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First Dual NK_1 Antagonists–Serotonin Reuptake Inhibitors: Synthesis and SAR of a New Class of Potential Antidepressants

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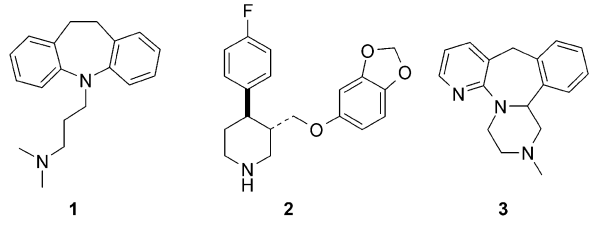
Abstract—Compounds combining NK_1 antagonism and serotonin reuptake inhibition are described, and potentially represent a new generation of antidepressants. Compound **24** displays good affinities for both the NK_1 receptor and the serotonin reuptake site (32 and 25 nM, respectively).

Depression is reported to affect up to 10% of the population, with a lifetime prevalence of 19%[1] and is linked with a significant mortality.

First-generation tricyclic antidepressants such as Imipramine (**1**) induce severe side effects (e.g., anticholinergic).[2] They were replaced in the 1980's by the selective serotonin reuptake inhibitors (SSRI) such as Paroxetine (**2**) (Scheme 1).



1 2 3

Scheme 1. Examples of first, second and third generation antidepressants.

SSRIs have fewer side effects than tricyclics, but nevertheless display their own side effects, such as gastrointestinal distress, anxiety, insomnia and sexual dysfunction due to their indirect activation (through elevation of 5-HT levels) of all 5-HT receptors.

More recently, third generation antidepressants have appeared, such as noradrenaline reuptake inhibitors (NRI), serotonin–noradrenaline reuptake inhibitors (SNRI) and noradrenaline–dopamine reuptake inhibitors (NDRI). The recently introduced Mirtazapine (**3**) is a noradrenergic and specific serotoninergic antidepressant (NaSSa) displaying affinities for the α_2, 5-HT_2, 5-HT_3 and H_1 receptors. Compared with SSRIs, Mirtazapine is reported to have a slightly faster onset of action, a beneficial effect on sleep quality, and fewer side-effects such as anxiety[3] and sexual dysfunction.[4]

However, a common problem in current antidepressant 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, increasing serotoninergic function, thus allowing alleviation of depressive symptoms. Indeed, clinical evidence shows that co-administration of a 5-HT_{1A} antagonist such as Pindolol has a beneficial effect on the onset of action of SSRIs.[5,6] Moreover, this combination has allowed major improvements for SSRI-resistant patients. Serotonin reuptake inhibitors with an added 5-HT_{1A} antagonism component are thus actively researched.[7,8]

Several lines of research[6,9] are being pursued for the discovery of new antidepressants with less side effects, a faster onset of action and a better rate of response, including non-monoaminergic approaches such as

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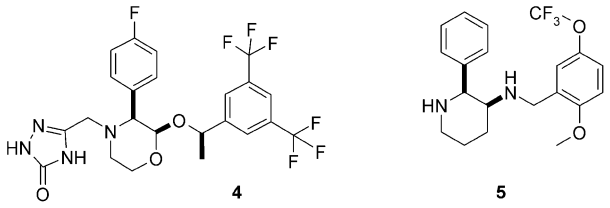
CRF[10–14] and NK_1 antagonists.[15–18] In mice, the genetic disruption of NK_1 receptor decreases anxiety-related behavior;[19] moreover NK_1 antagonists have been reported to have a faster onset of action than Imipramine (**1**) in an animal model of depression.[20]

Finally, robust efficacy in treating depression was reported in clinical trials for two NK_1 antagonists, MK-869[16] (**4**) and CP 122,721[22,21] (**5**) (Scheme 2).



Scheme 2. MK-869 and CP 122,721.

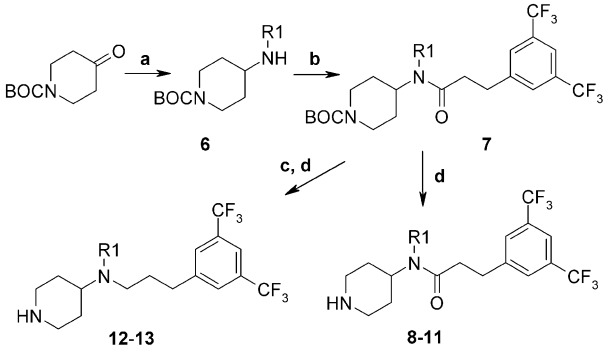
NK_1 antagonists are now believed to indirectly modulate 5-HT function, via Noradrenergic pathways[19,23] and have been shown to attenuate presynaptic $5HT_{1A}$ receptor function.[7,19]

Thus, combination of serotonin reuptake inhibition with NK_1 antagonism (modulating $5HT_{1A}$ function) may lead to a new class of antidepressants with an improved onset of action and a better efficacy.

