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Perspective

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Organosilicon Molecules with Medicinal Applications

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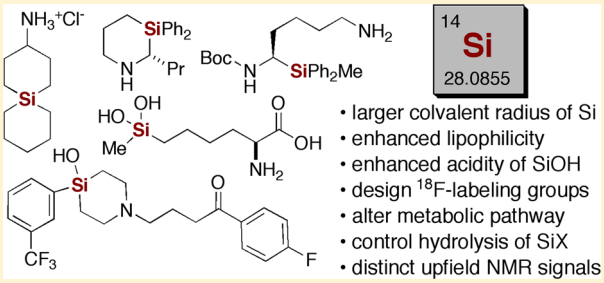
ABSTRACT: The incorporation of silicon and synthesis of organosilicon small molecules provide unique opportunities for medicinal applications. The biological investigation of organosilicon small molecules is particularly interesting because of differences in their chemical properties that can contribute to enhanced potency and improved pharmacological attributes. Applications such as inhibitor design, imaging, drug release technology, and mapping inhibitor binding are discussed.



1. INTRODUCTION

The diverse steric and substitution patterns available to organosilicon compounds provide opportunities to design and control stability, solubility, and pharmacokinetic properties. Numerous methods have been developed for the synthesis of new silicon-containing molecules and silicon derivatives of known drugs (Figure 1).[1−6] The development of high-throughput cellular and biochemical screening allows for the rapid biological assessment of organosilicon small molecules containing new molecular frameworks and non-natural functional groups. The medicinal applications of organosilicon molecules are particularly interesting because of differences in the chemical properties of silicon-containing molecules, such as silanols, silanediols, and silyl fluoride groups compared to traditional carbon-based functional groups. These differences afford the potential for unique and/or specific interactions between an organosilicon molecule and a biological macromolecule. The approval of bortezomib (Velcade), a proteosome inhibitor containing a boronic acid group, for the treatment of multiple myeloma in human patients highlights the successful application of non-natural functional groups in a therapeutically relevant manner.[7]

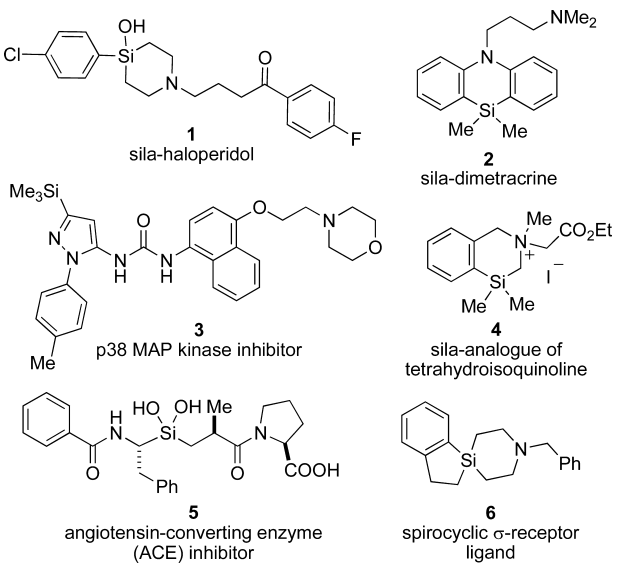


Figure 1. Examples of silicon-containing molecules of medicinal interest.

The strategic incorporation of silicon bioisosteres into known drug scaffolds is a method to optimize biological activity and reduce toxicity with the goal of increasing the therapeutic potential of a drug or to repurpose the drug for treatment of an alternate disease.[8,9] Silicon provides a logical choice as a carbon isostere because of their adjacent positions in group IV of the periodic table.[10] When silicon is incorporated into an organic compound, the chemical and physical differences contributed by the silyl group can provide compounds with unique properties. There are several important chemical properties of organic silicon that are relevant for medicinal chemistry (Table 1):[11]

(1) The larger covalent radius of silicon contributes to approximately 20% longer bond lengths, different bond angles, and different ring conformations compared to the corresponding carbon analogues. The larger size and covalent radius can provide an important influence on the conformation and reactivity of ring structures containing a silicon center.

(2) The increased lipophilicity of organosilicon molecules often enhances cell and tissue penetration and alters the potency and selectivity of the silicon structure relative to the carbon structure. For example, the log *P* of trimethylsilylbenzene is 4.7 whereas the carbon analogue *tert*-butylbenzene has a lower log *P* at 4.0.

(3) Silicon exhibits different bonding preferences compared to carbon based on the availability of 3d orbitals and low-lying Si−C or Si−X antibonding orbitals for hyper-

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Table 1. Comparison of Carbon and Silicon Properties Relevant for Medicinal Chemistry

property	carbon	silicon
covalent radius	77 pm	117 pm
bond length	1.54 Å (for C−C)	1.87 Å (for Si−C), ∼20% longer compared to carbon
lipophilicity	log *P* of $PhCMe_3$: 4.0	log *P* of $PhSiMe_3$: 4.7
electronegativity	2.50	1.74, reverses most bond polarity relative to carbon and changes reactivity, upfield chemical shift of silicon α-protons
acidity of X−OH	weakly acidic [$pK_{a(DMSO)}$ of Ph_3COH: 17.0]	more acidic than C−OH [$pK_{a(DMSO)}$ of Ph_3SiOH, 16.6], can readily condense to form Si−O−Si (in equilibrium)
stability of X−OC	stable	hydrolyzes under acidic conditions, depends on steric effects around silicon
stability of X−N	stable	hydrolyzes under acidic conditions
stability of X═C and X═X	stable	unstable, not observed

conjugation. In significant contrast to carbon, double and triple bonds with silicon, including silanones, are not favored. This differential bonding provides for unique bioisosteres that do not have stable carbon analogues, such as the geminal silicon diol as a mimic of the unstable hydrated carbonyl group, and can also influence the metabolic pathways of organosilicon molecules.

(4) The electropositive nature of silicon (relative to C, N, O, and H) contributes to an electron-deficient center in a molecule and reversed bond polarization relative to corresponding carbon bonds. In medicinal chemistry, this property enhances hydrogen-bonding abilities, increases the acidity of silanols, and may also affect metabolic pathways. The $pK_{a(DMSO)}$ of triphenylsilanol is 16.6 compared to the $pK_{a(DMSO)}$ of triphenylmethanol, which is 17.0.[12] In synthesis, the polarization of a Si−C or Si−X bond provides enhanced reactivity relative to the carbon analogue. In NMR spectroscopy, this results in a distinctive upfield chemical shift of the silicon α-protons (to ∼0 ppm).

(5) The Si−OC and Si−N bonds are thermodynamically stable but kinetically labile in aqueous and acidic conditions based on the steric environment around the silicon atom. This property can be useful for synthetic protecting groups and prodrug strategies.

(6) There is no known intrinsic "element-specific" toxicity associated with organosilicon small molecules.

This Perspective summarizes recent developments for the medicinal applications of silicon-containing small molecules and isosteres and demonstrates the continued growth in this area. While this review is not focused on synthetic methodology, representative syntheses will be highlighted in order to demonstrate the use of standard transformations and the stability of most organosilicon molecules under standard conditions. The reader is also referred to several earlier reviews describing the synthesis and biological activity of organosilicon molecules.[8,9,13−18] In addition to recent advances for drug design, the utility of organosilicon molecules will also be presented for unique applications related to imaging, drug release, and structural probes for protein-binding studies.

2. SILICON-CONTAINING AMINO ACIDS AND ANALOGUES

Silicon-containing amino acids are useful for the synthesis of peptides with improved physiochemical properties and in vivo activity. A growing number of systematic comparisons have been made and there are several interesting reports regarding applications of unnatural silicon-containing amino acids and therapeutically relevant compounds containing silicon. The incorporation of a silyl group has been shown to enhance lipophilicity (Figure 2), increase resistance to proteolytic

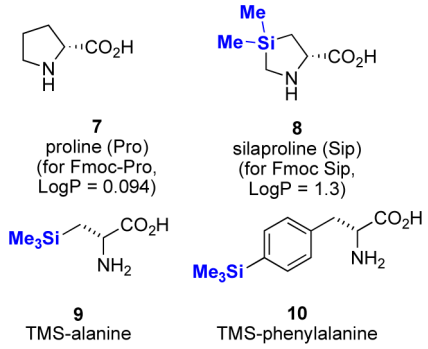

Figure 2. Examples of silyl amino acids.

degradation,[19] and increase cellular uptake.[20] Various unnatural silicon-containing amino acids are known, such as γ-(dimethylsila)proline (**8**, sila-proline, Sip),[21,22] β-TMS-alanine (**9**),[19,23] and β-TMS-phenylalanine (**10**).[24] TMS-alanine provides a simple isosteric replacement for *tert*-leucine[23] and has also been investigated as a replacement for phenylalanine based on the lipophilicity, as demonstrated for renin inhibitory peptides with marginal loss in activity.[19] The incorporation of sila-proline in a proline-rich cell-penetrating peptide (PPII) has been shown to enhance cellular uptake, based on cellular (HeLa) internalization studies with a CF-labeled peptide.[20,25,26] Incubation studies were performed with CF-labeled sila-peptide where uptake of the peptide was monitored with CLSM and quantified through flow cytometry experiments. Furthermore, circular dichroism and transmission electron microscopy (TEM) were used to show that that the incorporation of sila-proline does not perturb the secondary structure of the peptide and does not prevent peptide aggregation, which is observed based on the amphipathic character of PPII helices. Cell viability assays demonstrated no toxicity for the incorporation of sila-proline, even at the high concentration of 1.0 mM.

