Silicon Switches of Marketed Drugs

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Abstract: The application of organosilicon chemistry is a strategy to develop best in class drugs applied to targets that have been validated as tractable and drug-able. Silicon switches of known drugs have been synthesised and evaluated in biological assay systems then compared to their marketed all-carbon counterparts. Recent examples include the silicon switches of drugs haloperidol, fexofenadine, bexarotene and venlafaxine.

Key Words: Organosilicon chemistry, silicon switch, marketed drugs, validated targets.

INTRODUCTION

Seventeen new molecular entities (NMEs) were introduced in the market for the first time in 2002, this being the least productive year over the last decade. Although this slide in productivity has halted in the years 2003 and 2004 [www.fda.gov], the pharmaceutical sector is still again facing major challenges six years into the new millennium. Major reasons for the high attrition in development are poor pharmacokinetics, toxicity and lack of efficacy in clinical trials. The pharmaceutical industry needs to identify new and safe medicines with a genuine biomedical benefit, a clean intellectual property (IP) position, drug-like properties, chemical tractability and commercial viability. Sila-substitution (C/Si exchange) of existing drugs is a relatively recent approach in the search for drug candidates that have beneficial biological properties and a clear IP position. Such a silicon switch could be considered as a classical tetravalent bioisostere, however until recently the potential of exploiting the properties of organosilicon agents has not been fully utilised in drug discovery and development.

SILICON SWITCH TECHNOLOGY

Silicon is a Group 14 element and carbon and silicon have many similarities, one being that they form four covalent bonds with many other elements. However, the two elements also present some key differences which can be exploited by the medicinal chemist and silicon containing compounds can be produced that can have a pharmacological or pharmacokinetic benefit over their carbon counterparts [1-3]. The following are some of the fundamental differences between carbon and silicon that can be used to provide a benefit in drug design:

- Differences in atomic size that lead to different bond lengths and thus result in subtle changes in molecular size and shape.
- Differences in the electronegativity of the elements, that leads to alterations in bond polarization.
- Differences in lipophilicity, affecting compound permeability.
- Differences in the chemical reactivity of certain functional groups afford the potential to modify *in vivo* properties.
- The ability of silicon to enable chemistry which is not accessible to standard carbon chemistry, this then allows the generation of novel drug-like scaffolds.

Carbon and silicon differ in their covalent radius (r_c=77pm, r_{Si}=117pm) and this leads to differences in bond distance and the steric arrangement of these bonds when comparing analogous C-element and Si-element bonds. For example, the silicon containing bonds are always longer than the corresponding carbon analogues. This difference leads to subtle changes in the size and therefore shape of silicon containing compounds when compared to carbon. The average length of a C-C bond is 1.54 angstroms whereas a C-Si bond is 1.87 angstroms. These differences can lead to changes in the way the carbon and silicon analogues interact with specific proteins, thus providing both pharmacological and pharmacokinetic differences between the two compounds. Carbon and silicon also show a difference in their electronegativity, silicon being the more electropositive element. This effect gives rise to an increase in acidity of a silanol compared to that of the carbinol [4,5] and the hydrogen bond strength of the silanol will be more favourable than that of the carbinol. Therefore, in literature compounds where the carbinol functions as a hydrogen bond donor which is required at its target for receptor affinity, then the introduction of a silanol moiety may be beneficial in terms of potency. When comparing the carbon and silicon analogues, differences in the logP/logD of a molecule can be observed depending on the chemical environment of the silicon. In general, the silicon analogue is more lipophilic than its carbon equivalent. The effects of altering the lipophilicity of a molecule may reveal changes *in vivo*, which can manifest themselves in a number of ways. A small increase in lipophilicity can markedly increase the volume of distribution of the molecule, reflecting the increased tissue penetration. A consequence being that the molecule may be less prone to hepatic metabolism; therefore the plasma half-life of the molecule may be enhanced in situations where liver metabolism is significant in the parent carbon analogue. In addition, introduction of a silicon atom into polar molecules can increase the logP and improve the permeability through the blood brain barrier, enhancing CNS activity.

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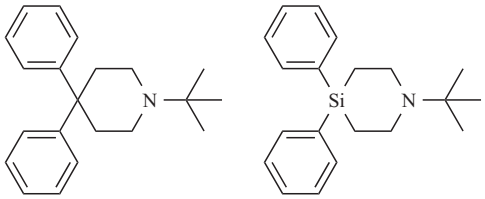
To date eight silicon-containing compounds have entered human clinical trials, however none of these are true silicon switches of known marketed drugs [1-3]. This review of recent literature will focus on the synthetic and medicinal chemistry associated with true silicon switches of marketed drugs.

SILICON SWITCH EXAMPLES

Sila-Budipine

Budipine (1) is a monoamine uptake inhibitor that has been launched by Altana AG for the treatment of Parkinson's disease.

