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NOVEL ETHER DERIVATIVES OF ALKYL PIPERIDINES AS POTENTIAL SIGMA / $5HT_2$ ANTIPSYCHOTIC AGENTS

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Abstract. A series of novel cinnamyl and propargyl ether derivatives of alkyl piperidines which show high affinity for sigma and $5HT_2$ receptors are described. The ligands exhibit high selectivities for these receptors over D_2 as well as good activity *in vivo* in an anti-mescaline scratch assay.

Schizophrenia and its associated affective disorders continues to exist without an effective treatment lacking the side effects associated with current antipsychotics. Despite enormous advancements in the areas of neurobiology and neurochemistry, which have broadened our understanding of normal and abnormal mental processes, there is still no clear understanding of the disease etiology.

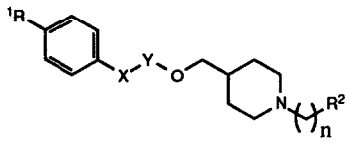
Traditional antipsychotic drugs such as the phenothiazines, butyrophenones and thioxanthenes are effective in treating the positive symptoms of schizophrenia, presumably through antagonist activity at dopamine D_2 receptors.[1] Their prolonged use, however, often leads to extrapyramidal side effects resembling idiopathic Parkinsonism.[2] The atypical antipsychotic clozapine has been show to be effective in treating both the positive and the negative symptoms of the disease, and is effective in many patents resistant to classical antipsychotic drugs. Unfortunately, clozapine produces agranulocytosis,[3] a potential life threatening side effect. Its mechanism of action is still unclear but multiple receptor systems including serotonin $5HT_{1c}$,[4] $5HT_2$, dopamine (DA) D_2, D_1, D_4 and glutamate[5-9] receptors may also play a role.

Given the lack of understanding of the neurochemistry in psychosis and the problems associated with current drugs, alternative mechanisms have been considered. Research in the area of the sigma (σ) receptor and its possible role in psychosis has steadily increased over the past few years. Based on activity in animal behavioral models, it has been suggested that a sigma receptor ligand might be useful as an antipsychotic agent .[10,11] There still exists much speculation as to the role of the σ binding site in the disease and whether or not it is a true receptor.[12] Evidence suggests, however, that there is a connectional relationship to the dopamine system through indirect modulation of dopaminergic function.[13,14]

There appears to be stronger evidence that the serotonin (5HT) neuronal system plays a key role in the disease process. Several reviews have appeared in the literature suggesting serotonin $5HT_2$ as well as $5HT_{1D}$ and $5HT_3$ are involved in mediating the negative effects of psychosis.[15,16,17] Although there appears to be a strong tie to the serotonin system, most studies involve the use of clinical candidates that have affinities for multiple receptors making any definitive conclusion difficult.

The novel compounds in the present study have combined σ and $5HT_2$ receptor affinities while having little or no affinity for the D_2 receptor (Tables 1 and 2). The σ and D_2 binding assays were performed using [^{3}H](+)-SKF-10,047 and [^{3}H]spiperone respectively as radioligands.[18] [^{3}H]Ketanserin was used as the radioligand in the $5HT_2$ receptor binding assay as reported by Wander.[19] They were also examined in an *in vivo* anti-mescaline scratch assay[20] to determine their potential in treating schizophrenia.

Table 1. Cinnamyl ether biological data.