Importantly, the chemical reactivity of silicon-containing amino acids is not dramatically different from those of their carbon analogues, and many silyl amino acids can be successfully employed in standard peptide coupling protocols. In numerous cases, enantiomerically-enriched silyl amino acids have been employed in peptide coupling without epimerization.[19−21,23,25,27,28] As such, several strategies have been investigated for the enantioselective synthesis of silicon-containing amino acids. For example, Sieburth developed an asymmetric reverse-aza-Brook rearrangement using (+)- or (−)-sparteine to dictate the absolute stereochemistry for the efficient synthesis of α-alkyl-α-aminosilane substrates.[27] Various

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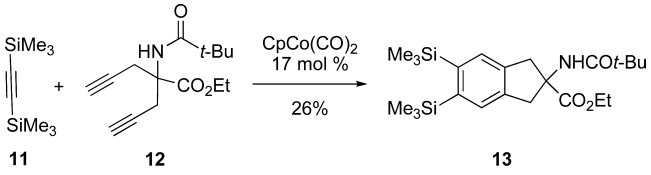
novel silicon-containing amino acid derivatives have also been synthesized. For example, a cobalt-catalyzed cyclotrimerization has been used for the simple, albeit low-yielding, synthesis of silicon-containing cyclic α-amino acid derivative **13** (Scheme 1).[29] The reader is referred to an excellent review by Bolm for

Scheme 1. Cyclotrimerization Strategy To Access Silicon-Containing Amino Acids

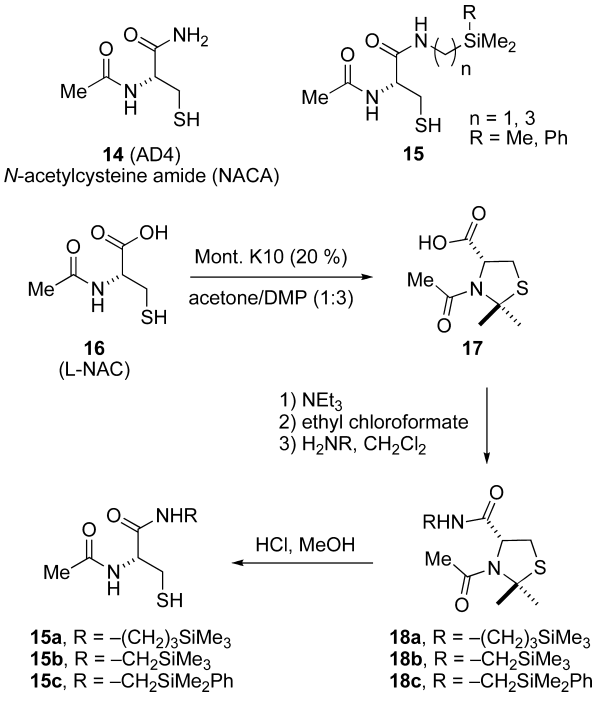


11 **12** **13**

additional details describing the synthesis of various silyl amino acids.[22] The recent syntheses of several new silicon-containing amino acids are described here.

West has reported silicon-derivatives of *N*-acetylcysteineamide **14** (NACA, AD4), an amide derivative of *N*-acetyl-L-cysteine (**16**), which is a powerful antioxidant and a precursor to glutathione.[30] The more lipophilic amide derivative **14** is known to be a better radical scavenger than *N*-acetyl-L-cysteine and is capable of crossing the blood–brain barrier, making it relevant for therapeutic applications for Alzheimer's disease, Parkinson's disease, and multiple sclerosis. The authors propose that sila-amide derivatives such as **15** will further enhance the lipophilicity, and these derivatives are expected to be useful in optimizing the pharmacokinetic properties. Sila-amides **15** are synthesized following a standard synthetic route involving protection and subsequent amidation with a silicon-containing amine, followed by deprotection with HCl (Scheme 2). The amines used in this strategy have also been used in other sila-amidation strategies.[31] The use of amino-functionalized silanes in amide coupling reactions provides a simple and general

Scheme 2. Sila-amide Derivatives of *N*-Acetyl-L-cysteine



14 (AD4)
N-acetylcysteine amide (NACA)

15

16
(L-NAC)

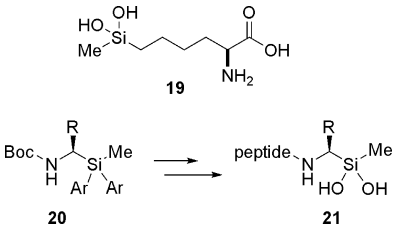
17

15a, R = –$(CH_2)_3SiMe_3$
15b, R = –CH_2SiMe_3
15c, R = –CH_2SiMe_2Ph

18a, R = –$(CH_2)_3SiMe_3$
18b, R = –CH_2SiMe_3
18c, R = –CH_2SiMe_2Ph

method to prepare silyl derivatives that should be applicable whenever a series of amides is prepared for biological investigation. The biological properties and activity comparison of sila-amides with the corresponding carbon analogues have not yet been reported.

In the course of investigating the synthesis and bioactivity of silanediol peptide isosteres,[5,17] Sieburth and Skrydstrup have developed various silanediol-containing amino acids (or precursors) that have unique capabilities for hydrogen-bonding, such as silanediol **19** (Figure 3).[32−37] In addition to standard



19

20 **21**

Figure 3. Silanediol-containing amino acid derivatives and precursors.

methods such as hydrolysis of a silyl ether, these synthetic strategies often involve incorporation of a diarylsilicon functional group (e.g., **20**), which can be cleaved upon protodesilylation under acidic conditions to reveal a silanediol (e.g., **21**). The diarylsilylamino acid mimics can be converted into silanediols directly or inserted into peptides through standard coupling procedures.[5,35] The details of the synthetic methods to access these silicon-containing amino acids and peptide isosteres will be discussed further in section 5.3.

3. STABILITY OF ORGANOSILICON MOLECULES

The stability of organosilicon molecules is an important consideration for their medicinal and clinical applications. There have been many individual cases noting the stability of various organosilicon small molecules; however, the stability strongly correlates with the size and functionality of the substituents attached (and adjacent) to silicon. Generally, organosilicon molecules are considered to be stable in aqueous and oxygen-rich environments, with a few exceptions. Si–H bonds of silicon hydrides are rapidly hydrolyzed in vivo. Although silyl ethers are generally sensitive to acidic environments, their hydrolysis rate can be effectively controlled based on the substitution on silicon. The reactivity of the alkoxysilane (Si–OC) bond is sufficiently different compared to the corresponding dialkyl ether (C–OC) bond because it is thermodynamically very stable but kinetically labile in aqueous and acidic conditions.[15,38,39] The stability and cleavage of Si–aryl bonds are effectively controlled based on the size and electronic nature of the aryl group and in some cases the adjacent functional groups that can coordinate to silicon. The balance of reactivity and stability for Si–aryl bonds has been utilized for the design and synthesis of silanediol mimics of transition state analogues.[17] Si=C bonds are unstable under almost all conditions and cannot be readily accessed during synthetic intermediates or metabolic pathways. Overall, the tunable stability of various silyl groups indicates broad potential for diverse biological applications, including imaging agents and prodrugs, as described later in this Perspective.