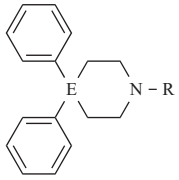


(**1**) Budipine (**2**) Sila-budipine

Fig. (1). Chemical structures of budipine and sila-budipine.

Its pharmacological profile has been reviewed [6] and aspects of its physicochemical properties have also been investigated. In the late 1980's Stasch [7] reported on the substitution of a carbon with a silicon atom within the core of 4,4-diphenyl budipine derivatives and the effect on the lipophilicity of the derivatives. This effect is illustrated in Table **1**.

Table 1. Effect of Sila-Substitution on Lipohilicity



E	logP	R	E	logP
C	0.49	H	Si	1.12
C	1.38	Me	Si	2.03
C	1.47	i-Pr	Si	2.07
C (budipine)	1.48	t-Bu	Si (sila-budipine)	2.08

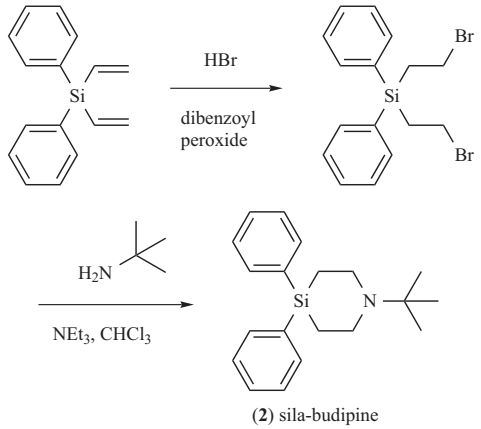
The lipophilicity is expressed as logP where P is the partition coefficient in an octanol/phosphate buffer at pH 7.4. All the sila-analogues show an increase in logP. In a centrally acting drug, one of the properties that plays an important role in determining if the drug molecule penetrates the blood-brain barrier is its lipophilicity. Modest increases in the lipophilicity of a molecule can improve its penetration of the blood-brain barrier. The logP is increased by 0.6 log units from budipine to sila-budipine (2). However, its *in vivo* pharmacological benefit as a result of this increase has not been reported. Sila-budipine also demonstrates a weaker affinity for the monoamine oxidase B receptor than budipine, although had similar affinities for other receptors studied (Table **2**) [7].

Table 2. Binding Affinities of Budipine and Sila-Budipine at Monoamine Oxidase B Receptor

	Budipine	Sila-budipine
IC_{50} μM*	2	18

* Inhibition of binding.

The synthesis of sila-budipine can be achieved in two simple steps from diphenyldivinylsilane (Fig. (**2**)) [8].

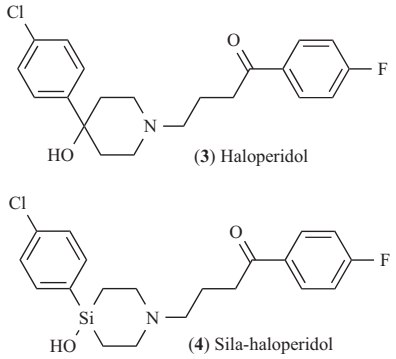


(**2**) sila-budipine

Fig. (2). Synthesis of sila-budipine.

Sila-Haloperidol

Although the exact pathogenesis of the neuropsychiatric disorder schizophrenia is not clear, it is generally accepted that changes in neurotransmitter systems are involved. Amongst these, is the excessive stimulation of dopamine D_2 receptors [9]. Dopamine over-activity is associated with the psychotic symptoms of schizophrenia such as delusions, hallucinations and thought disorder. The first generation antipsychotic haloperidol (3) acts by blocking the dopamine (D_2)



(**3**) Haloperidol

(**4**) Sila-haloperidol

Fig. (3). Chemical structures of haloperidol and sila-haloperidol.

receptor, as well as affecting other neurotransmitter receptors such as serotonin receptors. It is also associated with considerable adverse effects such as initiation of Parkinson-like symptoms, headache and cerebral seizures. Tacke *et al*. have synthesised sila-haloperidol (4) and examined the biological effects of sila substitution within the piperidine ring of haloperidol [10].

The 8-step synthesis of sila-haloperidol is illustrated in Fig. (**4**).

The sila-aza cyclic core of sila-haloperidol (4) was assembled by readily using standard synthetic protocols similar to that of sila-budipine. Sila-haloperidol was isolated as the hydrochloride salt. The authors also reported on the stability of the silanol. Mass spectral data of freshly prepared solutions of sila-haloperidol kept at 20 °C for 24 h, over a wide pH range, indicated only the presence of expected protonated sila-haloperidol, whereas the formation of disiloxane (5) (Fig. (**5**)) was not observed.

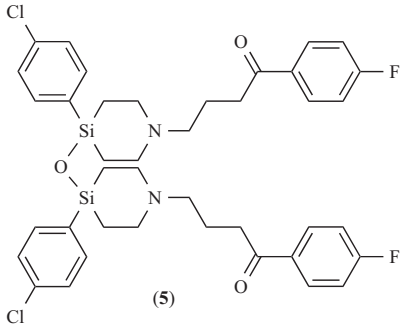


Fig. (5). Structure of disiloxane analogue of sila-haloperidol.