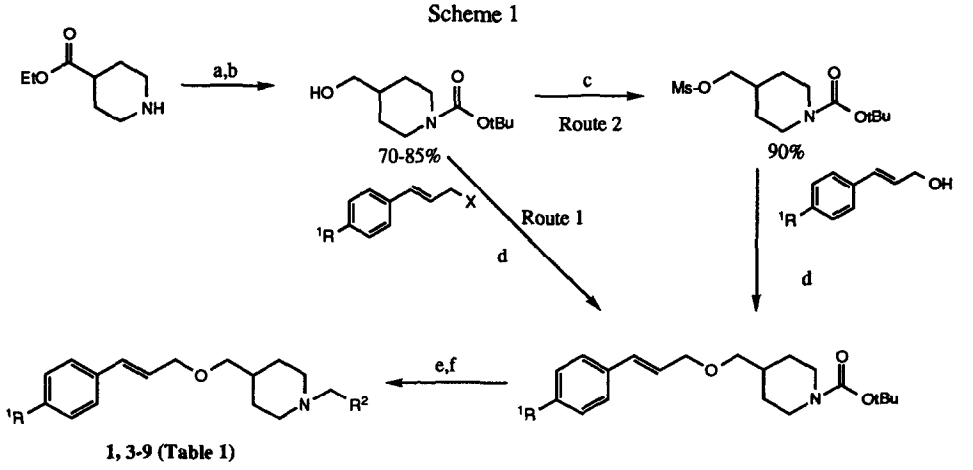


Ex.	X	Y	R^1	R^2	n	Sigma Ki, nM	D_2 Ki, nM	5 HT_2 Ki, nM	Anti-Mesc. ED_{50} mg/kg (PO)
1	CH=CH	CH_2	H	Ph	1	7	>10,000	44	6
2	CH=CH*	CH_2	H	Ph	1	90	>10,000	>10,000	nt
3	CH=CH	CH_2	H	Ph	2	5	241	250	5
4	CH=CH	CH_2	H	Ph	3	18	948	283	9
5	CH=CH	CH_2	H	cyclopropyl	1	5	>10,000	1,847	>30
6	CH=CH	CH_2	H	naphthyl	1	8	>10,000	284	>10
7	CH=CH	CH_2	H	CH=C(CH3)	1	8	>10,000	650	>30
8	CH=CH	CH_2	F	Ph	1	12	2,183	31	8
9	CH=CH	CH_2	CF_3	Ph	1	28	4,324	324	>10
10	CH=CH	CH=CH	H	Ph	1	212	>10,000	547	nt
11	PhC=CH	CH_2	H	Ph	1	22	620	29	>30

* Cis double bond, all others trans, nt=not tested

Examples **1**, and **3-9** were prepared via the method outlined in Scheme 1 following either route 1 or 2. Starting from commercially available ethyl isonipecotate and following protection as the t-butyl carbamate, the hydroxymethyl piperidine intermediate was prepared by lithium borohydride reduction. This intermediate was either treated directly with the appropriately substituted cinnamyl halide (route 1) or converted to the methanesulfonate derivative (route 2) and then coupled to cinnamyl alcohol. Deprotection with 3 molar HCl in ethyl acetate followed by N-alkylation afforded the target cinnamyl ether derivatives.

Scheme 1

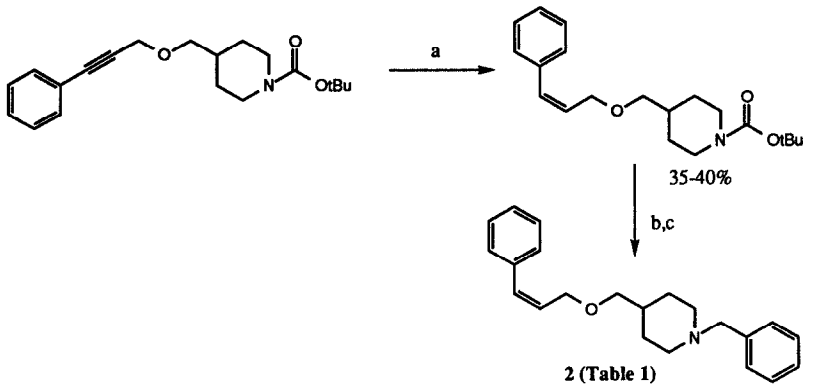


1, 3-9 (Table 1)

a) $(BOC)_2O$, NaOH, THF; b) $LiBH_4$, $B(OMe)_3$, THF; c) $(CH_3SO_2)_2O$, CH_2Cl_2, $(CH_3CH_2)_3N$; d) NaH, THF; e) 3M HCl/ethyl acetate; f) XCH_2R^2, K_2CO_3, ethanol X=Br or Cl

The *cis* double bond example **2** was prepared via reduction of the propargyl ether intermediate using palladium on barium sulfate[21] under atmospheric hydrogen followed by BOC deprotection and alkylation (Scheme 2). Standard partial reduction using palladium on calcium carbonate (Lindlar catalyst) using various reaction conditions produced the over reduced product.

