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Design, optimization, and in vivo evaluation of a series of pyridine derivatives with dual NK_1 antagonism and SERT inhibition for the treatment of depression

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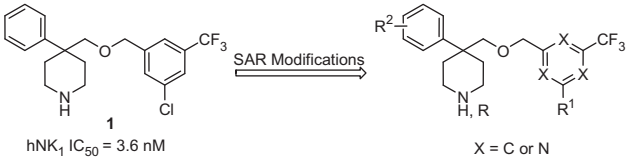
ABSTRACT

A series of substituted pyridines, ether linked to a phenylpiperidine core were optimized for dual NK_1/SERT affinity. Optimization based on NK_1/SERT binding affinities, and minimization of off-target ion channel activity lead to the discovery of compound **44**. In vivo evaluation of **44** in the gerbil forced swim test (a depression model), and ex-vivo NK_1/SERT receptor occupancy data support the potential of a dual acting compound for the treatment of depression.

The therapeutic potential of tachykinin receptor antagonists for the treatment of depression has been a subject of discussion for many years.[1] Although Phase II clinical trials with the NK_1 receptor antagonist Aprepitant[2] showed evidence of antidepressant efficacy, Phase III trials with Aprepitant as well as a follow-on NK_1 receptor antagonist Casopitant did not support these initial positive findings.[3] While these results have negatively impacted the development of NK_1 antagonists as single agents for the treatment of depression, there has been interest in the combination of NK_1 receptor antagonism with Serotonin Transporter (SERT) inhibitor activity as a potential means of potentiating the antidepressant effect of NK_1 antagonism.[4]

We set out to develop a series of molecules with dual acting NK_1 antagonism and SERT inhibition, with high affinity for both targets. Early efforts focused on identifying chemotypes that had good physicochemical properties and potential for brain uptake. A (4-phenylpiperidine-4-yl)-methyl ether chemotype, exemplified by **1**, was chosen as our starting point.[5] We designed a series of analogs directed toward improving NK_1/SERT affinity,[6] and decreasing off-target ion channel activity (Fig. 1). Initial SAR focus revolved around introducing a substituted pyridine on the ether side-chain as a means of increasing polarity in this series (Scheme 1).

Comparison of **1** with its direct pyridine analogue **6** showed that incorporation of a pyridine ring was tolerated, although potency was diminished three–four-fold for both NK_1 antagonism and SERT inhibition compared to **1** (Table 1). Modification around the left-hand phenyl ring significantly impacted both NK_1 and SERT binding affinities. In general, decreases in hERG flux activity paralleled the decrease in NK_1/SERT activity in this series. It should be noted that to date a 4-fluorophenyl substituent on the piperidine



1

hNK_1 IC_{50} = 3.6 nM
hSERT IC_{50} = 1.7 nM
Ca Flux IC_{50} = 5.2 μM
hERG Flux IC_{50} = 7.2 μM

X = C or N

Figure 1. SAR strategy around the 4-methyl-4-phenylpiperidine core.

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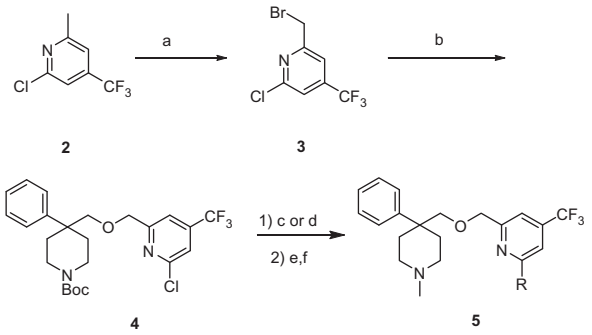
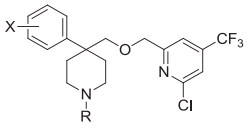


Scheme 1. Reagents and conditions: (a) NBS/CCl_4; (b) KOtBu/THF, *tert*-butyl 4-(hydroxymethyl)-4-phenylpiperidine-1-carboxylate; (c) $Pd(Ph_3P)_4$/MeCN/KOH/120°C, R-B$(OH)_2$; (d) $Pd(OAc)_2$, NaOtBu, rac-BINAP, toluene, 120°C, R = 1° or 2° amine; (e) TFA, CH_2Cl_2; (f) formaldehyde, $NaCNBH_4$, MeCN.