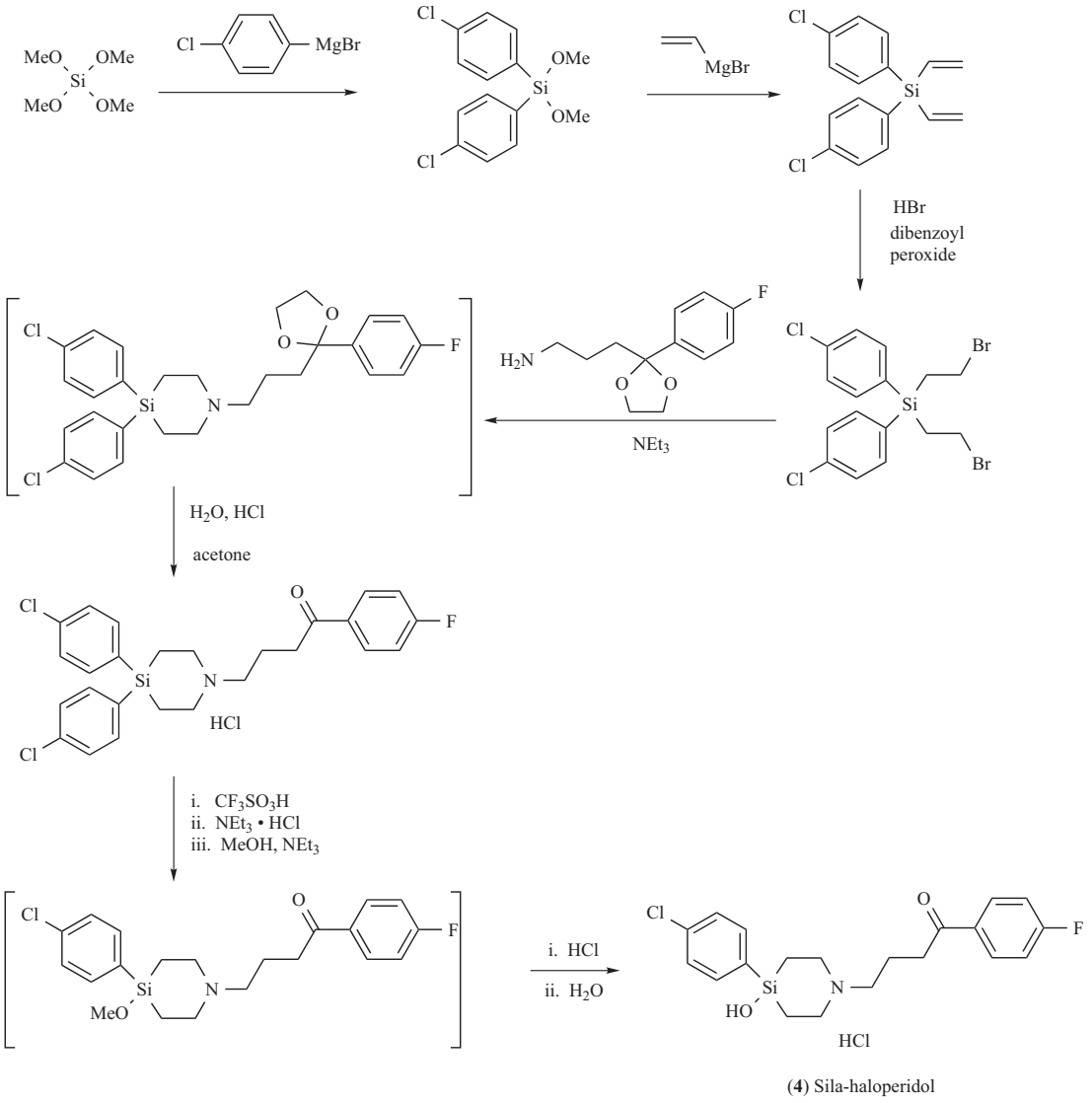


Fig. (4). Synthesis of sila-haloperidol.

Haloperidol and sila-haloperidol were evaluated for binding at the various dopamine receptors. Dopamine receptors are members of the GPCR superfamily. They are divided into two subtypes: Gs coupled (D_1 and D_5) and Gi coupled (D_2, D_3 and D_4). The C and Si analogues were evaluated for binding affinity against recombinant human dopamine receptors hD_1, hD_2, hD_4 and hD_5. The binding affinities are shown in Table **3**. Both the C and Si analogues displayed similar binding affinities for the hD_1, hD_4 and hD_5. However, at the hD_2 receptor, sila-haloperidol shows a robust five-fold greater binding affinity than its carbon analogue.