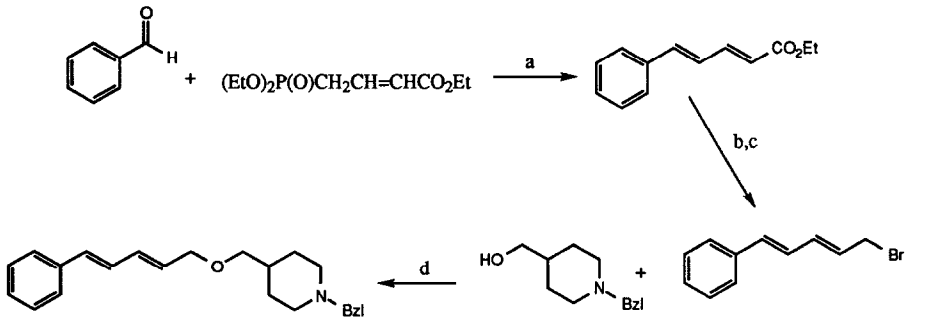
Scheme 2



a) 5% $Pd/BaSO_3$, freshly distilled quinoline, H_2 1 atm; b) 3M HCl/ethyl acetate; c) benzyl bromide, K_2CO_3, ethanol

The divinyl ether analog **10** was prepared via the route outlined in Scheme 3 and utilizes a modified Wittig[22] reaction of benzaldehyde and triethyl 4-phosphonocrotonate to give the divinyl ester adduct. DIBAL-H reduction followed by bromination provided 1-bromo-5-phenyl-2,4-pentadiene which was then coupled to N-benzyl-4-hydroxymethyl piperidine under standard conditions to give the target compound.

Scheme 3



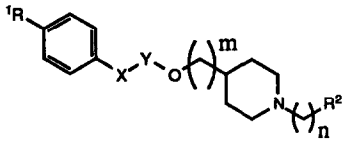
10 (Table 1)

a) NaH/DMF; b) DIBAL-H, THF, reflux; c) PBr_3, ether, 0°C; d) NaH/THF, RT

The propargyl ether derivatives were generally prepared through a coupling of propargyl chloride and the appropriately protected piperidine alcohol followed by deprotection and alkylation.

Example **18** was prepared via a straight forward coupling of N-benzyl-4-hydroxymethyl piperidine and 1-bromo-3-phenylpropane.

Table 2. Propargyl ether biological data.



Ex.	X	Y	R^1	R^2	m	n	Sigma Ki, nM	D_2 Ki, nM	5 HT_2 Ki, nM	Anti-Mesc. ED_{50} mg/kg (PO)
12	C≡C	CH_2	H	Ph	1	1	4	>10,000	254	>30
13	C≡C	CH_2	H	Ph	0	2	4	1,356	72	>10
14	C≡C	CH_2	H	Ph	2	2	7	131	21	4.1
15	C≡C	CH_2	H	cyclopropyl	2	1	1	>10,000	947	>10
16	C≡C	CH_2	H	p-F Ph	2	2	18	1,837	85	3.6
17	C≡C	CH_2	F	Ph	2	2	2	1,062	81	>10
18	CH_2CH_2	CH_2	H	Ph	1	1	27	554	180	>30

We have prepared two related series of compounds, both of which have several examples whose pharmacological profile suggest their potential use as novel antipsychotics. Exampes **1**, **3**, **4** and **8** of the cinnamyl ether derivatives along with **14** and **16** of the progargyl ether series showed good *in vivo* activity. There appears, however, to be closer agreement to 5HT_2 binding than to σ binding in this anti-mescaline scratch assay. This is not to suggest 5HT_2 is the only neurochemical system involved in the *in vivo* profile. More likely the anti-mescaline activity reflects a combination of multiple receptor activities. One may be tempted to attribute any differences in activity to absorption, metabolism and distribution differences among these analogs. However, given that many of the structural differences are quite subtle, the likelihood that there is a drastic change in pharmacokinetic properties is remote.

In previous studies[23,24] we examined the distance requirements between the piperidine nitrogen and the centroid of the distal aromatic ring verses sigma binding affinities. Although computer modeling and energy minimization has not been done on the two series of compounds described in this publication, based on the structural similarities it is expected that similar results would be obtained. To that end, example **10** offers support to the conclusions drawn in those studies. For example, one of our initial models suggested an upper distance limit for the distal

aromatic ring to the piperidine nitrogen was 6±2 Å to maintain good σ binding. **10** has a rigid and extended linker to the aromatic ring which may be pushed beyond this limit and thus decrease σ binding affinity. Although the data presented here is limited, it is apparent $5HT_2$ affinity is more sensitive to substituent changes. Subtle modifications such as going from N-benzyl **1** to N-phenethyl **3** and *trans* **1** to *cis* **2** double bonds reduces $5HT_2$ affinity.

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