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Dual NK_1 Antagonists—Serotonin Reuptake Inhibitors as Potential Antidepressants. Part 2: SAR and Activity of Benzyloxyphenethyl Piperazine Derivatives†

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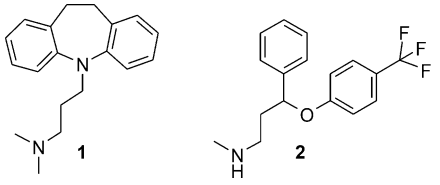
Abstract—The synthesis, structure–affinity relationship and activity of benzyloxyphenethyl piperazine derivatives combining NK_1 antagonism and serotonin reuptake inhibition is described. Compound **7u** was shown to be active in animal models of 5-HT reuptake inhibition and central NK_1 receptor blockade, and was demonstrated to be orally active in an integrated model sensitive to both mechanisms. This class of compounds potentially represents a new generation of antidepressants.

Depression is reported to affect up to 10% of the population[2] and is linked with a significant mortality. Antidepressant therapies using tricyclics (such as imipramine **1**) or Selective Serotonin Reuptake Inhibitors (SSRIs) such as fluoxetine **2** are efficacious in about 70% of patients but are associated with side effects such as dry mouth and blurred vision for tricyclics, and gastrointestinal distress, anxiety, insomnia and sexual dysfunction for the SSRIs.

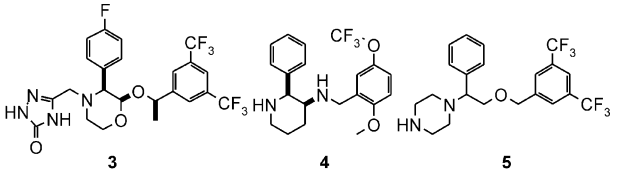
Another common problem in current therapies is their slow onset of action, since a delay of about 4 weeks is normally observed between the beginning of the treatment and alleviation of the symptoms. This delay appears to parallel the progressive desensitization of somatodendritic $5HT_{1A}$ receptors which in turn gradually increases serotoninergic function. Indeed, clinical evidence shows that co-administration of a $5\text{-}HT_{1A}$ antagonist such as pindolol has a beneficial effect on the onset of action of SSRIs.[3,4]

Several lines of research[4,5] are being pursued along these lines for the discovery of new antidepressants, as well as non-monoaminergic approaches such as estrogen,[6,7] CRF[8–14] and NK_1[15] receptor ligands (Scheme 1).



Scheme 1. First- and second-generation antidepressants.

Thus far, NK_1 antagonists[15–18] seem especially promising. Indeed, in an animal model of depression,[19] NK_1 antagonists have a faster onset of action than imipramine (**1**). In clinical trials, two NK_1 antagonists, MK-869[16] (**3**) and CP 122,721[20,21] (**4**) were reported to have robust efficacy in treating depression (Scheme 2).



Scheme 2. NK_1 antagonists: MK-869, CP 122,721 and compound **5**.

†For Part I, see ref 1.

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The mode of action of NK_1 antagonists is now believed to involve an indirect modulation of 5-HT function, via Noradrenergic pathways.[22,23] NK_1 receptor knock-out mice and wild-type mice treated with NK_1 antagonists have an attenuated presynaptic $5HT_{1A}$ receptor function.[23–25] The combination of serotonin reuptake inhibition with NK_1 antagonism (modulating $5HT_{1A}$ function) may thus lead to a new class of antidepressants with an improved onset of action and better efficacy.

The optimisation of a family of phenoxyacetamides with dual affinities for the NK_1 receptor and the Serotonin Reuptake Site has recently been reported,[1] while Merck has described in the patent literature compounds claimed to have a similar profile.[26] We now report the SAR and in vivo activity of benzyloxyphenethyl piperazine derivatives that similarly combine Serotonin Reuptake Inhibition and NK_1 antagonism.

Screening[27–29] of NK_1 antagonists from the UCB compound collection against the Serotonin Transporter (ST) resulted in the identification, amongst others, of compound **5** (Table 1), which displays excellent affinity for the NK_1 receptor but moderate affinity for the ST. This compound was used as a starting point for this work.

Chemistry

The key alcohols **6** were prepared by either substitution of a bromo phenylacetic ester with the Boc-protected piperazine followed by reduction, or by an efficient, three component reaction[30,31] between an arylboronic acid, glycolaldehyde and the Boc-protected piperazine. Enantiopure **6** were prepared by reaction of homochiral phenylglycinols with the activated *N*-tosyl diethanolamine derivative. Alcohols **6** were then *O*-benzylated and deprotected to afford the corresponding compounds **7** in racemic (**7a**–**q**) or enantiopure (**7r**–**u**) form (Scheme 3).

Table 1. Affinities of compounds **2**–**7** for the NK_1 receptor and the Serotonin Transporter (ST)

