Bioorganic & Medicinal Chemistry Letters 24 (2014) 1611–1614

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of a cyclopentylamine as an orally active dual NK_1 receptor antagonist–serotonin reuptake transporter inhibitor

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ARTICLE INFO

Article history:
Received 20 December 2013
Revised 10 January 2014
Accepted 14 January 2014
Available online 27 January 2014

Keywords:
NK_1 receptor (NK_1R) antagonist
Serotonin reuptake transporter (SERT) inhibitor
Dual NK_1 receptor antagonists–serotonin reuptake transporter inhibitor

ABSTRACT

Cyclopentylamine **4** was identified as a potent dual NK_1R antagonist–SERT inhibitor. This compound demonstrated significant oral activity in the gerbil forced swimming test, suggesting that dual NK_1R antagonists–SERT inhibitors may be useful in treating depression disorders.

Serotonin reuptake inhibitors (SSRIs) such as paroxetine[1] and fluoxetine (Chart 1) have demonstrated an improved safety profile over the first-generation tricyclic antidepressants like imipramine (Chart 1),[2] but they still suffer from a few side effects including gastrointestinal distress, anxiety, insomnia, weight gain and sexual dysfunction. In addition, SSRIs take weeks to months to produce a therapeutic effect.[3–5] The delay in onset for efficacy with SSRIs presumably results from activation of the inhibitory role of serotonin 1A ($5\text{-}HT_{1A}$) autoreceptors. Upon administration of an SSRI, increased synaptic serotonin (5-HT) can act at $5\text{-}HT_{1A}$ receptors to reduce the firing of serotonergic neurons, resulting in a muted increase of synaptic 5-HT. After initial desensitization of the $5\text{-}HT_{1A}$ autoreceptors with repeated SSRI treatment, the serotonergic neurons resume normal firing, allowing an increase of synaptic 5-HT, thereby generating a therapeutic antidepressant response. Indeed, a beneficial effect on the onset of action of SSRIs has been observed in clinical studies with co-administration of $5\text{-}HT_{1A}$ antagonists.[6,7] Moreover, this combination therapy has resulted in significant improvements among SSRI-resistant patients.[6,7] Another potential combination therapy might involve neurokinin-1 receptor (NK_1R) antagonists[8–12] and SSRIs. NK_1R antagonists alone may not be sufficient in treating depression in humans, but since NK_1R antagonists indirectly modulate 5-HT function[13,14] and attenuate presynaptic $5\text{-}HT_{1A}$ receptor function, NK_1 receptor antagonism may augment the antidepressant activity of SSRIs. Consistent with this hypothesis, Bourin et. al. showed that GR205171 (Chart 1), a selective and brain penetrant NK_1R antagonist, selectively potentiated the antidepressant activity of sub-efficacious doses of the SSRIs, citalopram and paroxetine, in the mouse forced swimming test (FST).[15] A more recent investigation has shown that NK_1R antagonism lowers occupancy requirement for antidepressant-like effects of SSRIs in the gerbil forced swimming test.[16] Thus, combination therapy of SSRIs with NK_1R antagonists may be viable in the treatment for depression with potential for improved efficacy, reduced side effects and a more rapid onset of clinical efficacy. However, combination therapy with two different compounds may be challenging primarily because of enhanced risk of drug–drug interactions and potentiation of dose-related or idiosyncratic side effects and pharmacokinetic interactions. An alternative to combination therapy of two different drugs would be a single compound that acts as both a serotonin reuptake transporter (SERT) inhibitor and an NK_1R antagonist. To this end, Ryckmans et al. identified a series of benzyloxyphenethyl piperazine derivatives as dual NK_1R antagonists–SERT inhibitors.[17,18] One of the best compounds in the series, (*S*)-1-(2-(3,5-dibromobenzyloxy)-1-phenylethyl)piperazine (**1**, Chart 1), demonstrated oral activity in an animal model of depression sensitive to both mechanisms. We recently reported that 4-((3,5-bis(trifluoromethyl)-benzyloxy)-methyl)-4-phenylpiperidine (**2**, Chart 1), a potent NK_1R antagonist originated from Merck Research Laboratories,[19] is not only a potent NK_1R antagonist but also a potent SERT inhibitor.[20] Subsequent ring expansion studies led to a series of 4,4-disubstituted homopiperidines as potent dual-acting NK_1R

