Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2555–2558
Bioorganic & Medicinal Chemistry Letters

(*R*)-Sila-venlafaxine: A selective noradrenaline reuptake inhibitor for the treatment of emesis

Graham A. Showell,[a,*] Matthew J. Barnes,[a] Jürgen O. Daiss,[b] John S. Mills,[a,†] John G. Montana,[a,‡] Reinhold Tacke[b] and Julie B. H. Warneck[a]

[a]*Paradigm Therapeutics Ltd, 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GP, UK*
[b]*Institut für Anorganische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany*

Received 9 November 2005; revised 19 December 2005; accepted 19 December 2005
Available online 2 March 2006

Abstract—Sila-substitution of drugs (the carbon/silicon switch) is a concept that is being successfully used for the development of new chemical entities. The (*R*)-sila-analogue of the antidepressant venlafaxine is devoid of the serotonin reuptake inhibition observed with the marketed drug, leading to a selective noradrenaline reuptake inhibitor displaying anti-emetic properties.

Organosilicon chemistry has been demonstrated to be a powerful source of chemical diversity in drug design.[1–3] Silicon, a Group 14 element, and carbon have many similarities, one being that they readily form four covalent bonds with many other elements. However, the two elements also present some important differences which can be exploited by the medicinal chemist and stable silicon-containing compounds can be synthesized that can have modified pharmacological profiles compared to their carbon counterparts. Carbon and silicon differ in their covalent radius (r_c = 77 pm, r_{Si} = 117 pm) leading to differences in bond distance and the steric arrangement when comparing analogous C-element and Si-element bonds. Silicon-containing bonds are always longer than the corresponding carbon analogues (the C–Si bond is approximately 25% longer than the C–C bond) and this difference leads to subtle changes in the size and therefore shape of silicon-containing compounds when compared to carbon.

Venlafaxine (**1**, Fig. 1, Effexor™, Efexor™ and Trevilor™) is a serotonin-noradrenaline reuptake inhibitor (SNRI) used in the treatment of depression which, in contrast to the tricyclic antidepressants, shows no affinity for neurotransmitter receptors.[4–6] Venlafaxine is marketed as a racemate and during our earlier synthetic studies[7] on sila-analogues we sought to obtain the racemates and individual enantiomers of both venlafaxine (**1**)[8] and sila-venlafaxine (**2**) in order to compare their individual pharmacological profiles. The single sila-enantiomer (***R***)-**2** shows an interesting monoamine reuptake pharmacological profile that is not observed with the enantiomers of **1**.[7]

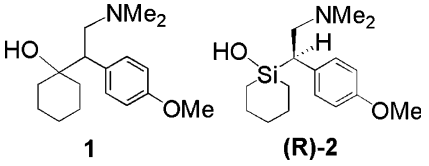
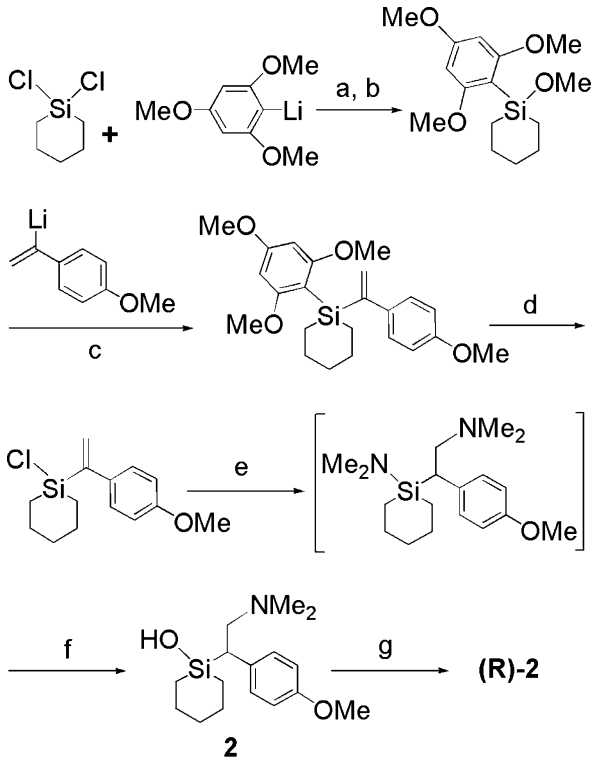


Figure 1. Structures of venlafaxine (**1**) and (*R*)-sila-venlafaxine ((***R***)-**2**).