Table 1
In vitro profiling data for the first generation pyridine analogues **6**–**11** produced via Scheme 1



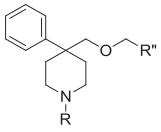
Compd.	R	X	hNK_1[a] IC_{50} (nM)	hSERT[a] IC_{50} (nM)	Ca flux IC_{50} (μM)	hERG flux IC_{50} (μM)
6	H	H	11	7.4	2	28
7	CH_3	H	12	6.3	7	25
8	CH_3	4-Cl	430	23	11	23
9	H	4-F	29	9.0	7	20
10	CH_3	4-F	45	4.3	5	6
11	CH_3	2-F	52	88	6.3	43

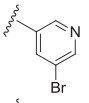
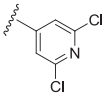
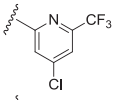
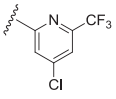
[a] Values are the mean of two experiments.

was the best tolerated modification on the 4-phenylpiperidine ring. Alkylation of the piperidine nitrogen with a methyl group improved SERT binding affinity slightly, while having little impact on NK_1 affinity. Additional alkyl groups were explored on the piperidine nitrogen, but a methyl substituent was determined to be optimal.[7]

Altering the position of the pyridine nitrogen impacted NK1 affinity significantly, demonstrating a clear preference for 2- and 4-substituted pyridines. Comparison of **6** and **15** (and **7**/**16**) shows a further preference for having the trifluoromethyl group in the 4-position relative to the pyridine nitrogen (Table 2). Removal of substitution on the 4-position significantly decreased NK_1 binding affinity as demonstrated by example **13**. In contrast to the above

Table 2
In vitro profiling data for 'right-hand' substituted pyridine analogues **12**–**16** produced via Scheme 2



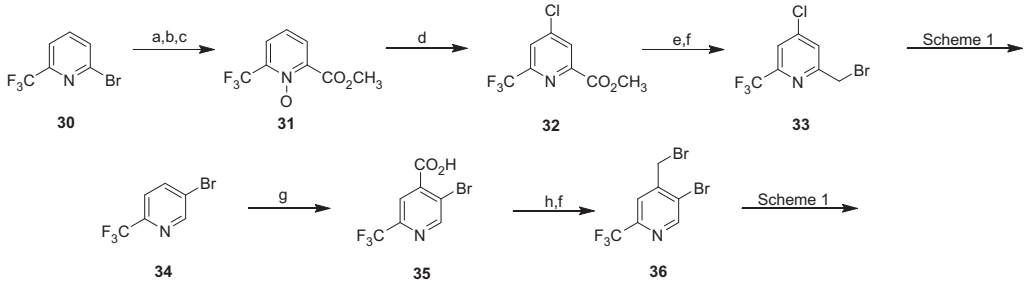
Compd.	R	R″	hNK_1[a] IC_{50} (nm)	hSERT[a] IC_{50} (nM)	Ca flux IC_{50}(μM)	hERG flux IC_{50} (μM)
12	H		600	10	21	15
13	CH_3		480	3.1	30	13
14	H		34	6.6	7	33
15	H		74	6.3	7	25
16	CH_3		66	14	7	12

[a] Values are the mean of two experiments.

findings the pyridine nitrogen position had minimal effects on SERT potency.

Additional modification of the pyridine ring was explored fixing the trifluoromethyl group in the 4-position while altering the 2-position with a variety of acyclic and cyclic amines. This exercise lead to analogues with significant improvements in NK_1 and SERT affinities, as well as in some examples, decreasing off-target ion channel activity in the flux assays (Table 3). Both acyclic and cyclic amines possessed good NK_1/SERT binding affinities. There was a clear preference for tertiary amines having better dual activity than secondary amines, although branching alpha to the nitrogen improved potency as in secondary amine **20**. Extended branching of the alkyl groups decreased both NK_1 and SERT affinities as in example **22**. Addition of a second basic amine as in the 4-methyl piperazine **28** also significantly decreased both NK_1 and SERT affinities.

In vitro profiling of one of the better analogues in this series compound **25**, demonstrated that introduction of an amino functionality has a positive impact on protein free fraction (human,



Scheme 2. Reagents and conditions: (a) BuLi, THF, CO_2; (b) mCPBA, CH_2Cl_2; (c) MeOH, HCl; (d) $POCl_3$, 100°C; (e) $NaBH_4$, MeOH; (f) CBr_4, Ph_3, CH_2Cl_2.