A systematic study of the methanolysis rate for a series of α-silylamino acid derivatives (**22**) provides an excellent example of how the steric environment and adjacent functional groups

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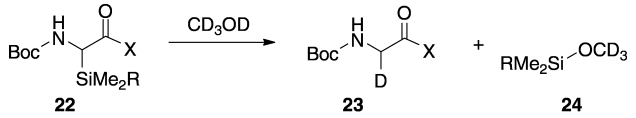
effect stability (Scheme 3).[40] While α-aminosilyl groups are typically stable, the stability of α-silylcarbonyl derivatives is

Scheme 3. Stability of α-Trialkylsilylamino Acid Derivatives



R	X	half-life
Me	OMe	11.5 h at 20 °C
Et	OMe	23 days at 20 °C
i-Pr	OMe	36 days at 20 °C
t-Bu	OMe	56 days at 20 °C
t-Bu	NHMe	56 days at 57 °C

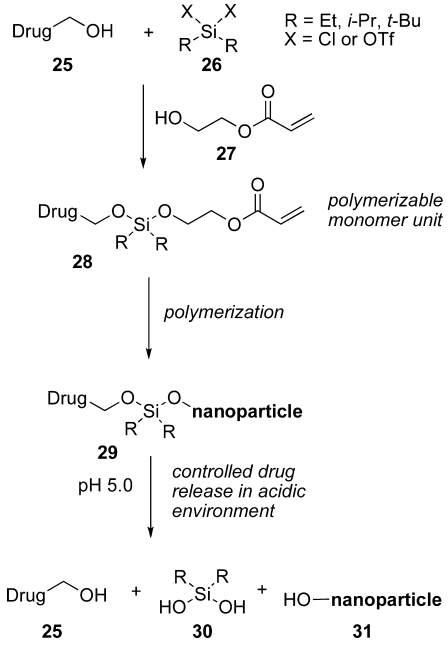
heavily dependent on both the steric environment around silicon and the type of carbonyl group. In the case of an α-silyl ester, incremental changes in the steric environment around silicon (i.e., Me vs Et) demonstrate a significant effect on the stability. The rate of methanolysis (with CD_3OD at 20 °C) is extended from $t_{1/2}$ = 11.5 h for a methyl group to $t_{1/2}$ = 23 days for an ethyl group. Replacing the ester with an amide demonstrates the superior stability of an α-silylamide substrate where the half-life is increased to 56 days at 57 °C. This increased stability suggests broad potential for silicon-containing amino acids to be employed in the synthesis of bioactive peptides and pharmaceutical compounds.

4. SILYL ETHERS AND DRUG DELIVERY STRATEGIES RELATED TO SILICON

The ability to control the hydrolysis rate of a silyl ether can be important for medicinal applications related to drug release and delivery in the case of silyl linkers or silicon-based nanoparticles.[15,38,39] Utilizing the reactivity of N- and O-silylated compounds, acid-sensitive prodrugs have been previously explored.[41,42] For example, silyl ether prodrugs of antiulcer prostaglandins (attached to polybutadiene) have been designed to degrade under the acidic conditions of the stomach.[43] In a recent report, Desimone and co-workers described controlled drug delivery from biocompatible nanoparticles using a bifunctional silyl ether (CO−Si−OC) strategy for a prodrug linkage (Scheme 4).[44] Each prodrug−nanoparticle conjugate (**29**) is synthesized from a bifunctional dialkylsilane electrophile (**26**) and a hydroxy-containing therapeutic compound (**25**) to afford a polymerizable monomer (**28**), which allows facile incorporation in a nanoparticle with near-quantitative encapsulation. The rate of drug release can be controlled by altering the size of the alkyl substituents on the silyl linker **26** (i.e., Et, *i*-Pr or *t*-Bu) with release occurring over the course of hours, days, or months. Upon release under acidic conditions, the authors used HPLC analysis to demonstrate that there is no silyl ether functionality remaining in the therapeutic agent.

The synthesis and properties of silicon can also be useful in the design of materials for controlled drug release systems without covalent attachments. Ha and co-workers have described the use of fluorinated polysilsesquioxane (FPSQ) hollow spheres as fluorinated drug release carriers.[45] FPSQ carriers can be synthesized with high fluoroalkyl surface coverage upon hydrolytic condensation of (trifluoropropyl)-trimethoxysilane (FTMS) in an aqueous solution. The controlled release of two fluorinated drugs (5-fluorouracil and

Scheme 4. Controlled Drug Delivery from Biocompatible Nanoparticles with a Bifunctional Silyl Linker



flucytosine) was investigated, and results demonstrated that the release of these fluorinated drugs occurs more slowly than a nonfluorinated drug (e.g., captopril) over 24 h. Previous groups have demonstrated similar results using fluorocarbon-modified silica; however, a strategy using the postmodification of silica materials may lead to limited fluorine content in the materials, making this direct strategy more advantageous.[46,47]

Although silyl ethers are often observed to be hydrolytically sensitive, there are also examples where these molecules demonstrate sufficient stability and differential biological activity. Padron and co-workers have investigated a series of enantiomerically-pure disubstituted tetrahydropyrans containing a silyl ether, with the idea that the addition of a lipophilic silyl group will increase cellular uptake and enhance antiproliferative effects for this class of heterocycle (Figure 4).[48] In their initial report, several trans-disubstituted

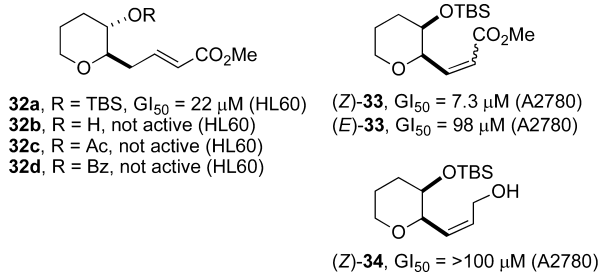


Figure 4. Cytotoxicity of tetrahydropyrane silyl ethers.

tetrahydropyrans such as **32** were synthesized and screened against HL60 (human promyelocytic leukemia) and MCF7 (human breast cancer) cells using a protein-binding sulforhodamine B (SRB) assay. As a general trend, the presence of the secondary *tert*-butyldimethylsilyl ether group (**32a**) increased the cytotoxicity of these compounds relative to the free hydroxyl derivative (**32b**) and also relative to compounds examined with other protecting groups (e.g., allyl, Ac, and Bz);

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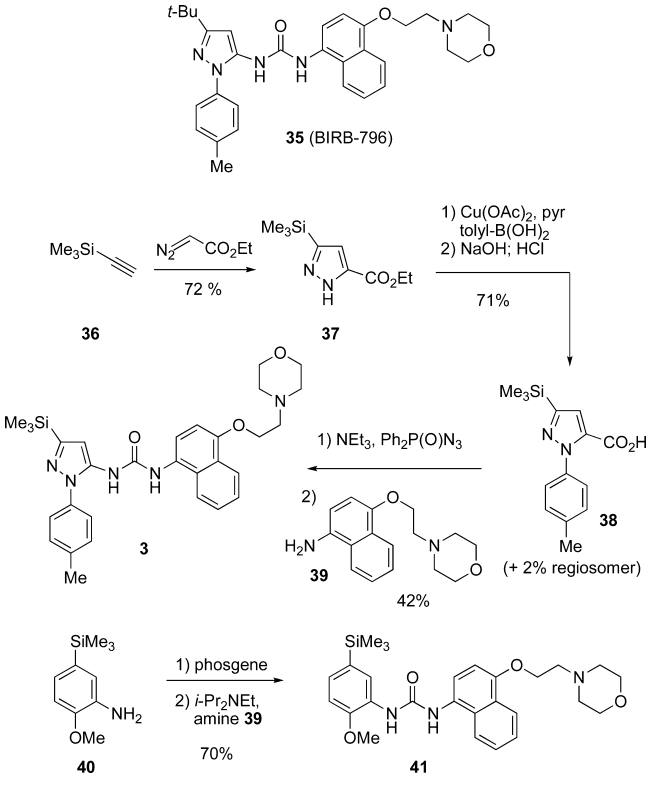
however, not all silyl ethers demonstrated activity, indicating that the presence of the silyl group was not sufficient to promote cytotoxic activity. In a subsequent report, the authors then examined a series of related cis-disubstituted tetrahydropyrans (**33** and **34**), and their results confirmed that the presence and stereochemistry of an α,β-unsaturated ester, in combination with a silyl group, are important in determining the level of cytotoxicity.[49] Silyl ether analogues of leinamycin antibiotic fragments containing a biologically-active 1,2-dithiolanon *S*-oxide motif have also shown enhanced cytotoxicity toward human cancer cells for the silyl ether compared to the corresponding hydroxyl compound.[50] These examples demonstrate a trend that silyl ethers may be capable of enhancing cytotoxicity for molecular structures already containing features that contribute to cytotoxicity.

