R	D_2 K_i, nM[a]	5HT_{2A} K_i, nM[a]	5HT_{1A} K_i, nM[a,b]	α_{1A} K_i, nM[a]	DOF K_i, nM[a]
8	CF_3	10	0.35	4.90	1.92	101
10	[c]	21	0.09	2.0	2.72	616
12a	Me	22	0.01	7.5	1.34	885
12b	Et	34	0.01	5.0	3.03	164
12c	*n*-Pr	27	0.45	5.5	3.96	196
12d	*c*-Pr	21	0.30	12.0	2.22	35
12e	*i*-Pr	67	0.75	12.0	3.61	278
12f	Ph	22	4.75	41.8	10.91	272
12g	4MePh	15	3.00	28.1	13.54	194
12h	4ClPh	5	0.10	56.0	5.64	166
12i	4FPh	6	2.45	66.7	10.26	78
12j	3-Pyridyl	6	0.95	4.5	3.31	358
12k	CH_2Ph	26	0.04	20.9	5.27	201
12l	$(CH_2)_2Ph$	33	0.95	37.2	10.33	511
12m	2-Furyl	5	0.55	7.9	1.38	35
12n	5-(1,2-Oxazoyl)	3	0.08	6.5	1.88	150

[a] Values are geometric means of at least three experiments.
[b] All compounds are partial agonists with 60–80% intrinsic functional activity.
[c] Free primary amine as seen in Scheme 1.

Table 2. 5-Substituted aminoindane amides



Compound	R	D_2 K_i, nM[a]	$5HT_{2A}$ K_i, nM[a]	$5HT_{1A}$ K_i, nM[a,b]	α_{1A}, K_i, nM[a]	DOF, K_i, nM[a]
9	CF_3	8	0.15	1.0	0.30	143
13a	Me	15	0.33	1.1	3.18	2202
13b	Et	21% at 100 nM	0.25	2.0	0.45	184
13c	*n*-Pr	21% at 100 nM	0.50	2.0	0.90	269
13d	*c*-Pr	27% at 100 nM	0.45	2.0	0.73	137
13e	*i*-Pr	17% at 100 nM	0.65	1.0	0.49	219
13f	4FPh	10	1.65	7.8	15.58	135
13g	3-Pyridyl	5	0.68	7.7	17.37	202

[a] Values are means of at least three experiments.
[b] All compounds are partial agonists with 60–80% intrinsic functional activity.

D_2, 5-HT_{2A}, 5-HT_{1A}, and α_{1A} as well as having the lowest binding affinity for DOF with micromolar activity.

Interesting differences between the 5- and 6-substituted 1-aminoindane amides were clearly seen in D_2 binding with additional differences seen in the serotonin and adrenergic receptors as well. Of particular note in both series, the acetamide analogs stood out as having superior pharmacological profiles including a reduced affinity for dofetilide binding.

In summary, a series of novel 5- and 6- substituted aminoindanes were synthesized and evaluated for in vitro affinity at D_2 and 5-HT (2A and 1A subtype) receptors, as well as adrenergic α_{1A} and hERG K^+ channel receptors. This series of compounds possess potent activity at 5-HT_{2A} providing ample separation from D_2 activity suggesting the potential for wide therapeutic index between efficacy and EPS. Addition of potent binding at 5-HT_{1A} may provide an additional efficacy driver and lead to better treatment of cognitive and affective symptomology in schizophrenia. Although both 5- and 6- substituted aminoindanes showed varying pharmacologic profiles across these receptors, the methyl amides **12a** and **13a** from each series stood out as leading candidates for further development. Work is in progress to separate and fully characterize the stereoisomers of these leads. Future SAR around the 1-aminoindane scaffold should focus on small amides or amide isosteres and avoid higher homologs and branched alkyl substrates. This SAR indicates that changing the B-ring heterocycle to a carbocycle with an external amide is a viable strategy toward identifying new chemical space with atypical antipsychotic pharmacology.

References and notes

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14. Standard filtration receptor binding techniques were used to evaluate the affinity of compounds for recombinant receptors. The dopamine D_2 receptor binding assay utilized cell membranes prepared from CHO cells expressing human dopamine D_{2L} receptors radiolabeled with [^{3}H]spiperone. The 5-$HT_{2\ A}$ receptor binding assay utilized cell membranes prepared from Swiss 3T3 cells expressing human 5-HT_{2A} receptors radiolabeled with [^{3}H]ketanserin. The 5-HT_{1A} receptor binding assay utilized cloned human 5-HT_{1A} receptor radiolabeled with [^{3}H]8-OH-DPAT. The adrenergic α_{1A} receptor binding assay utilized cloned rat alpha1a in fibroblast cell membranes radiolabeled with [^{3}H]prazosin. The hERG potassium channel binding assay utilized HEK-293 cells that contained the hERG channel radiolabeled with [^{3}H]dofetilide. Membrane preparations and radioligand were incubated in the presence, or absence, of varying concentrations of the compound of

interest until steady state was reached. Nonspecific binding was determined by addition of high concentrations of haloperidol, unlabeled ketanserin, phentolamine, WAY 100135, and unlabeled dofetilide for the D_{2L}, 5-HT_{2A}, 5-HT_{1A}, adrenergic α_{1A}, and hERG potassium channel assays, respectively. Unbound radiolabel was separated from bound radiolabel by vacuum filtration. The amount of bound radiolabel was determined by liquid scintillation spectrophotometry. The relationship between concentration and percent inhibition of specific binding was fit using nonlinear regression to determine IC_{50} concentration. IC_{50} concentrations were converted to K_i affinity constants using the Cheng–Prusoff equation.