We now report the discovery of a family of potential antidepressants that combine serotonin reuptake inhibition and NK_1 antagonism.

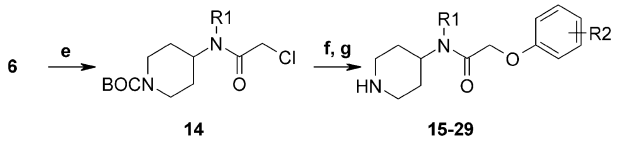
Results

Screening of the UCB compound collection on both the NK_1 receptor and the serotonin transporter (ST) according to published procedures[24–26] allowed the discovery of compound **8**. This compound displays modest affinities for both the NK_1 receptor and the ST and was used as a starting point for this study. The preparation of analogous compounds **9**–**13** and **15**–**29** starts with the reductive amination of N-BOC protected piperidone with aromatic amines,[27] yielding the intermediate aminopiperidines **6** (Scheme 3). Coupling of amines **6** with a dihydrocinnamic acid derivative using HOBT/DCC[28] gave the intermediate amides **7**, which were deprotected with TFA to allow the isolation of compounds **8**–**11**. Compounds **12** and **13** were obtained by Borane reduction of amides **7** (with R_1 = 4-fluorophenyl and 4-fluorobenzyl) in THF followed by deprotection with TFA.



Scheme 3. (a) Amine, $NaBH(OAc)_3$, dichloroethane, AcOH; (b) acid, HOBT, DCC, DIPEA, THF–CH_3CN; (c) BH_3–THF, THF; (d) TFA, CH_2Cl_2.

Protected amines **6** react with chloroacetyl chloride in CH_2Cl_2 in the presence of solid K_2CO_3 to afford the intermediate chloroacetamides **14**.[29] Addition of phenols to derivatives **14** in acetonitrile in the presence of Cs_2CO_3 followed by TFA deprotection allows the isolation of compounds **15**–**29** (Scheme 4).[30]



Scheme 4. (e) Chloroacetyl chloride, K_2CO_3, CH_2Cl_2; (f) phenol, Cs_2CO_3, CH_3CN; (g) TFA, CH_2Cl_2.

Amides **9**–**11** had a better affinity than **8** for the NK_1 receptor while affinity for the ST remained unchanged. Reduction of the amide **8** to the amine **12** allowed a significant increase in binding profile on both targets. Reduction of amide **9** to **13** allowed an increase in affinity for the ST but lowered the affinity for the NK_1 receptor (Table 1).

Table 1. Affinities[26] of compounds **8**–**13** for the NK_1 receptor and the serotonin transporter (ST), and their lipophilicity

Compd	R_1	pIC_{50} NK_1[a]	pIC_{50} ST[a]	log k'_{IAM}
8	4-Fluorophenyl	6.7	6.6	2.9
9	4-Fluorobenzyl	7.5	6.5	2.9
10	3-Methylbenzyl	7.6	6.7	3.2
11	2-Chlorobenzyl	7.0	6.7	3.2
12	4-Fluorophenyl	7.3	7.4	3.9
13	4-Fluorobenzyl	6.9	7.6	3.8

[a]Values are means of two experiments.

The immobilized artificial membrane (IAM) stationary phase method was chosen for mimicking the properties of the passage over a cell membrane. At physiological pH, the measured[31] value of membrane affinity for amide derivatives (**8**–**11**) predicts excellent drug absorption properties[32] if no major efflux mechanisms are involved. In contrast the reduced compounds **12**–**13** are characterized by an enhanced lipophilicity (log k'_{IAM} of 3.9 and 3.8, respectively), thus lowering their potential as orally active CNS agents.[33] Moreover, such high values are often linked with poor solubility and increased metabolism.

The exploration of the structure–affinity relationship of this family of compounds was hampered by the scarcity of commercially available dihydrocinnamic acids. We therefore modified the scaffold to a central, more hydrophilic glycolyl part, and diversity was introduced from a combination of readily available anilines, benzylamines (seven R_1 derivatives) and phenols (five R_2 derivatives).

Scanning the R_1 moiety with a fixed 3,5-bis-trifluoromethyl phenyl (**15**–**21**) showed that both phenyl and benzyl moieties were allowed, with the exception of the 3,5-dichloro derivative **20** which displayed low affinity for the NK_1 receptor (Table 2).