Table 3. Binding Affinities of Haloperidol and Sila-Haloperidol at Dopamine Receptors

	Ki (nM), hD_1	Ki (nM), hD_2	Ki (nM), hD_4	Ki (nM), hD_5
Haloperidol	100	4	6	37
Sila-haloperidol	95	0.85	10	21

For assay conditions see reference [10].

Sila- substitution of haloperidol has modulated the receptor selectivity profile. This improved affinity at the hD_2 receptors might be a consequence of improved hydrogen bonding of the silanol. It is not yet known if this would be physiologically beneficial. However, according to the authors of the report, haloperidol and sila-haloperidol would be expected to differ substantially *in vivo*. Metabolic studies on haloperidol [11] show that haloperidol is converted into a pyridinium type metabolite (7) which is suspected to lead the adverse Parkinsonism-type side effects of haloperidol (Fig. (**6**)).

The equivalent water-elimination intermediate, (6) is not chemically possible in sila-haloperidol as the silicon-carbon double bond would not be stable under physiological conditions. Hence, sila-haloperidol may show a more favorable side effect profile *in vivo* as compared to haloperidol.

Sila-Fexofenadine

Classical antihistamines, H_1 receptor antagonists, used for the treatment of allergies are generally non-selective and suffer from sedative side effects. The second generation of antihistamines, such as terfenadine, cause less sedative side effects and less impairment of intellectual and motor-functions. Terfenadine however, has been associated with cardiovascular side effects that include prolonged QT interval, torsades de point, and ventricular fibrillation. Terfenadine (8) is converted *in vivo* to its pharmacologically active metabolite terfenadine carboxylate (9) on its first entry through the liver (Fig. (**7**)). The metabolite exerts the beneficial effects of the drug and is not associated with adverse cardiovascular ef-

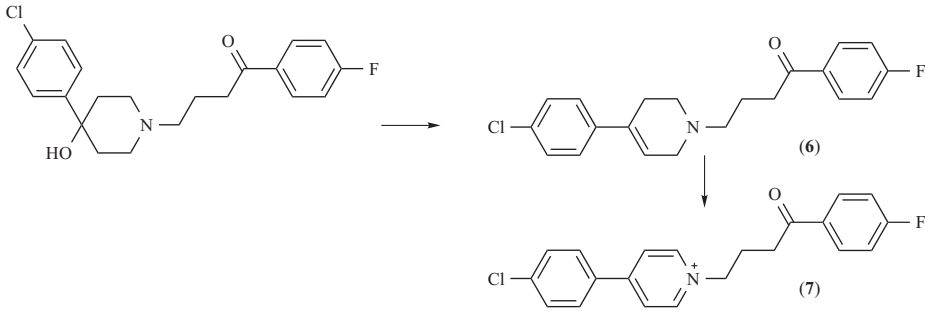


Fig. (6). Metabolism of haloperidol.

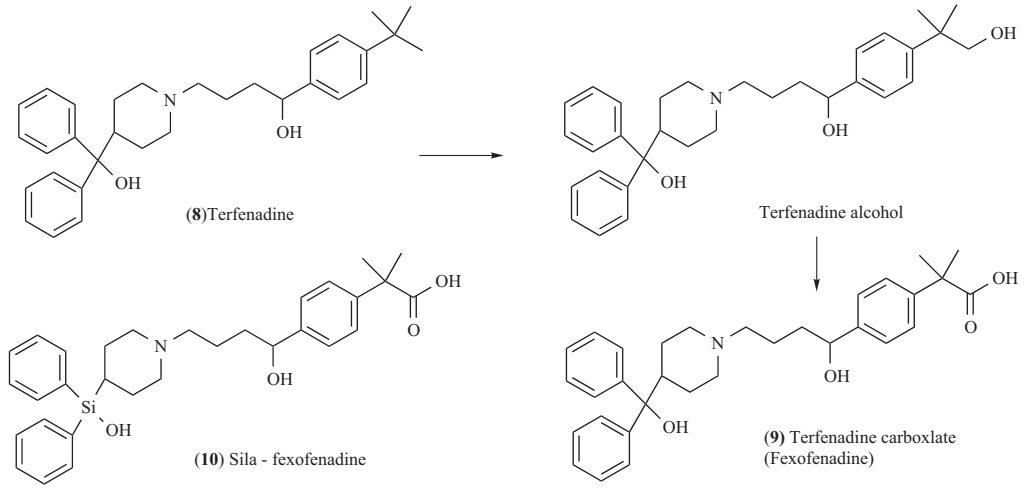


Fig. (7). Terfenadine and its metabolites.

fects. However, the tefenadine that reaches the systemic circulation without being metabolised, causes the observed cardiotoxicity by blocking the hERG ion channel. The active metabolite, terfenadine carboxylate, is devoid of these properties and is marketed as fexofenadine (9), as a market leader in the treatment of allergies.