Compd (configuration)	R_1	R_2	pIC_{50} NK_1[a]	pIC_{50} ST[a]
2 fluoxetine	—	—	—[b]	8.2
3 MK 869	—	—	10.0[c]	—
5	—	**3′, 5′-di CF_3**	**8.3**	**6.6**
7a	4-F	3′, 5′-di CF_3	7.0	6.8
7b	4-OMe	3′, 5′-di CF_3	7.3	7.0
7c	3-Cl	3′, 5′-di CF_3	8.8	6.6
7d	3-iPr	3′, 5′-di CF_3	7.4	6.5
7e	3-OMe	3′, 5′-di CF_3	9.0	6.7
7f	2-F	3′, 5′-di CF_3	8.3	6.7
7g	2-Cl	3′, 5′-di CF_3	8.8	6.7
7h	2-OMe	3′, 5′-di CF_3	8.2	6.6
7i	3,4-di Cl	3′, 5′-di CF_3	8.3	6.7
7j	2,3-di F	3′, 5′-di CF_3	8.5	6.5
7k	—	3′, 5′-di Me	7.6	—[d]
7l	—	3′, 5′-di ^{t}Bu	7.0	6.0
7m	—	3′-Cl	6.4	8.1
7n	—	3′, 5′-di F	6.7	9.1
7o	—	**3′-CF_3, 5′-F**	**7.9**	**7.8**
7p	—	**3′-Br, 5′-I**	**8.9**	**7.6**
7q	—	**1′-OMe, 3′, 5′-di Br**	**8.1**	**8.2**
7r (*R*)	—	3′, 5′-di Cl	7.6	7.9
7s (*S*)	—	**3′, 5′-di Cl**	**8.5**	**8.6**
7t (*R*)	—	3′, 5′-di Br	7.9	7.5
7u (*S*)	—	**3′, 5′-di Br**	**8.5**	**8.0**

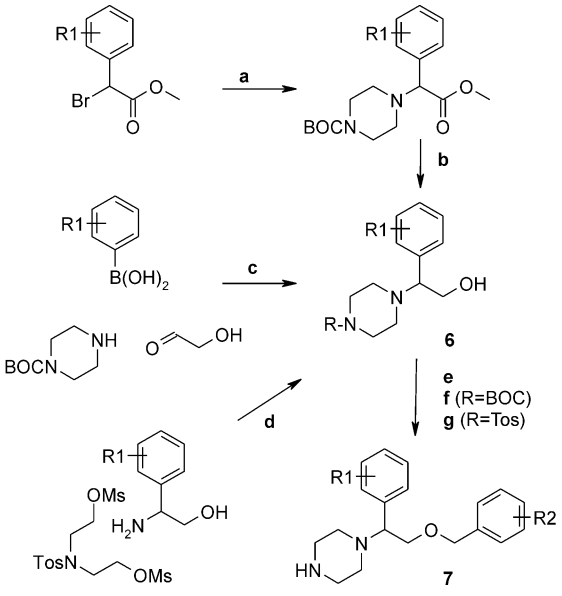
[a]Values are means of two experiments.
[b]Less than 50% inhibition at 10^{-5} M.
[c]See ref 32.
[d]Not tested.

Results

Modification of R_1 while keeping R_2 substitution constant showed that the NK_1 receptor does not tolerates 4-substituents while affinities for the ST were slightly improved (**7a**, **7b**). Substitution of the 3-position with chloro- or methoxy- was beneficial to NK_1r binding (**7c**, **7e**) but affinities for the ST were unaffected. Finally 2-substitution with a chloro group (**7g**) was found to improve affinities for the NK_1r but again left affinities for the ST unchanged. 3,4- and 2,3-Disubstitutions were not beneficial (**7i**, **7j**). We then turned to modification of R_2 in order to improve affinity for the ST.

Substitution with small (**7k**) or large (**7l**) alkyl groups led to an overall loss of affinities. Monosubstitution (**7m**) or disubstitution with the smaller fluoro atoms (**7n**) led to an important reduction of the affinities toward NK_1r while ST binding was greatly improved. Unsymmetrical disubstitution with the 3′-CF_3, 5′-F (**7o**) or 3′-bromo 5′-iodo (**7p**) provided compounds with high affinities for both targets. Trisubstitution (**7q**) was also beneficial.

At this stage, enantiopure compounds bearing the 3′,5′-dichloro and 3′,5′-dibromo substitution (**7r**–**7u**) were prepared. Fortunately, in each case, the *S* enantiomers displayed very high affinities toward both targets, while



Scheme 3. Preparation of benzyloxyphenethyl piperazines: (a) BOC-piperazine, K_2CO_3, DMF, rt; (b) $LiBH_4$, THF, reflux; (c) CH_2Cl_2, rt; (d) Et_3N, DMF, 80 °C; (e) NaH, THF, Benzyl bromide, NaI, 60 °C; (f) TFA–CH_2Cl_2; (g) AcOH–HBr, 90 °C.

the *R* enantiomers proved to be inferior. Compounds **7s** and **7u** were selected for further examination in vivo.

To assess the central 5-HT reuptake blockade properties of the compounds, we tested their ability to increase extracellular 5-HT levels in the frontal cortex of freely moving rats by using intracerebral microdialysis.[33] Intraperitoneal administration of **7u** (3.2×10^{-5} mol/kg, $n=2$) increased 5-HT levels up to 250% of baseline for more than 3 h. In this model, **7s** was found to be poorly active, possibly because of metabolic instability or limited brain penetration. Activity of **7u** as a NK_1 antagonist was assessed using the gerbil foot-tapping model as described by Rupniak.[34] At the dose of 3.2×10^{-5} mol/kg (ip, $n=5$), **7u** decreased by 45% the duration of the foot-tapping, indicating efficacious central blockade of NK_1 receptors. Finally, in the isolation-induced guinea pig pup vocalization test, an integrated behavioural model sensitive to both SSRI and NK_1 antagonists,[35] **7u** was shown to be orally active, as it was able to attenuate by 50% (1×10^{-5} mol/kg, $n=8$) and 99% (3.5×10^{-5} mol/kg, $n=8$) the duration of vocalizations.

In conclusion, we were able to optimise a family of benzyloxyphenethyl piperazines to the level of fluoxetine for the ST, with an added affinity for the NK_1 receptor. One of the best compounds in this family was shown to be active in animal models indicative of 5-HT reuptake inhibition and central NK_1 receptor blockade, and was demonstrated to be orally active in an validated animal model of depression sensitive to both mechanisms.

Further developments in this area will be reported in due course.

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