In order to streamline the synthesis of (***R***)-**2** for its amenability to large-scale synthesis, the original synthesis[7] was adapted to avoid the use of highly flammable reagents. This modified procedure[9] (Scheme 1) utilises the acid labile trimethoxyphenyl protecting group[10] allowing several key intermediates to be isolated by crystallisation techniques. Compound (***R***)-**2**, isolated in multi-gram quantities as its crystalline hydrochloride salt for biological evaluation, was obtained from its racemate by the fractional crystallisation of the (+)-camphorsulfonic acid salt. The absolute configuration of (***R***)-**2** was deter-

Keywords: Sila-substitution; Noradrenaline reuptake inhibitor; Anti-emetic.
* Corresponding author. Tel.: +44 1223 477910; fax: +44 1223 477911; e-mail: gshowell@paradigm-therapeutics.com
† Present address: AstraZeneca, Mereside, Alderley Park, Macclesfield SK10 4TG, UK.
‡ Present address: Argenta Discovery, 8/9 Spire Green Centre, Flex Meadow, Harlow CM19 5TR, UK.

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.12.062



Scheme 1. Synthesis of (*R*)-sila-venlafaxine ((***R***)-**2**). Reagents: (a) *n*-hexane; (b) MeOH; (c) *n*-hexane; (d) HCl-Et_2O; (e) Me_2NH, *n*-BuLi, THF; (f) AcOH, KOAc, Et_2O; (g) (+)-CSA, acetone then conversion to the HCl salt.

mined by X-ray diffraction studies on the hydrobromide salt.[7]

The in vitro biological results in human recombinant transporter assays (Table 1) show (***R***)-**2** to be a selective noradrenaline reuptake inhibitor portraying an in vitro pharmacological profile not demonstrated by either of the enantiomers of **1**.[7] (S)-Venlafaxine ((**S**)-**1**) is a potent and selective serotonin reuptake inhibitor (SSRI), whereas the *R*-enantiomer ((***R***)-**1**) is non-selective between the serotonin and noradrenaline reuptake sites. In order to profile (***R***)-**2** further, the compound was tested in vitro across a panel of 68 common receptors/channels and 16 enzymes and is inactive in the majority of assays (<50% inhibition at 10 μM), including opioid receptors. Weak affinity at Ca^{2+} and Na^+ channels is observed (Table 1), although no functional activity at these channels was realised on further investigation. Compound (***R***)-**2** was also profiled in vitro for its effects on cytochrome-P450 enzymes. Venlafaxine (**1**) has been evaluated in clinical studies and demonstrates low to negligible drug interaction potential at CYP2D6, CYP1A2, CYP2C19 and CYP3A4.[11] Similarly (***R***)-**2** also displays low in vitro activity at these CYP enzymes (<50% inhibition, 10 μM).

Table 1. In vitro profile of (***R***)-**2**

Target	IC_{50}[a,b] (μM)	Noradrenaline reuptake selectivity
Noradrenaline reuptake[c]	0.2 (±0.1)	
Serotonin reuptake[c]	4.2 (±2.3)	21
Dopamine reuptake[c]	4.9 (±1.4)	25
Ca^{2+} channel (L, verapamil)	8.6[d]	43
Ca^{2+} channel (L, diltiazem)	2.7[d]	14
Na^+ channel (site 2)	5.1[d]	26

[a] Values are means of 5 determinations, standard deviation is given in parentheses. Monoamine reuptake receptor binding activities were determined using radioligand cellular uptake inhibition assays. Radioactivity levels were detected by scintillation counting.
[b] Inactive (<50% inhibition) at all other receptors/enzymes/channels (see Supplementary information) at a concentration of 10 μM.
[c] Human recombinant transporter assay.
[d] $n = 1$.

Venlafaxine (**1**) and racemic sila-venlafaxine (**2**) have identical physicochemical properties (measured $pK_a = 9.7$ and measured log D at pH 7.4 = 0.9, measured log $P = 3.1$), and based on the evidence that **1** achieves high clinical efficacy in the treatment of depression one would have high confidence that (***R***)-**2** would also readily reach its site of action in the CNS. In general, silicon is more lipophilic than carbon; however in this chemical environment, the silanol in **2** is more acidic than the corresponding carbinol in **1**. The two effects appear to cancel each other leading to both compounds having the same log P profile. Structurally (***R***)-**2** forms a different shape from that of **1**. The sila-cyclohexane ring is more flattened than the cyclohexane ring of **1** due to the increased Si–C bond lengths compared to the C–C bonds (Fig. 2).[7] The introduction of silicon into the core structure of **1** has provided molecules that provide conformations which cannot be achieved with any other carbon-based analogues of **1**, therefore exploring new chemical space and providing drug-like structures with a modified pharmacological profile.