Table 2. Affinities[26] of compounds **15**–**29** for the NK_1 receptor and the serotonin transporter (ST), and their lipophilicity

Compd	R_1	R_2	pIC_{50} NK_1[a]	pIC_{50} ST[a]	log k'_{IAM}
15	4-Fluorophenyl	3,5 di CF_3	6.5	6.2	2.5
16	3-Methylbenzyl	3,5 di CF_3	7.1	6.6	3.3
17	2-Chlorobenzyl	3,5 di CF_3	6.9	6.8	3.2
18	3-Chlorophenyl	3,5 di CF_3	6.7	6.8	3.0
19	3,4-Dichlorophenyl	3,5 di CF_3	7.5	6.8	3.4
20	3,5-Dichlorophenyl	3,5 di CF_3	<5[b]	6.8	3.4
21	3-Chlorobenzyl	3,5 di CF_3	7.6	6.8	3.4
22	3,4-Dichlorophenyl	3-F, 5-CF_3	<5[b]	7.4	3.0
23	3,4-Dichlorophenyl	3,5 di Cl	7.0	7.5	3.2
24	3,4-Dichlorophenyl	3,5 di Me	**7.6**	**7.5**	2.7
25	3,4-Dichlorophenyl	3,5 di F	5.9	7.6	2.5
26	3-Chlorobenzyl	3-F, 5-CF_3	<5[b]	7.0	2.9
27	3-Chlorobenzyl	3,5 di Cl	6.9	7.3	3.1
28	3-Chlorobenzyl	3,5 di Me	7.0	7.6	2.6
29	3-Chlorobenzyl	3,5 di F	<5[b]	7.7	2.4

[a]Values are means of two experiments.
[b]Less than 50% inhibition at 10^{-5} M.

Optimization of R_2 using the most promising R_1 substituents (3,4-dichlorophenyl and 3-chlorobenzyl) was then started, using a series of 3,5-disubstituted phenols (Table 2). Interestingly, introduction of smaller substituants in the 3,5 positions consistently increased the affinity for the ST. Unsymmetrical R_2 substituents such as 3-fluoro 5-trifluoromethyl were not tolerated and induced a loss of affinity for the NK_1 receptor. An optimal overall profile in terms of affinities and physicochemical properties (k'_{IAM}) was obtained with 3,5-dimethylphenyl (**24**, **28**) and 3,5-dichloro phenyl (**23**) substituents.

In vitro, compound **24** behaved as a NK_1 antagonist inhibiting substance P-induced contraction of the isolated guinea pig ileum[34] (pA2 value of 6.88). To assess central 5-HT reuptake blockade properties of **24**, we tested its ability to increase extracellular 5-HT in the frontal cortex of freely moving rats by using intracerebral microdialysis.[35] Intraperitoneal administration of the compound (3.2×10^{-5} mol/kg, $n=2$) increased 5-HT levels up to 350% of baseline. The peak effect raised 1 h after the injection but was very transient since 5-HT levels returned to baseline after only 2 h, thus suggesting a rapid metabolism of the compound.

Thus, to the best of our knowledge, for the first time dual NK_1 antagonists and serotonin reuptake inhibiting compounds are described. Such dual compounds offer a potential as a new generation of antidepressants. Further developments will be reported in due course.

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26. The affinity of the test compounds for the ST was evaluated by a [^{3}H]paroxetine binding assay. This binding was

performed as described by Marcusson et al.[24] with slight modifications. 100–200 μg of membrane proteins from rat cerebral cortex were incubated for 120 min at 25 °C in 2 mL of a 50 mM Tris–HCl (pH 7.4) buffer containing 2 mM $MgCl_2$ and 0.05 nM radioligand. Non specific binding defined as the residual binding was measured in the presence of 5 μM imipramine.

The affinity of the test compounds for the human NK_1 receptor was measured as described by Aharony et al.[25] Briefly, 10–20 μg of membrane proteins from CHO cells expressing the human NK_1 receptor were incubated for 60 min at 25 °C in 0.5 mL of the same buffer as above, supplemented with 100 μg/mL bacitracine and 0.25 nM [^{3}H] substance P. The nonspecific binding was measured in the presence of 1 μM CP-96345.