5. SILICON ISOSTERES AND TRANSITION STATE ANALOGUES

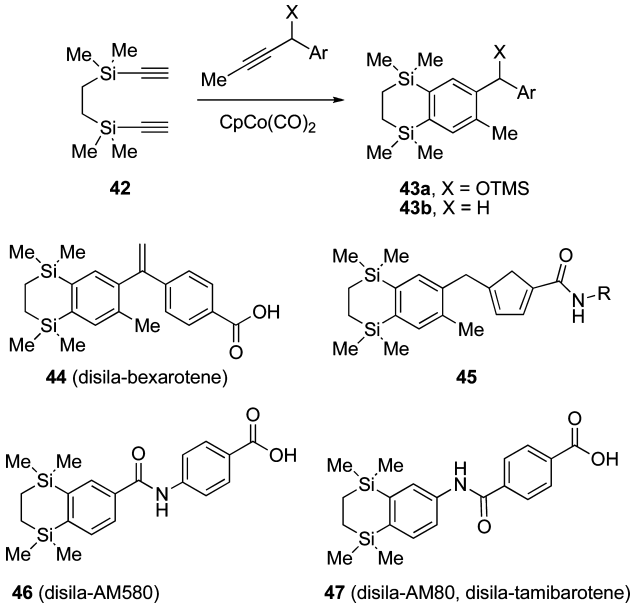
5.1. Silicon Isosteres with Tetraalkylsilyl Groups. Incorporating silicon as an isosteric replacement for carbon (i.e., a carbon−silicon switch strategy) is an attractive area of research for drug design.[10,51] Trimethylsilylpyrazoles have been investigated as new silicon isosteres for kinase inhibitors, such as analogues of **35** (BIRB-796), a non-peptide inhibitor of p38 mitogen-activated protein kinase (MAPK).[3,52] To obtain the direct silicon analogue (**3**), trimethylsilylpyrazole **37** was prepared using a [3 + 2] cycloaddition of trimethylsilylacetylene with ethyl diazoacetate (Scheme 5). A second silicon analogue (**41**) was designed in which an electron-rich silicon-substituted aryl ring replaced the silylpyrazole ring. Although sila derivatives **3** and **41** showed almost equivalent inhibition compared to **35** in the p38 MAP kinase enzyme assay, analogue **3** demonstrated slightly enhanced stability to degradation by human liver microsomes. In vivo data in an LPS-induced model of TNF-α release indicated similar efficacy and suggests that sila-analogue **3** induces TNF-α suppression more quickly (59% compared to 41% at 30 min). Future time-course experiments in a range of assays are needed to demonstrate whether this rate acceleration is a general trend for silicon isosteres based on their lipophilic property and the increased ability to penetrate cell/tissue membranes.

The incorporation of silicon as an isosteric replacement may be useful as a general strategy for the fine-tuning of optimized functionality of nuclear receptor ligands. Silicon analogues of receptor-selective retinoid agonists have been synthesized and investigated to fine-tune the pharmacodynamic and pharmacokinetic properties.[53−56] Bexarotene derivatives with a silicon-containing backbone (disila-bexarotene, **44**) have been investigated where the longer Si−C bond lengths are expected to alter the ring conformation. Bexarotene (Tagretin) is an anticancer agent targeting the retinoid X receptor (RXR), a member of the nuclear hormone receptor family that is a ligand-dependent transcription factor. The cobalt-catalyzed [2 + 2 + 2] cyclotrimerization of 1,2-bis(ethylenyldimethylsilyl)-ethane (**42**) provides efficient access to disila-bexarotene **44** (Scheme 6).[53] Synthesis and comparison of the crystal structures obtained for **44** and bexarotene structures confirm that the incorporation of silicon induces greater conformational flexibility in the backbone of the silicon derivative, which may be important for receptor binding. The cyclotrimerization route can be extended to prepare diverse disila-heterocycle scaffolds such as **45**, which have been identified as GnRH antagonists for the treatment of diseases related to gonadotropin-releasing hormone (GnRH), such as cancer, HIV, and Alzheimer's disease.[54−56] All disila analogues of retinoids were found to be equipotent compared to the carbon analogue, and in some cases an increase in the pharmacological potency was observed. Disila-tamibarotene (**47**) displays up to 10-fold higher activity in RAR-receptors.[57] This result is attributed either to the increased binding affinity of the silicon analogues or to differences in allosteric binding modes. In a subsequent study, the sila-bexarotene analogues were investigated as inducers of

Scheme 5. Synthesis of Silicon Analogues of Inhibitor 35



Scheme 6. Synthesis of Silicon Isosteres of Retinoid Agonists



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stem cell differentiation.[55] These analogues did not demonstrate the ability to induce stem cell differentiation; however, enhanced toxicity (as indicated by a decrease in the number of cells relative to the carbon analogue) was observed at 10 μM, which provided evidence that the incorporation of silicon is affecting the activity and/or distribution of the molecule.

Kim and co-workers have reported the design and synthesis of silyl analogues of MK-056 (**48**) as a silicon switch approach to identify new TRPV1 antagonists as a treatment to silence pain signaling pathways.[58] TRPV1 is a ligand-gated nonselective cation channel vanilloid receptor 1 (VR1) with high Ca^{2+} permeability. The goal of their study was to search for antagonists that have beneficial pharmacodynamic or pharmacokinetic properties. The authors synthesized and compared activity for Ca^{2+} influx activity for seven sila-substituted 1,3-dibenzylthioureas (**49a–c**) including $SiMe_3$, $SiMe_2Et$, and $SiEt_3$ groups as bioisosteres of the *tert*-butyl group, which is known to be essential for the potency of **48**. While none of the derivatives were as potent as the carbon analogues, the trimethylsilyl group was the best bioisostere for the *tert*-butyl group and exhibited almost equipotent activity to **48** with an IC_{50} of 0.15 vs 0.11 mM (Figure 5), demonstrating the first example of the *tert*-

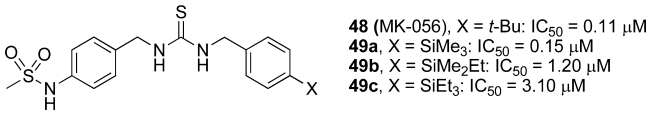


Figure 5. Comparing medicinal properties of silyl analogues of TRPV1 antagonists.

butyl group in **48** being replaced without dramatic loss of activity. The use of triethylsilyl or the replacement of one methyl group on the TMS group led to a significant loss of activity.

Degrado and co-workers have recently described the use of organosilane amines as potent inhibitors and structural probes of influenza A virus M2 proton channel (Figure 6).[59] Degrado

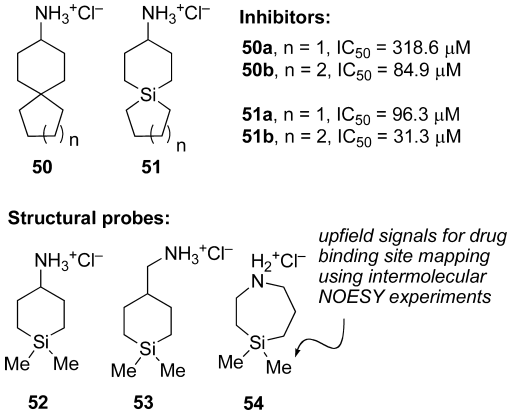
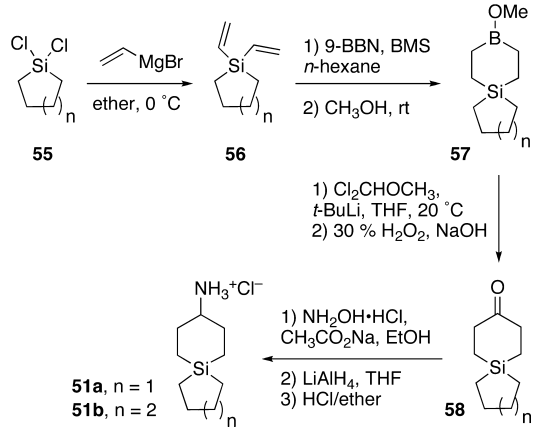


Figure 6. Silaspirane amines studied as inhibitors and probes for mapping protein-binding sites of the influenza A virus M2 proton channel.

selected organosilane amines to investigate because hydrophobicity is known to play a critical role in improving the antiviral potency of inhibitors of the M2 proton channel for anti-influenza drugs. There is a hydrophobic binding pocket that favors binding of molecules such as adamantane and spirane amines, and the authors had previously observed a correlation between the hydrophobicity of spirane amines and their antiviral potency. Therefore, the design of silicon-containing inhibitors (e.g., **51–54**) was envisioned to take advantage of synergistic effects of size and lipophilicity to improve potency (Scheme 7). Silaspirane amine inhibitors **51–**

Scheme 7. Representative Synthesis for Silaspirane Amines 51



54 maintained potency compared to the corresponding carbon analogues for wild type proteins, and exhibited enhanced potency as inhibitors against the drug-resistant A/M2-V27A mutant. For example, silaspirane amine **51b** was 2.7-fold more potent against A/M2-V27A compared to the corresponding carbon analogue **50b** (IC_{50} of 31.1 vs 84.9 μM). The authors propose that this rather dramatic increase in potency for the sila analogue is the result of the larger size and increased lipophilicity of silicon, which can provide a better hydrophobic contact between the inhibitor and the channel. In a novel approach, the authors successfully utilized the electropositive property of these organosilicon molecules as structural probes for mapping the inhibitor binding site of the A/M2 protein. The chemical shifts of the organosilane amine compounds **52–54** (e.g., the methyl groups on silicon) were shifted upfield and thus clearly distinguished from the signals of the protein, allowing them to be effective structural probes using intermolecular NOESY experiments.