Continuing their work on sila-substituted drugs, Tacke *et al.* [12], synthesised the sila analogue of fexafenadine in order to investigate its pharmacological properties. The synthesis of sila-fexofenadine is illustrated in Fig. (**8**). The key precursors (11) and (12) were coupled under standard reaction conditions. A subsequent series of reduction and hydrolysis reactions afforded sila-fexofenadine (10).

The carbon and the sila analogues of fexafenadine were profiled against a panel of histamine receptors (histamine central H_1 receptor, peripheral H_1, H_2 and H_3 receptors) in a radioligand binding assay (Table **4**).

The two compounds show a similar profile within experimental variations. In this instance, substitution of the quaternary carbon of fexafenadine with silicon does not alter the binding affinity in an *in vitro* system, and demonstrates the simple bioisoteric nature of silicon and carbon at these receptors.

Sila-Bexarotene

Bexarotene (Targretin™) (13) is a RXR-selective retinoid agonist that is used in the treatment of cutaneous T-cell lymphoma. It is in phase 3 clinical trials for non-small-cell lung cancer [13]. Retinoids are analogues of retinoic acid, an active metabolite of vitamin A. They are ligands of two classes

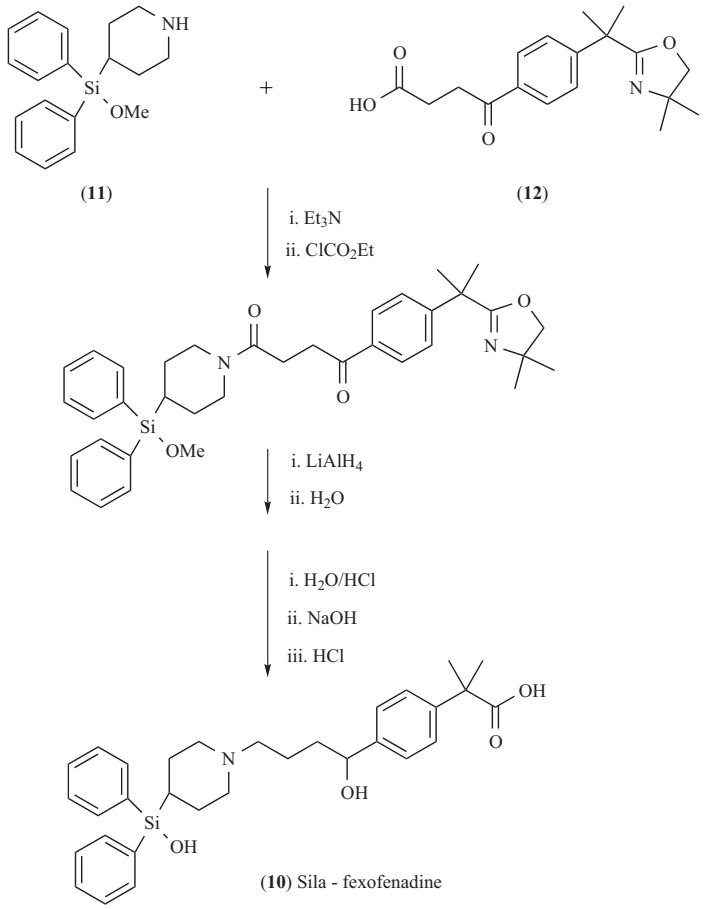


Fig. (8). Synthesis of sila-fexofenadine.

Table 4. Binding Affinities of Fexafenodine and Sila-Fexofenadine at Histamine Receptors

	H_1 central	H_1 peripheral	H_2 peripheral	H_3 peripheral
Fexafenadine	0.9	3.4	0% @ 1 μM	14% @ 1 μM
Sila-fexafenadine	0.3	1.3	4% @ 1 μM	6% @ 1 μM

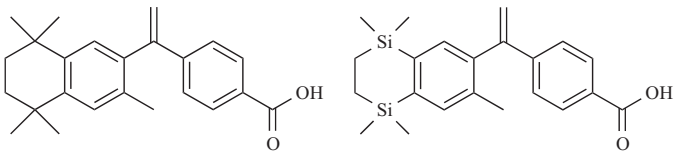
For assay conditions see reference [12]. Data expressed as Ki (μM) or % inhibition of binding.

of nuclear receptors namely, retinoid acid receptors (RARs) and retinoid X receptors (RXRs), each of them contains subtypes α, β and γ. RXRs form heterodimers with various receptor partners such as RARs, vitamin D receptor (VDR), thyroid hormones receptors (TRs) and peroxisome proliferator-activated receptors (PPARs). Retinoids bind to and activate the receptors causing them to act as transcription factors that regulate the expression of genes which control cell differentiation and proliferation. Various synthetic retinoids (receptor agonists and antagonists) have been developed and tested for their clinical utility [14].

Daiss and Tacke [15] introduced silicon into the core of the bexarotene molecule and investigated its agonist activity.