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29. Typical procedure for the coupling with chloroacetyl chloride. **14** derivative: 4-[(2-chloroacetyl)-(3,4-dichlorophenyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester. 7.00 g (20 mmol) of the corresponding compound of type **6** (R_1 = 3,4-dichloro-phenyl) were dissolved in 250 mL of CH_2Cl_2, 11.20 g (80 mmol) of potassium carbonate were added and the mixture was cooled to 0 °C. 9.16 g (80 mmol) of chloroacetyl chloride were added, and the mixture was stirred overnight. The reaction was quenched by addition of a solution of 6.8 g of sodium bicarbonate in 100 mL of water, the aqueous phase was decanted and extracted twice with 50 mL of CH_2Cl_2. Combined organic phases were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The resulting residue was triturated with hexane. The product was obtained as a pink solid, 7.86 g, yield 93%. $C_{18}H_{23}Cl_3N_2O_3$ = 421.75, ^{1}H NMR ($CDCl_3$), δ (ppm) 1.3 (m, 2H), 1.4 (s, 9H), 1.8, (m, 2H), 2.8 (m, 2H), 3.6, (s, 2H), 4.2 (m, 2H), 4.6 (m, 1H), 7.1 (dd, 1H), 7.3 (d, 1H), 7.6 (d, 1H). ^{13}C NMR ($CDCl_3$), δ (ppm): 28.6 (C($\underline{C}H_3$)), 30.5 (NCH($\underline{C}H_2$)$_2$), 41.2 (BOCN($\underline{C}H_2$)$_2$), (CO$\underline{C}H_2$Cl), 54.2 (N$\underline{C}$H), 80.1 (O$\underline{C}$(CH_3)) 129.9, 131.8, 132.3, 134.0, 134.4, 137.1 (C aromatics), 154.7 (OCON), 165.9 (CCON). MS (LC–MS, APCI) $MH^+ - BOC$ = 321 (100%), 323, 325.

30. Compound **24** *N*-(3,4-dichloro-phenyl)-2-(3,5-dimethylphenoxy)-*N*-piperidine-4-yl-acetamide. 1.95 g (6 mmol) of cesium carbonate were suspended in 30 mL of Acetonitrile. 0.37 g (3 mmol) of 3,5 dimethylphenol was added and the mixture was stirred for 15 min. A solution of 1.26 g (3 mmol) of the **14** derivative (R_1 = 3,4-dichloro-phenyl) in 10 mL of Acetonitrile was added and the reaction was stirred for 7 h. The solvent was removed under reduced pressure, the residue was partitioned between 30 mL of 0.1 N NaOH and ethyl acetate. The aqueous phase was decanted and extracted twice with 30 mL of ethyl acetate. Combined organic phases were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting solid was purified by flash chromatography on silica gel using CH_2Cl_2–EtOH–aqueous ammonia (98–1.8–0.2%, v/v/v) as eluant. The product was obtained as a solid, 0.98 g, yield 64.4%.

The compound was dissolved in 5 mL of CH_2Cl_2 and the solution was cooled to 0 °C. 6 mL of TFA were added and the solution was stirred for 3 h. The solvent was removed under reduced pressure, the residue was partitioned between aqueous sodium bicarbonate and CH_2Cl_2. The aqueous phase was decanted and extracted twice with 10 mL of CH_2Cl_2. Combined organic phases were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting solid was dissolved in a mixture of 2-butanone and isopropanol, and a saturated solution of HCl in ether was added. The solvent was removed, the solid was recrystallized from isopropanol to afford the solid hydrochloride, 575 mg, yield 88%. $C_{21}H_{24}Cl_2N_2O_2$ = 407.34 g mol^{-1}, mp 220 °C, ^{1}H NMR (DMSO-d_6), δ (ppm): 1.50 (m, 2H), 1.9 (m, 2H), 2.2 (s, 6H), 2.9 (m, 2H), 3.3 (m, 2H), 4.3 (s, 2H), 4.6 (m, 1H), 6.4 (s, 2H), 6.6 (s, 1H), 7.4 (d, 1H), 7.7 (s, 1H), 7.8 (d, 2H). ^{13}C NMR (DMSO-d_6), δ (ppm): 21.2 (2 CH_3), 26.7 (NCH($\underline{C}H_2$)$_2$), 40.4 (N$\underline{C}$H), 50.6 (N($\underline{C}H_2$)$_2$), 66.6 (O$\underline{C}H_2$CO), 112.6, 123.0, 131.0, 131.5, 132.0, 132.2, 132.6, 137.1, 138.8, 158.1 (aromatic C), 166.9 (CON). MS (LC–MS, APCI) MH^+ = 407 (100%), 409, 411.

31. IAM chromatography: capacity factors (k'_{IAM}) were established on an IAM.PC.DD 2 Drug-Discovery HPLC Column 30×4.6 mm (Regis Tech Inc., Morton Grove, IL, USA). The mobile phase consisted of different mixtures of phosphate buffer saline (pH 7.4) and acetonitrile as co-solvent. The published data are the extrapolated values at 0% in CH_3CN.

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