5.2. Silanol Isosteres. Silanols provide a particularly interesting isostere because of the enhanced hydrogen-bonding abilities and acidity of silanols relative to carbon analogues. In a series of reports, Tacke has described the systematic evaluation for a series of silanol analogues of venlafaxine (**59**), a serotonin/noradrenaline reuptake inhibitor, which highlights both the synthetic and medicinal features of silanol isosteres **60** and (*R*)-**60** (Figure 7).[60] A modular synthetic route to obtain racemic sila-venlafaxine **60** features the use of an acid-labile, bulky 2,4,6-trimethoxyphenyl (TMOP) group as a new protecting group for a masked silanol (Scheme 8).[61] The TMOP group is stable to a wide range of conditions but can be removed efficiently and selectively with HCl (at 0 °C), conditions that are complementary to the Si–C cleavage of other aryl, vinyl, or allyl silanes. The TMOP group is also advantageous because it increases the crystalline properties of the intermediates and has a low UV detection limit. This modular synthetic route allows the preparation of analogues such as desmethoxy **61** and silacyclopentane **62**. Attempts to synthesize silacyclobutane **63** resulted in ring-opening due to

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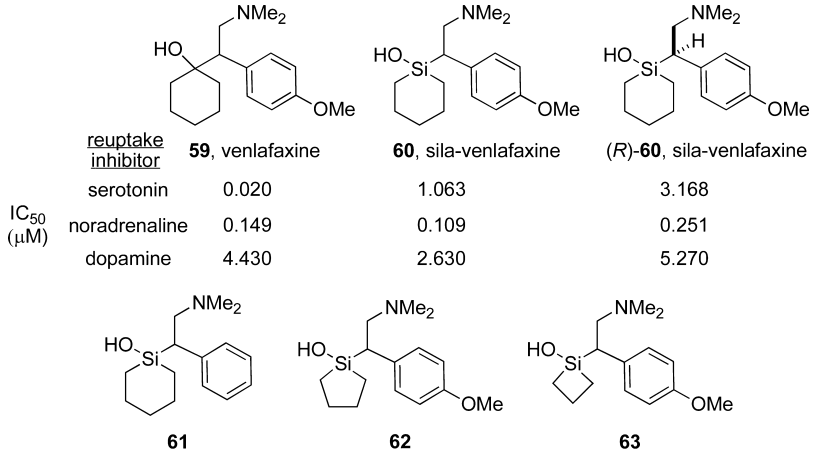
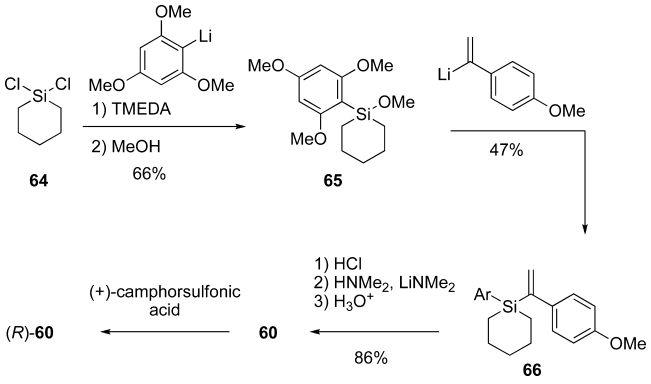


Figure 7. Venlafaxine and silicon isosteres.

Scheme 8. Synthesis of Sila-venlafaxine with a TMOP Protecting Group



the higher ring strain relative to silacyclohexane **60**. The single enantiomer (*R*)-**60** was obtained using fractional crystallization of the (+)-camphorsulfonic acid salt as the final step. X-ray crystal structure analyses were used to compare the solid-state ring conformations for the carbon and silicon structures, demonstrating that the introduction of silicon into the cyclic scaffold provides a conformation that is not accessible with the corresponding carbon analogue.

Biochemical experiments were performed for this series of venlafaxine analogues (**60**–**62**) to determine the ability of silicon conformational effects, stereochemistry, and ring size to modulate the pharmacological selectivity profile between serotonin, noradrenaline, and dopamine reuptake transporters (Figure 7). The screening results confirm that incorporating silicon affects the selectivity profile because silyl analogue (*R*)-**60** is a selective noradrenaline reuptake inhibitor while (*S*)-venlafaxine (**59**) is a selective serotonin reuptake inhibitor. Silacyclopentane **62** exhibits activity similar to that of **60**; however, this compound exhibits reduced selectivity for noradrenaline. The desmethoxy derivative **61** remains mildly selective for noradrenaline reuptake but exhibits a weaker activity profile overall.[62] These results suggest the importance of ring conformation and the subtle effects that the larger covalent radius of silicon can have on the binding selectivity. Further screening was performed for these sila-venlafaxine analogues using a series of in vitro inhibition assays with 68 common receptors/channels and 16 enzymes to identify the general target specificity. In the majority of the assays, including opioid receptors and cytochrome-P450 enzymes, no activity (<50% inhibition at 10 mM) was observed.[63]

Silicon analogues of haloperidol and trifluperidol (i.e., **1** and **69**) have also been synthesized and studied in order to develop an antipsychotic agent with reduced side effects (Figure 8).[64,65]

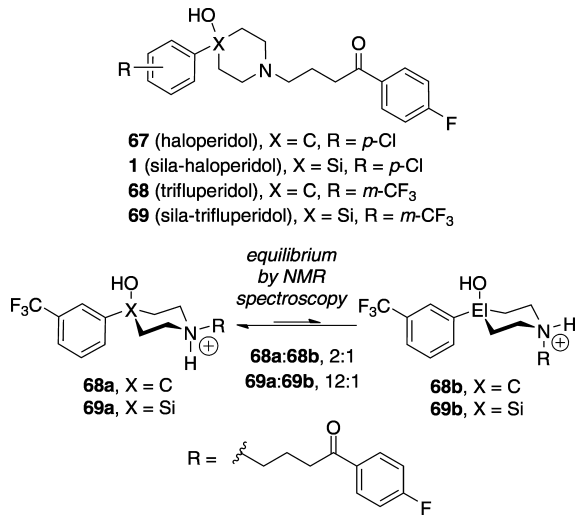


Figure 8. Comparison of haloperidol and silicon analogues.

Sila-substitution was performed in a region that is known to tolerate substitution without changing the affinity for dopamine receptors, and sila-analogue **1** was observed to change the selectivity profile. The incorporation of silicon led to a 4.7-fold increase in the affinity/potency for hD2 receptors. In comparative studies, sila-haloperidol **1** shows a higher potency at human dopamine D_2 receptors and exhibits higher subtype selectivity at dopamine and σ receptors than haloperidol **67**. Sila-trifluperidol **69** exhibited bioactivity similar to that of the carbon analogue **68**. From these studies, it has been observed as a general trend that sila-substitution can change the receptor selectivity profile.[1] X-ray structure analysis demonstrated that analogous chair conformations exist for the carbon and silicon piperidinium skeletons (Figure 8); however, NMR analysis revealed a different ratio of two ammonium isomers (2:1 vs 12:1).[65] The equilibrium between the SiOH and the siloxane (Si–O–Si) was investigated under physiological (pH 7.4) and alkaline conditions (pH 10.0), and it was shown that the disiloxane is cleaved rapidly such that the silanol is the only

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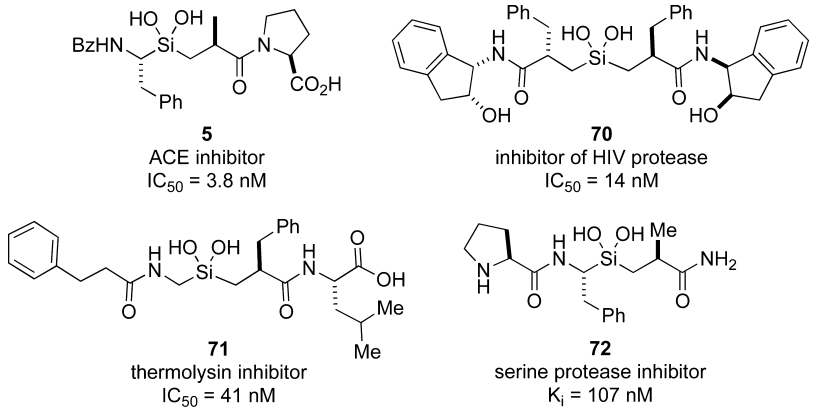
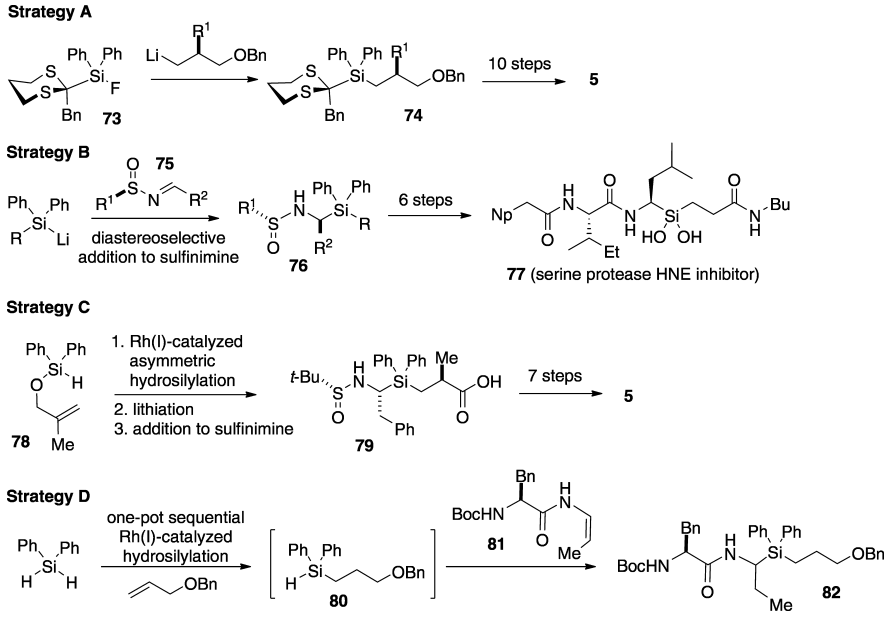


Figure 9. Examples of silanediol protease inhibitors.