Venlafaxine (**1**) is generally well tolerated in the clinical setting, however one of the adverse effects reported is nausea,[12] an effect that may be a consequence of its mixed serotonin/noradrenaline reuptake profile. It has been shown, from studies published in the literature, that noradrenergic neurons are found in the area postrema within the brain and noradrenaline can induce emetic events through post-synaptic α2 receptors at this site.[13] Therefore, we postulated the simple hypothesis that the use of a centrally acting selective noradrenaline reuptake inhibitor would inhibit the reuptake of noradrenaline, resulting in a transient accumulation of the neurotransmitter in the synaptic cleft. This build up of noradrenaline may act as an agonist on the pre-synaptic α2 receptors leading to a negative feedback inhibition of noradrenaline release and subsequently halting an emetic response through the post-synaptic receptors. In order to test the theory that a selective noradrenaline reuptake inhibitor may have utility in the treatment of emesis, (***R***)-**2** was evaluated in a ferret model of morphine-induced emesis.[14] (***R***)-**2** hydrochloride was dosed orally 2 h prior to the emetogen (morphine, 0.125 mg/kg, sc) and the animals were monitored for retching and vomiting events for up to 2 h following the administration of morphine. The data are summarised in Figure 3.

At 50 mg/kg (***R***)-**2** completely abolishes emetic episodes and almost complete inhibition (93%) is achieved at 5 mg/kg. In male ferrets, dosed at 5 mg/kg orally, (***R***)-

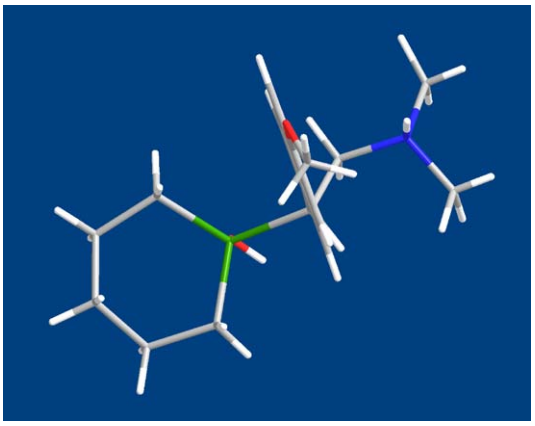


Figure 2. X-ray crystal structure of (***R***)-**2** HBr. The silicon is green, nitrogen is blue, and oxygen is red. The bromide atom has been omitted for clarity. The C–Si bonds within the ring are 1.85 Å and the sila-containing ring is more flattened than the equivalent cyclohexane ring in **1** (see Ref. 7 for X-ray crystallography details and further discussion).

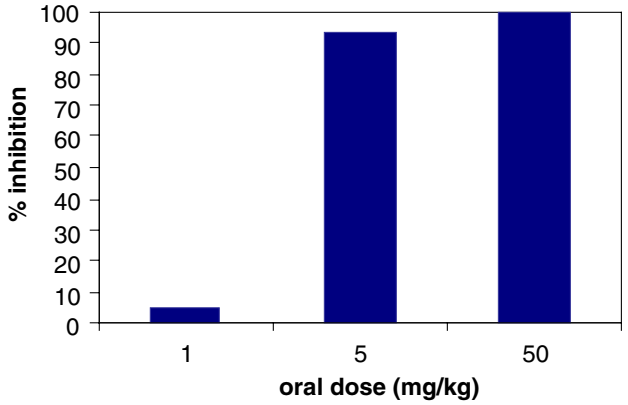


Figure 3. Anti-emetic profile of (***R***)-**2** in a morphine-induced model of emesis in the ferret. The test compound (***R***)-**2** was dosed orally in ferrets 2 h prior to the emetogen (morphine, 0.125 mg/kg, sc). Group size, $n = 4$. The ferrets were monitored for emetic episodes for 2 h.