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http://dx.doi.org/10.1016/j.bmcl.2014.01.036
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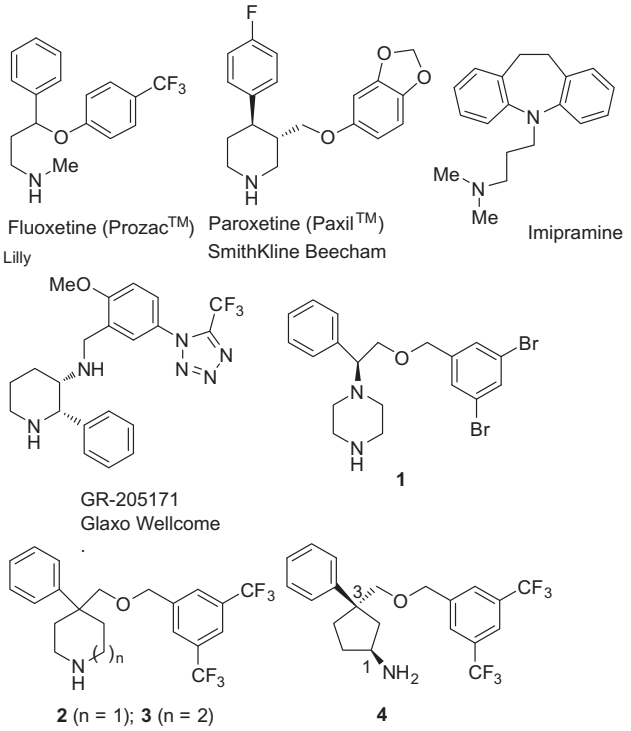
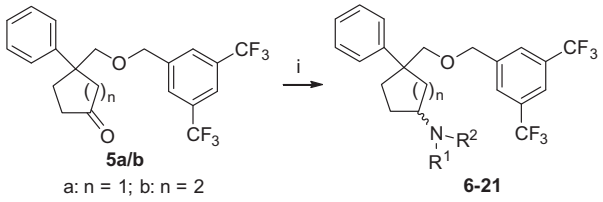


Chart 1.

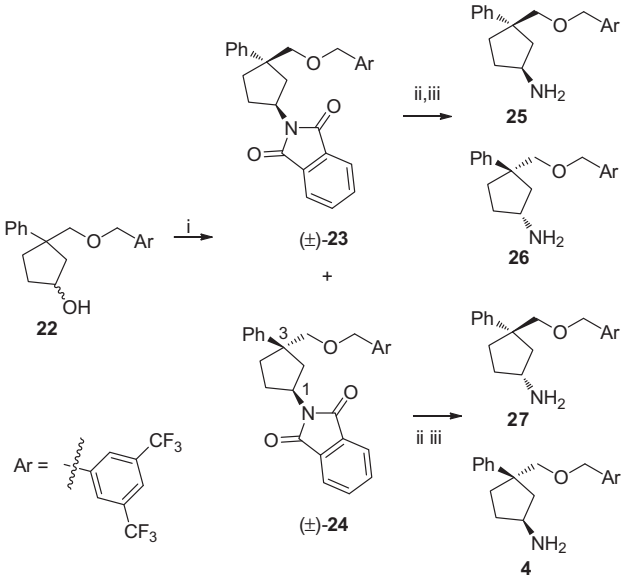
antagonists–SERT inhibitors as exemplified by compound **3**.[20] As part of our efforts in the area, we explored cyclopentyl- and cyclohexylamine analogs to assess the impact of modifying the amine part of the pharmacophore. This exercise culminated in the discovery of the cyclopentylamine **4** (Chart 1) with balanced dual NK_1R antagonism and SERT inhibiton. This Letter describes the SAR leading to **4**, along with the synthesis and in vivo studies of this compound.

Scheme 1 describes the synthesis of cyclopentyl- and cyclohexylamine analogs as mixture of diastereomers. The readily available cyclic ketones **5a**/**b**[20] underwent titanium(IV) isopropoxide-promoted reductive amination with various primary and secondary amines to provide secondary and tertiary amines **6**–**21** as mixtures of diastereomers (Table 1).

Our initial attempts to make cyclopentyl primary amines **4** and **25**–**27** through reductive amination of cyclopentanone **5a** with ammonia failed under various conditions. Therefore, we developed an alternative Mitsunobu reaction route involving cyclopentanol **22** as shown in Scheme 2. Cyclopentanol **22** as a mixture of two diastereomers was readily prepared from methyl 2-phenylacetate in five steps following the procedures recently disclosed from this laboratory.[20] Mitsunobu reaction of **22** with phthalimide under typical conditions gave a mixture of two diastereomers, which were readily separated by silica gel chromatography to provide



Scheme 1. Reagents and conditions: (i) R^1R^2NH, Ti(O*i*-Pr)$_4$, 65 °C, 2 h; $NaBH_4$, EtOH, rt, 1 h, 25–85%.