Scheme 9. General Synthetic Strategies To Access Silanediol Peptidomimetics as Protease Inhibitors



species detectable. The detailed metabolic studies of these silanol compounds have been performed and provide important information about the differences in metabolism of silicon-containing molecules, which will be described further in section 8.

5.3. Silanediol Isosteres as Transition State Analogues. Using an elegant design that exploits the different bonding preference of silicon, Sieburth has pioneered the use of silanediols as protease inhibitors, such as angiotensin-converting enzyme (ACE) inhibitor **5**, HIV protease inhibitor **70**, thermolysin metalloprotease inhibitor **71**, and serine protease inhibitor **72** (Figure 9).[66,67] The bonding preferences for silicon favor the geminal diol (i.e., silanediol) over the silanone (i.e., Si=O), which is proposed to mimic the hydrated carbonyl as a transition state analogue. As a validation of this design, Sieburth reported the first crystal structure of an organosilicon inhibitor (e.g., **71**, K_i = 41 nM) bound to the active site of a receptor (i.e., thermolysin) where the silicon interacts with the binding site.[68] The X-ray crystal structure analysis confirms the interaction of silanediol **71** with the zinc active site, mimicking the presumed tetrahedral transition state. Compared to the related phosphoric acid inhibitors that must be delivered as the ester prodrug, the silanediol is active in the neutral form and does not require protection or activation.

The design and validation of silanediols as protease inhibitors has led to an increased understanding of the limitations and challenges for the synthesis of complex organosilicon structures. Addressing these synthetic challenges has prompted the development of several generations of synthetic methodology to access silanediol peptidomimetics, with a particular focus on developing chiral, enantioenriched compounds (Scheme 9).[5,17,32−37,69] Sieburth and co-workers first developed a synthetic strategy to access silanediols utilizing the addition of a chiral organolithium species to functionalized silicon electrophile **73** as a key step (Scheme 9, strategy A). The resulting chiral diphenylsilane **74** can be carried through multiple steps, and then the silanediol can be revealed by an acid-mediated protodesilylation.[66] This procedure was used to demonstrate the first synthesis of ACE inhibitor **5** in a total of 14 steps. Although this first generation route provided initial access to material for biological evaluation, this methodology suffered from a high number of synthetic steps, cost, and scalability and relied on the separation of diastereomers. Sieburth subsequently reported a more concise route employing a dihydrosilole and asymmetric hydroboration to access

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fluorosilane electrophiles, which are also useful as pronucleophiles.[33]

Several routes have been reported that utilize the diastereoselective addition of silicon nucleophiles to chiral sulfinimines such as **75** as a key step (Scheme 9, strategy B) in order to streamline the procedure and improve access to enantioenriched material.[32−35,70] The key diastereoselective methodology for the addition of silyllithium reagents to sulfininimes (**75**) was first developed by Scheidt and co-workers.[71] Skrydstrup has utilized this strategy to access a variety of diaryl precursors to silanediol peptidomimetics, such as silicon analogues of serine protease HNE inhibitor **77** and fibrillating hexapeptide NFGAIL silanediol precursor **83**.[35,72] Skrydstrup and co-workers have also utilized this silyl-lithiation route to access chiral diarylsilylamino acid analogues **84**−**88** (Figure 10).[34,36]

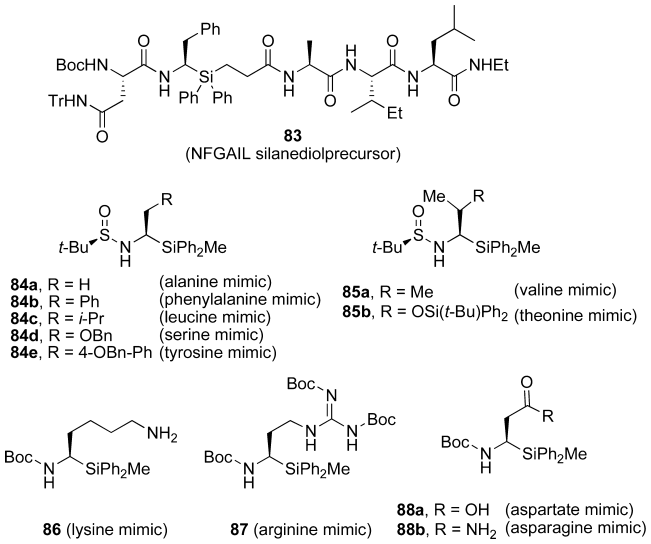


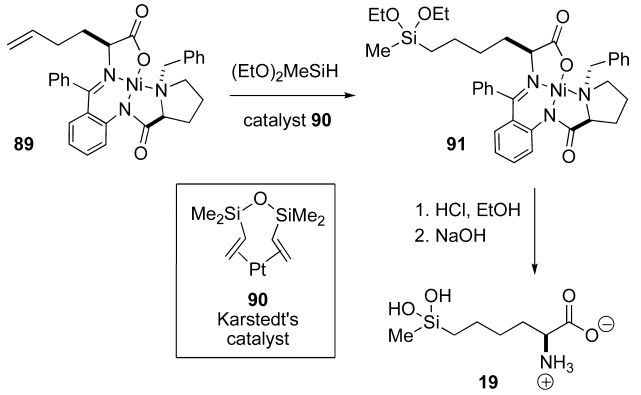
Figure 10. Silicon-containing amino acids and peptidomimetics.

An enantioselective synthetic strategy was developed by Sieburth and co-workers utilizing a Rh(I)-catalyzed hydrosilylation to further streamline the synthesis and access enantiopure material (Scheme 9, strategy C).[37] This strategy also employs the selective addition of a silyllithium reagent to a sulfinimine. The route was successfully demonstrated for the synthesis of an intermediate to ACE inhibitor **5** in only four steps while controlling formation of a single stereoisomer. Recently, this enantioselective hydrosilylation strategy has also been utilized for the synthesis of serine protease inhibitor **72** in 11 steps.[67]

Most recently, Skrydstrup has reported the utility of a one-pot sequential hydrosilylation strategy for the rapid assembly of silane-based peptidomimetic analogues (Scheme 9, strategy D).[73] The synthetic strategy takes advantage of a highly regioselective Rh(I)-catalyzed intermolecular hydrosilylation of enamides **81** with diphenylsilane, which is demonstrated using a stepwise and one-pot sequential fashion. Notably, this strategy can be applied to highly functionalized enamides (such as **81**), thereby allowing for the rapid assembly of complex diphenylsilanes such as **82** as silanediol peptidomimetic precursors. Although the hydrosilylation currently affords a 1:1 mixture of diastereomers, the use of a chiral catalyst can be envisioned to afford an asymmetric version of the hydrosilylation, which the authors indicate is a current goal.

Sieburth has recently developed a synthetic route to prepare enantiopure δ-silanediol amino acid **19** to study the properties and bioactivity as a potential inhibitor of the enzyme arginase. Because of the ability of silanediols to mimic hydrated carbonyls as effective protease inhibitors, it was proposed that the silanediol could mimic the structure of a hydrated guanidine group. The synthesis of silanediol **19** was accomplished upon Pt(0)-catalyzed hydrosilylation of nickel complex **89** with diethoxy(methyl)silane, followed by hydrolysis of the chiral auxiliary and silyl ether (Scheme 10).[74] The authors use ^{1}H

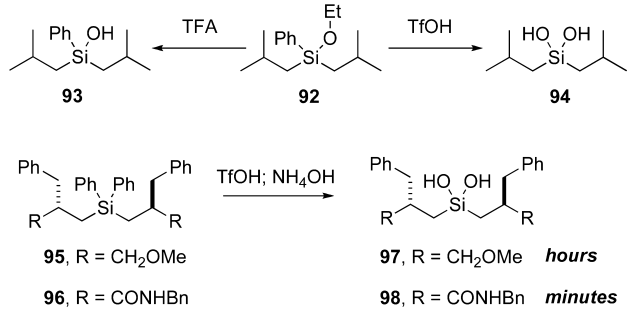
Scheme 10. Synthetic Strategy To Access Silanediol Arginase Inhibitor 19



NMR spectroscopy to monitor the tendency of the silanediol to condense in aqueous solutions at different pH levels. Both acid and base conditions catalyze the oligomerization; however, the oligomers could be readily depolymerized back to the monomer in basic media (e.g., at pH 11). The authors hypothesize that the reversibility of the condensation process is due to the water solubility of the oligomeric byproducts, allowing for proper equilibrium to occur. Upon biological evaluation of silanediol **19**, no inhibition of arginase was observed, indicating that the neutral silanediol is not recognized by the enzyme as an effective mimic of the hydrated guanidine group.