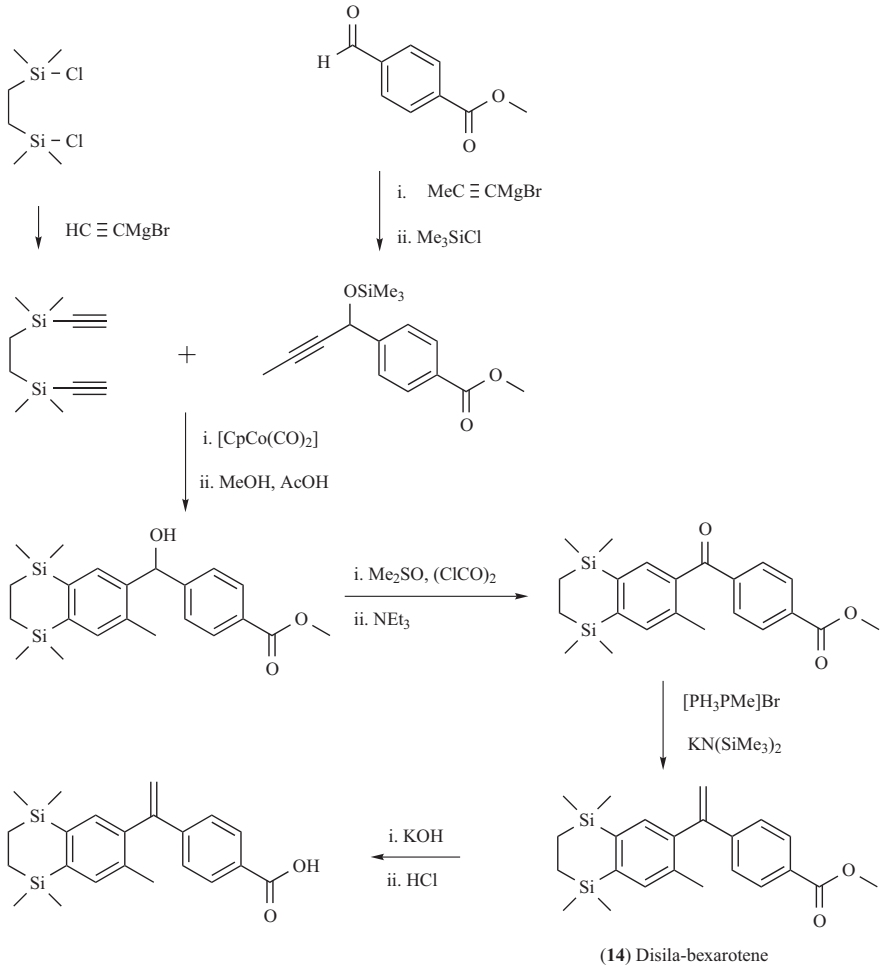
The elegant 6-step synthesis of disila-bexarotene (14) is illustrated in Fig. (**10**). The key step in the synthesis is the efficient cobalt catalysed Vollhardt cyclisation [16] to construct the disila ring system of bexarotene.

The RXR agonist activity of disila-bexarotene was assessed and compared to that of bexarotene and a positive control, 9-*cis* retinoic acid (9-*cis* RA). The agonist activity was measured at different concentrations in a hRXR β cell-based luciferase reporter assay. These data are summarised in Fig. (**11**). Bexarotene shows a higher agonist response against hRXRβ than the positive control, 9-*cis* retinoic acid and the disila analogue of bexarotene shows a comparable response to bexarotene.



(**13**) Bexarotene (**14**) Disila-bexarotene

Fig. (9). Chemical structures of bexarotene and disila-bexarotene.



(**14**) Disila-bexarotene

Fig. (10). Synthesis of disila-bexarotene.

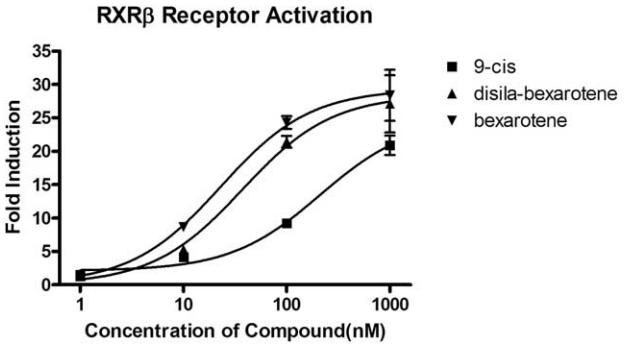


Fig. (11). Effect of bexarotene and its disila analogue on hRXRβ receptor activation.

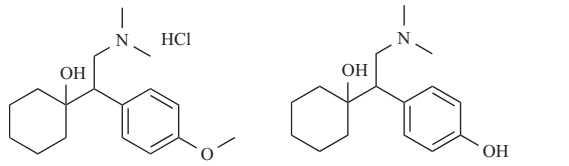
The disila substitution of the tetrahydronaphthalene core of bexarotene gives an equally potent compound in *in vitro* activation of the hRXRβ receptor and demonstrates how silicon can effectively be used as bioisostere for carbon. Tacke has also shown by X-ray crystallography that a greater twist occurs in the disila ring of disila-bexarotene (14) as compared to the tetrahydronaphthyl ring of bexarotene itself. The X-ray crystal structure of RXRα receptor complexed with its natural ligand (9-*cis*-retinoic acid) indicates that there is accessible volume space in the receptor pocket [17]. This clearly accommodates the more conformationally flexible disila tetrahydronaphthyl ring of di-sila bexarotene.