Scheme 2. Reagents and conditions: (i) Ph_3P, DEAD, phthalimide, 0 °C, 2 h, 28% (±)-**23**; 25% (±)-**24**; (ii) chiral HPLC, AD column for (±)-**23** and OJ column for (±)-**24**, 20 × 250 mm, 95% heptane/5% ethanol, 10 mL/min flow rate; (iii) hydrazine, toluene, 80 °C, 85–90%. Ar: 3,5-bis(trifluoromethyl)phenyl.

(±)-**23** and (±)-**24** in 28% and 24% yields, respectively. Separation of the enantiomers of (±)-**23** and (±)-**24** by HPLC on a chiral column furnished four enantiomerically pure stereoisomers: (1*R*,3*S*)-**23**, (1*S*,3*R*)-**23**, (1*S*,3*S*)-**24**[21] and (1*R*,3*R*)-**24**. These four isomers were individually subjected to phthalimide removal by treatment with hydrazine in hot toluene to give four cyclopentylamines: **25**, **26**, **27** and **4**.[22] To establish the relative and absolute stereochemistry of these isomers, we converted (1*R*,3*S*)-**25** and (1*S*,3*S*)-**4** to their tartaric acid salts which were recrystallized from ethanol to give single crystals for X-ray diffraction analysis (Fig. 1).

The cyclopentyl- and cyclohexylamine analogs in Table 1 were tested as mixtures of diastereomers to get an initial assessment of activity. Although it was appreciated that individual enantiomers might have different profiles for NK_1 antagonism and SERT inhibition, this approach allowed us to efficiently identify preferred amine substituents. Indeed, these initial results showed that small alkyl amines were preferred for dual NK_1R/SERT activity, with SERT inhibition being particularly sensitive to steric bulk. Thus compounds **6**, **13**, **14**, **16**, and **17** retained dual activity while compounds such as **7**–**12** and **18**–**21** had diminished activity against SERT even though NK_1R antagonist potency was retained in some cases.

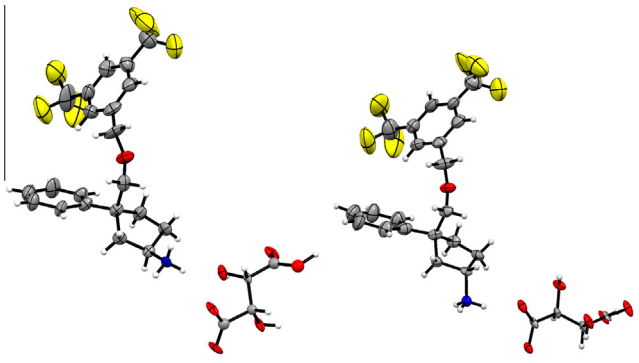
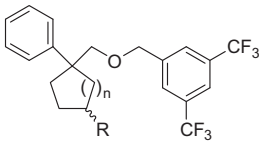
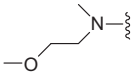
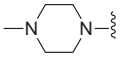


Figure 1. Thermal ellipsoid plots (35% ellipsoids) of the tartaric acid salts **25** (left) and **4** (right).

Table 1
IC_{50} values of diastereomeric cyclopentyl- and cyclohexylamines[a,b,c]



Compd	R	*n*	hNK$_1$R (nM)	hSERT (nM)
6	Me_2N	**1**	8.0	57
7	*i*-Pr_2N	**1**	470	>1000
8		**1**	16	530
9		**1**	20	>1000
10		**1**	14	>1000
11		**1**	4.7	>1000
12		**1**	45	>1000
13	MeNH	**2**	16	190
14	EtNH	**2**	14	150
15		**2**	74	680
16	Me_2N	**2**	48	250
17	Et_2N	**2**	38	280
18		**2**	120	>1000
19		**2**	93	970
20		**2**	350	>1000
21		**2**	120	520

[a] All values are the mean of at least two separate assay determinations.
[b] For assay conditions, see Ref. 19.
[c] Mixture of diastereomers.

Prompted by these findings, we decided to focus on primary amines and to invest the effort in preparing individual enantiomers in the cyclopentane series (Scheme 2 and Table 2). All four cyclopentylamine stereoisomers exhibited good NK_1R binding activity, but surprisingly, SERT activity was significantly better for **4** compared with the other stereoisomers (Table 2). Overall, **4** was the most potent dual NK_1R antagonist and SERT inhibitor.

The antidepressant effect of **4** was evaluated in the gerbil forced swimming test (FST), in which immobility (i.e., no swimming or struggling) is seen as a measure of despair.[23] Gerbils were used in the forced swim test because mice and rat NK_1 receptors are not highly homologous with the human NK_1 receptor, whereas guinea pigs and human NK_1Rs are highly homologous. This behavioral test is one of the most widely used preclinical paradigms for predicting antidepressant activity of drug candidates. The compound was administered by oral gavage 30 min prior to testing, and the

Table 2
IC_{50} values of cyclopentylamines[a,b]

Compd	hNK$_1$R (nM)	hSERT (nM)
4	7.5	4.7
27	31	210
25	19	350
26	11	130

[a] All values are the mean of at least two separate assay determinations.
[b] For assay conditions, see Ref. 19.