As shown in the examples above, the most versatile and frequently used silanediol precursors often involve the use of diphenylsilanes, which can be transformed to the silanediol upon protodesilylation under specific acidic conditions. The Si−Ph bond is stable to typical TFA conditions used for the removal of a *tert*-butyl ester protecting group and yet labile under standard TfOH conditions for peptide deprotection (Scheme 11). Several reports do not carry out the final

Scheme 11. Acidic Cleavage of the Silyl−Phenyl Bond To Access Silanediols



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protedesilylation step or isolate the target silanediol because of the harsh acidic conditions and the propensity for condensation to occur during this final transformation. Sieburth has noted that the reactivity/stability of the Si−Ph bond is highly dependent on the neighboring functionality of the substrate. For example, the cleavage of the Si−Ph bond in amide **96** occurs rapidly (i.e., minutes) while cleavage of the Si−Ph bond for the non-amide substrate **95** occurs more slowly (i.e., hours). This rate difference is attributed to the intramolecular assistance of the amide during cleavage. Both Carroll and Skrydstrup have investigated the use of electron-rich aryl groups that can be more readily transformed to reveal the desired silanediol motif or allow selective access to the corresponding silanol product.[32,75]

5.4. Hydrogen Bonding in Other Bioactive Silanols and Silanetriols. Silanetriols have also recently been investigated for bioactivity because of their unique physical and electronic properties and high number of hydrogen bonding sites that can mimic hydrated transition states occurring during the hydrolytic cleavage of carboxylic acid derivatives. Three stable silanetriols (**99**−**101**) have been synthesized, each containing bulky substituents on silicon for steric protection to inhibit condensation (Figure 11).[76] All

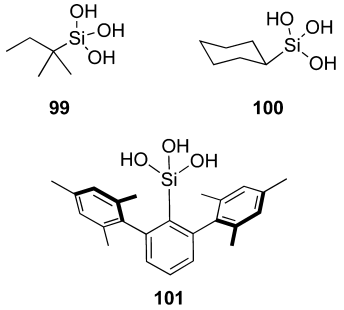

Figure 11. Silanols and silanetriols exhibiting antimicrobial activity.

three silanetriols provided reversible inhibition of the AChE activity at 100 μM, ranging from 10% to 45% inhibition relative to a known inhibitor, galanthamine hydrobromide. Cyclohexylsilanetriol **100** afforded the highest inhibition rate of the three analogues, with an IC_{50} of 121 μM. Although only moderate inhibition was observed, these results provide initial support for further development of silanetriols as bioactive molecules.

Several examples of trialkylsilanols (structures not shown) have been reported to improve antimicrobial activity relative to their carbon analogues.[77,78] This enhanced activity is attributed to the higher acidity, and consequently higher hydrogen-bonding capabilities, of silanols compared to alcohols and a greater balance of hydrophobic/hydrophilic regions. The minimal lethal concentrations (MLC) for silanols were found to be lower than carbon analogues against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. For example, the MLC for *E. coli* was found to range from 0.10% to 2.36% (g/g) for silanols and from 0.7% to 13.54% (g/g) for analogous alcohols. A linear free energy relationship between antimicrobial activity, the partition coefficient, and hydrogen bond acidity was demonstrated, which can be modified by changing structural features.[77]

5.5. Silanediol Hydrogen-Bonding Properties. Further insights into the synthesis and hydrogen-bonding properties of silanols and silanediols have been provided based on recent investigations into the acidity and activity of organosilicon molecules such as **102**−**105** as hydrogen-bonding organocatalysts (Figure 12).[79−83] In addition to the implications for

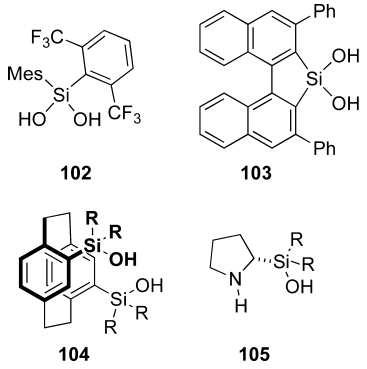

Figure 12. Examples of hydrogen-bonding silanol and silanediol organocatalysts.

medicinal applications, understanding the acidity and binding interactions of organic silanols has important implications for catalysis, molecular recognition, and supramolecular assembly. Franz and co-workers reported the synthesis and first example of silanediols (e.g., **102**) as hydrogen-bonding organocatalysts.[79,80] Various NMR spectroscopy binding studies and X-ray crystallography, mass spectrometry, and computational studies provide insight into the hydrogen-bonding properties of silanols and silanediols, including the acidity, self-association, and hydrogen-bonding activation of carbonyls, such as amides and aldehydes. Mattson[82] and Bolm[83] have subsequently reported the synthesis and evaluation of new silanediols (**103**) and bis-silanols (**104**), respectively, as hydrogen-bonding catalysts. In order to expand the functionality, Franz and Min recently reported the design and enantioselective synthesis of new bifunctional pyrrolidinylsilanol catalysts (e.g., **105**), demonstrating the importance of using a silyl fluoride electrophile to access silanols with different steric environments while maintaining high enantioselectivity for the formation of a C−Si bond.[84]

6. TRIALKYLSILYL DERIVATIVES OF DRUGS AND BIOLOGICALLY-ACTIVE MOLECULES

Many examples of bioactive organosilicon small molecules utilize the strategic incorporation of silicon into a known scaffold or result from investigating a series of silyl derivatives to determine how the incorporation of a silyl group will influence the known biological activity of a molecule. Silatecans, analogues of the topoisomerase inhibitor camptothecin containing a lipophilic silyl group, such as **107** (Karenitecin, BNP-1350, BioNumerik Pharmaceuticals) and **108** (DB-67, Tigen Pharmaceuticals), are familiar examples of bioactive organosilicon compounds because of their emerging success in clinical trials (Figure 13).[85,86] Lipophilic analogues of camptothecin have been designed to reduce the toxicity of camptothecins, which is attributed to the instability of the γ-lactone. Silatecans have been shown to increase cell penetration, enhance blood stability, and improve pharmacokinetics.[86] For example, Karenitecin (**107**) is currently undergoing phase III clinical trials in advanced ovarian cancer patients.[85,87] The investigation of lipophilic derivatives of anticancer compounds is a current strategy that has been examined for several drugs, which may have enhanced potential

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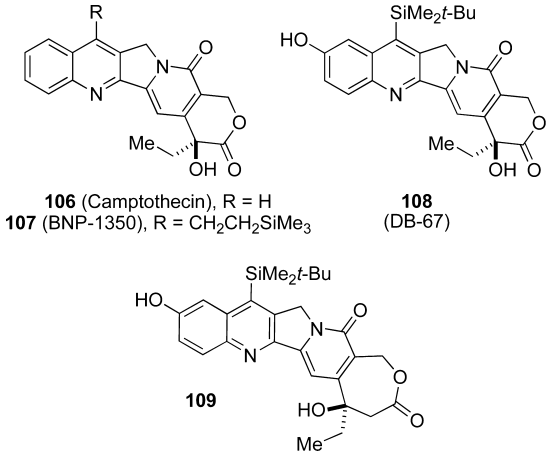
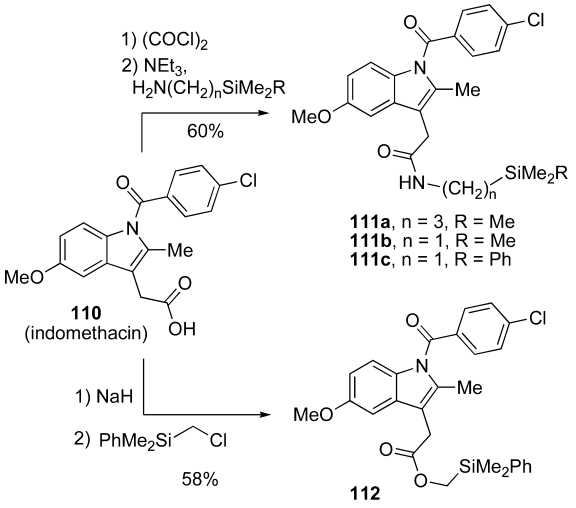