Sila-Venlafaxine

Venlafaxine hydrochloride (15) is an example of a newer class of antidepressant drugs that acts by blocking the reuptake of the neurotransmitters noradrenaline and serotonin. It is categorized as a selective noradrenaline – serotonin reuptake inhibitor with greater selectivity for the serotonin site. Venlafaxine inhibits the reuptake of serotonin and noradrenaline at a dose of 225 mg/day, and at higher doses of 300 mg/day or higher, it also inhibits dopamine reuptake.

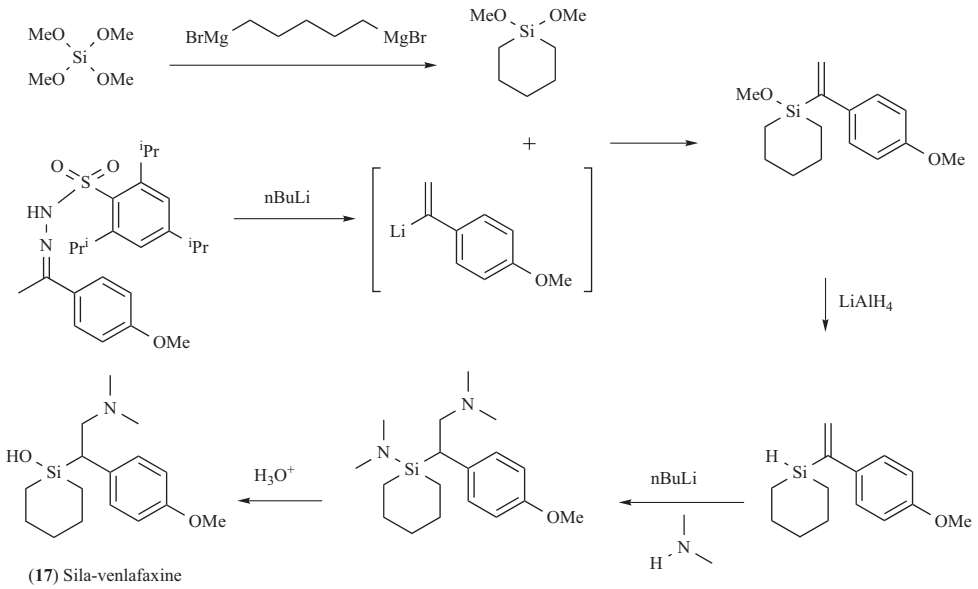
Venlafaxine is administered in its racemic form. It is extensively metabolised in the liver *via* the P450 enzymes to its O-desmethyl analogue (16). This is also a potent selective noradrenaline – serotonin reuptake inhibitor.

The sila analogue of venlafaxine has been synthesised [18, 19]. Two protocols have been described for the synthesis of sila-venlafaxine (17) (Fig. (**13**) and Fig. (**14**)). The original synthesis (Fig. (**13**)) was modified to avoid the use of highly flammable reagents such as lithium aluminium hydride and allow it to be more amenable to large-scale synthesis. The use of the acid labile trimethoxyphenyl protecting group (18) (Fig. (**14**)) allowed the key intermediates to be isolated as crystalline solids in multigram quantities [18].



(**15**) Venlafaxine (**16**) O-des methyl venlafaxine metabolite

Fig. (12). Venlafaxine and its O-des methyl metabolite.



(**17**) Sila-venlafaxine

Fig. (13). Original synthesis of sila-venlafaxine.