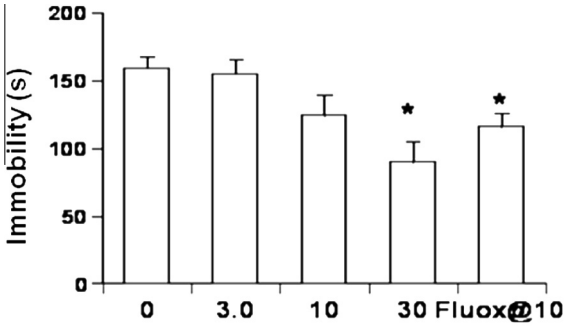


Figure 2. Effects of various oral doses of (1*S*,3*S*)-**4** (3.0, 10, 30 mg/kg) and fluoxetine (10 mg/kg, PO) in gerbil FST. Results are expressed as mean immobility time ± SEM. $^*P < 0.01$. T-30: 30 min pretreatment time.

results were expressed as the immobility time during the 6-minute test period (mean ± SEM) for the 10 gerbils tested in each group. Figure 2 shows the effect of various oral doses of compound **4** and fluoxetine (positive control) at 10 mg/kg (PO). The lower oral doses of **4** (3.0 and 10 mg/kg) did not modify the immobility times in gerbils when compared to the vehicle-treated control group. However, **4** at 30 mg/kg (PO) decreased immobility time. We also tested **4** in a locomotor activity assay to determine whether the results obtained in the gerbil FST were impacted by a possible increase in spontaneous locomotor activity and found that compound **4** at 30 mg/kg (PO) produced no significant changes in locomotor activity as compared with the vehicle-treated control group. At the 30 mg/kg dose, the plasma concentration of **4** was 300 nM and the brain concentration was 7400 nM, indicating that **4** had good brain uptake, but that high brain concentrations were required for efficacy. Clearly, free fraction data and/or CSF concentrations are needed to better understand the PK-PD relationship.

Compound **4** was identified as a balanced dual NK_1R antagonist and SERT inhibitor with oral activity in the gerbil FST. Because of its oral activity, excellent brain penetration, and low molecular weight, this compound represents a potential lead compound in the search for potent dual NK_1R antagonists–SERT inhibitors as novel anti-depressant candidates.

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21. *(1S,3S)-**24**:* HPLC retention time: 8.43 min (AD column, 4.6 × 250 mm, flow rate 1 mL/min, 90% hexanes/10% ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.2 (3H, m), 2.5 (2H, m), 2.59 (1H, dd, J = 10.8, 10.4 Hz), 3.51 (1H, d, J = 8.8 Hz), 3.56 (1H, d, J = 8.8 Hz), 4.48 (1H, d, J = 13.2 Hz), 4.53 (1H, d, J = 13.2 Hz), 4.95 (1H, m), 7.31 (5H, m), 7.59 (2H, s), 7.68 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.40, 33.82, 38.38, 49.66, 51.45, 71.75, 77.98, 123.32 (q, J = 271 Hz), 121.32, 123.09, 126.30, 126.80, 126.99, 128.07, 131.56 (q, J = 32 Hz), 132.06, 133.89, 141.23, 146.88, and 168.28. HRMS m/z calcd for $C_{29}H_{22}F_6NO_3$ $(M-H)^-$ 546.1504, found 546.1493. (1*R*,3*R*)-**8**: HPLC retention time: 7.64 min (AD column, 4.6 × 250 mm, flow rate 1 mL/min, 90% hexanes/10% ethanol). The NMR data is identical to that of its (1*S*,3*S*)-**7**. HRMS m/z calcd for $C_{29}H_{22}F_6NO_3$ $(M-H)^-$ 546.1504, found 546.1494.
22. *Compound **4**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (1H, m), 1.60 (2H, broad s), 1.74 (1H, dd, J = 6.0, 12.8 Hz), 2.09 (2H, m), 2.19 (1H, m), 2.48 (1H, dd, J = 6.8, 12.8 Hz), 3.40 (1H, d, J = 8.8 Hz), 3.44 (1H, d, J = 8.8 Hz), 3.53 (1H, quintet, J = 7.2 Hz), 4.43 (2H, s), 7.25 (5H, m), 7.55 (2H, s), and 7.73 (1H, s). HRMS m/z calcd for $C_{21}H_{22}F_6NO$ $(M+H)^+$ 418.1607, found 418.1625.
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