2 displays a plasma half-life of 1.1 h with a C_{max} of 225 ng/ml. At the 1 mg/kg dose, however, the compound is virtually inactive and the emesis levels in the ferret are comparable to morphine alone. In the same ferret emesis model ondansetron,[15] a marketed $5HT_3$ receptor antagonist anti-emetic agent, was evaluated and shows no effect (16 mg/kg) when administered orally.

Emesis is a complex, multifactorial process for which, presently, there is no therapeutic regime suitable for treating all underlying biological emesis-related processes. The $5HT_3$ receptor has been identified as an important receptor involved in the treatment of cancer chemotherapy-related emesis, ondansetron being a key therapeutic agent in use by oncology clinicians. However other areas for treatment, such as post-operative nausea and vomiting (PONV), are not well covered by effective therapies. A number of post-operative factors can influence the risk of PONV, and the relief of pain, often associated with the use of opioids such as morphine, exacerbates emetic episodes. As numerous neuronal pathways converge on the vomiting centre within the brain new anti-emetics, operating by different mechanisms of action may therefore provide an important way forward in the future treatment of emesis.

In conclusion, (***R***)-**2**, a selective noradrenaline reuptake inhibitor, has been demonstrated to effectively inhibit emetic episodes caused by an emetogen, such as morphine, in a well-characterized animal model. Its oral efficacy in such a model suggests that compounds with this mechanism of action may have clinical utility in the prevention and treatment of PONV, particularly in settings where morphine is used for post-operative pain relief. More extensive pharmacological studies on (***R***)-**2**, including other validated animal models of emesis, will be presented in due course.

Acknowledgments

The authors thank Professor Robert Naylor (University of Bradford, UK) and Porsolt and Partners (Le Genest-Saint-Isle, France) for in vivo studies, Ian Cooper (Pharmorphix Ltd., Cambridge, UK) for physicochemical measurements on racemic **1** and **2**, MDS Pharma Services (Taiwan) and Cerep (France) for in vitro assays, Dr. Christian Burschka (University of Würzburg, Germany) for X-ray crystallography studies, Professor Paul Andrews (St. George's Hospital Medical School, London, UK), Dr. David Otway, Dr. Parminder Pooni, Dr. David Miller and Dr. Chris Earnshaw (Paradigm, Cambridge, UK) for helpful discussion.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2005.12.062.

References and notes

1. Showell, G. A.; Mills, J. S. *Drug Discov. Today* **2003**, *8*, 551.
2. Bains, W.; Tacke, R. *Curr. Opin. Drug Discov. Dev.* **2003**, *6*, 526.
3. Mills, J. S.; Showell, G. A. *Expert Opin. Investig. Drugs* **2004**, *13*, 1149.
4. Maj, J.; Rogoz, Z. *J. Neural Transm.* **1999**, *106*, 197.
5. Einarson, T. R.; Arikian, S. R.; Casciano, J.; Doyle, J. J. *Clin. Ther.* **1999**, *21*, 296.
6. Gutierrez, M. A.; Stimmel, G. L.; Aiso, J. Y. *Clin. Ther.* **2003**, *25*, 2138.
7. Daiss, J. O.; Burschka, C.; Mills, J. S.; Showell, G. A.; Warneck, J. B. H.; Tacke, R. *Organometallics* **2006**, *25*, 1188.
8. Yardley, J. P.; Morris Husbands, G. E.; Stack, G.; Butch, J.; Bicksler, J.; Moyer, J. A.; Muth, E. A.; Andree, T.; Fletcher, H., III; James, M. N. G.; Sielecki, A. R. *J. Med. Chem.* **1990**, *33*, 2899.
9. Showell, G. A.; Miller, D.; Mandal, A. K.; Tacke, R.; Daiss, J. WO2004094436, 2004; *Chem. Abstr.* **2004**, *141*, 395661.

10. Daiss, J. O.; Penka, M.; Burschka, C.; Tacke, R. *Organometallics* **2004**, *23*, 4987.
11. Ereshefsky, L.; Dugan, D. *Anxiety* **2000**, *12*(Suppl 1), 30.
12. Cunningham, L. A. *Ann. Clin. Psychiatry* **1997**, *9*, 157.
13. Beleslin, D. B.; Štrbac, M. *Neuropharmacology* **1987**, *26*, 1157.
14. Wynn, R. L.; Essien, E.; Thut, P. D. *Eur. J. Pharmacol.* **1993**, *241*, 47.
15. Markham, A.; Sorkin, E. M. *Drugs* **1993**, *45*, 931.