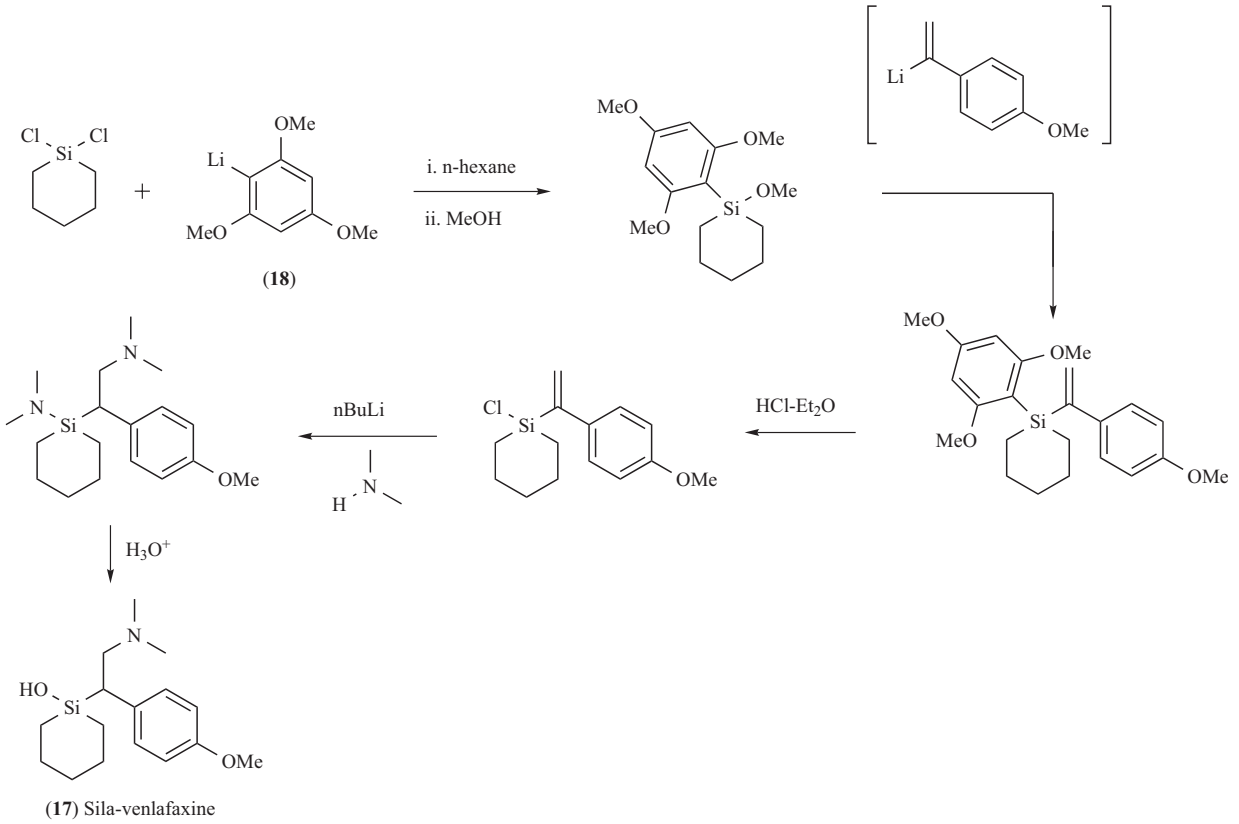


Fig. (14). Alternative synthesis of sila-venlafaxine.

It is interesting to note that the measured physicochemical properties of the two carbon and silicon analogues of venlafaxine are very similar (Table **5**).

Table 5. Comparison of Physicochemical Properties of Venlafaxine and Sila-Venlafaxine

	pKa	LogP	LogD $_{7.4}$
Venlafaxine	9.7	3.13	0.88
Sila-venlafaxine	9.7	3.21	0.92

In this instance, the effect of the increased acidity of the silanol is cancelled out by the greater lipophilicity of the silicon as compared to the carbinol of venlafaxine, leading to a high similarity in the physicochemical profile of the two compounds. This would indicate that sila-venlafaxine would have a similar brain penetration profile as compared to venlafaxine.

The *in vitro* pharmacological profile of the two compounds was assessed for inhibition of serotonin, noradrenaline and dopamine reuptake (Table **6**).

It was observed that inhibition of noradrenaline and dopamine reuptake inhibition was essentially unchanged by sila-venlafaxine as compared to venlafaxine. However, the reuptake inhibition of serotonin was significantly reduced. Hence, the pharmacological profile has been altered by the introduction of silicon into the core of venlafaxine with sila-venlafaxine being a selective noradrenaline reuptake inhibitor [19, 20].

Table 6. Effect of Venlafaxine and Sila-Venlafaxine on Serotonin, Noradrenaline and Dopamine Reuptake

IC_{50} (μM)	SERT	NET	DAT
venlafaxine	0.02	0.15	4.43
Sila-venlafaxine	1.06	0.11	2.63

FUTURE PROSPECTS

The key differences between silicon and carbon such as differences in the atomic bond lengths of the two elements, electronegativities, lipophilicities, reactivity and stability of certain functional groups allow the use of silicon to be a powerful new tool which is available to medicinal chemists in an effort to design novel drug-like molecules. For instance, the increase in the binding affinity of sila-haloperidol at the hD_2 receptor as compared to its all carbon counterpart, and the altered selectively profile of sila-venlafaxine as compared to venlafaxine, demonstrates this difference between silicon and carbon in drug like molecules. In the case

of launched drugs as reviewed here, the use of silicon has not only demonstrated an altered pharmacological profile or its use as a novel bioisostere, but also opened up new chemical space allowing novel IP. It has also been demonstrated by Tacke and co-workers extensive chemical work that these silicon molecules can be accessed in a relatively straightforward manner.

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Received: February 02, 2006 **Revised: April 07, 2006** **Accepted: April 08, 2006**