Figure 13. Examples of silicon derivatives of camptothecins.

based on recent evidence that lipophilic derivatives may preferentially localize/accumulate in tumors.[88] To facilitate access to sila-camptothecin analogues, Curran developed an efficient synthetic route to silatecans and homosilatecans (such as **109**) based on a tin- or palladium-promoted cascade reaction of isonitriles with iodo-*N*-propargylpyridones.[89,90]

Several sila-amide derivatives of indomethacin (**110**), a multitargeted drug that belongs to the family of nonsteroidal anti-inflammatory drugs (NSAIDs), have been prepared in an effort to increase the safety and activity of these compounds for the treatment of cancer.[31] By increasing the COX-2/COX-1 selectivity, the authors expected to diminish the side effects currently prohibiting the use of indomethacin as a therapeutic agent. Sila-amide derivatives such as **111a–c** were readily generated by amidation of the indomethacin carboxylate using a series of amino-functionalized silanes (Scheme 12). As seen in

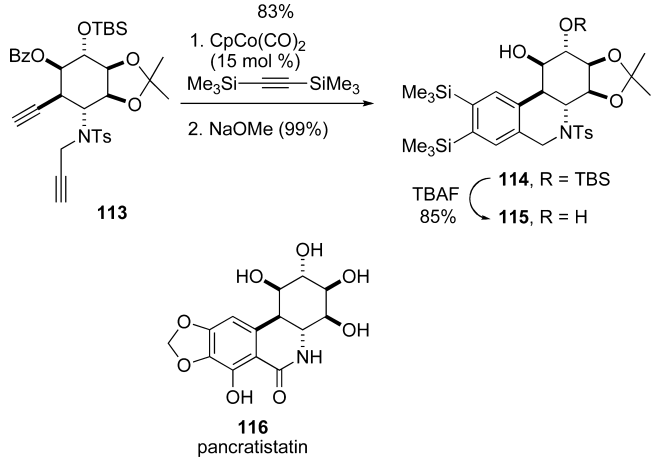
Scheme 12. Synthesis of Silicon Analogues of Indomethacin



the case of silyl-amide derivatives of *N*-acetyl L-cysteine, the use of amino-functionalized silanes provides a simple and general method to prepare silyl derivatives that is applicable whenever a series of amides is prepared for biological investigation. Sila-ester derivatives, such as **112**, can also be accessed using standard chemistry. Screening the sila-amides in COX-1 and COX-2 enzyme assays demonstrated selective inhibition of COX-2 relative to COX-1 (~1000-fold selectivity) while also demonstrating more potent anticancer activity (IC_{50} = 4.8–19.2 mM) relative to indomethacin (IC_{50} > 100 mM) in human pancreatic cancer and multiple myeloma cells. Further experiments have demonstrated that sila-indomethacins are active against allografted human pancreatic cancers in mice.[91] Although this COX-2 selectivity matches trends observed for other indomethacin amides, the authors postulate that the sila-amide derivatives may also have additional pharmacokinetic advantages.[9,31]

Hudlicky and co-workers have prepared silyl derivatives of pancratistatin (**116**) based on SAR studies suggesting that the aromatic ring had the greatest opportunity for productive structural modification. A cobalt-catalyzed cyclotrimerization strategy was employed using bis-trimethylsilylacetylene to prepare silylated analogues (e.g., **115**) of the phenanthridone core of pancratistatin (Scheme 13).[92] As described above for

Scheme 13. Cyclotrimerization Strategy for the Synthesis of Silicon Derivatives



the synthesis of amino acid derivative **13**, the cyclotrimerization of silylalkynes represents a general strategy to access silyl-substituted aryl ring derivatives. Notably, the TBS silyl ether of **114** can be deprotected with TBAF without affecting the arylsilyl groups. A series of silyl derivatives were synthesized and profiled for activity against seven cancer cell lines, demonstrating that several unexpected structural variations were tolerated and the silyl analogues maintain most of the activity (GI_{50} = 1.5 mg/mL) of the full natural product (GI_{50} = 0.032 mg/mL). The direct activity comparison of silicon derivative **115** with pancratistatin could not be performed because the fully oxygenated core was not amenable to the cyclotrimerization strategy because of steric issues.

Although there is no known intrinsic "element-specific" toxicity associated with silicon, the addition of a silyl group or incorporation of silicon has been shown to enhance toxicity for relevant cytotoxic structures (vide supra). Padron and co-workers have studied the cytotoxicity of TMS oxacycles such as **119** containing a chlorovinyl group as a pharmacophore, in analogy to the antitumor activity observed for marine natural products containing a chlorovinyl group. The authors had previously noted that lipophilicity was an important feature for activity in this class of molecules,[93] leading them to investigate the incorporation of a silyl group at the C(3) position. The TMS oxacycles can be readily prepared in a single step from linear precursor **117** using an iron(III)-promoted silylalkyne

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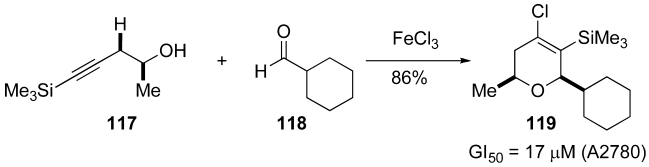
Prins cyclization (Scheme 14).[94] The presence of the silyl group generally enhanced the cytotoxic activity of these

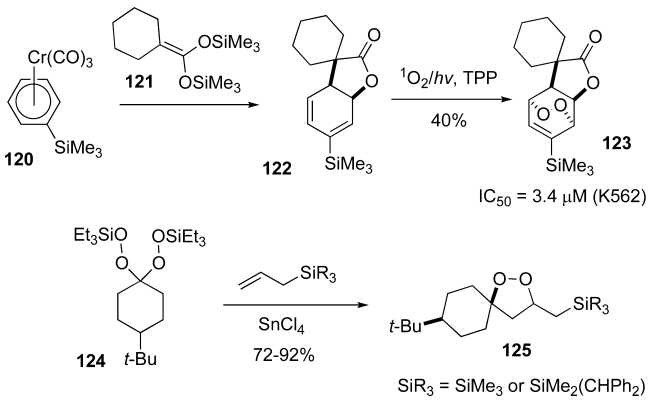
Scheme 14. Cytotoxicity of Chlorovinyl-TMS Oxacycles Containing Silyl Groups



chlorovinyl oxacycles against human solid tumor cells (GI_{50} = 17 μM); however, the effect was not specific to silicon. Other alkyl substitution effects were also found to enhance cytotoxic activity.

On the basis of the activity and therapeutic potential of peroxide-containing natural products, silyl-substituted endoperoxides have also been prepared and examined for cytotoxicity.[95] Endoperoxide lactones such as the artemisians are of specific interest for the treatment of various antiviral and parasite infections (e.g., the *P. falciparum* malaria parasite). Peroxylactones such as **123** can be prepared in two steps using a double nucleophilic addition of a bis(TMS) ketene acetal (**121**) followed by a [4 + 2] cycloaddition with singlet oxygen (Scheme 15). The cytotoxic activity for several synthetic

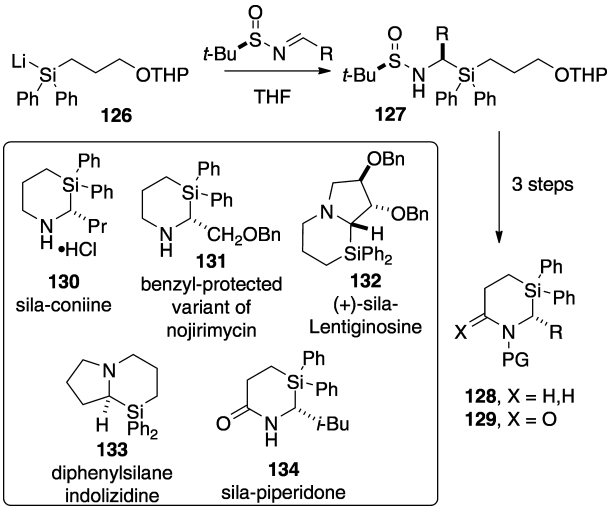
Scheme 15. Synthesis of Silicon-Containing Endoperoxides



peroxylactones was profiled in a panel of six cancer cell lines using an SRB assay. Three of the peroxylactones examined, two containing a TMS group and one containing an isopropyl substituent, demonstrated notable activity with IC_{50} values better or comparable (IC_{50} = 3.4−12.8 μM) to those of known cytotoxic compounds, such as cisplatin (IC_{50} = 9.5−25.8 μM). Using an alternative cyclization strategy, Woerpel and Ramirez have demonstrated that endoperoxides such as **125** can be prepared using allylsilanes to trap peroxycarbenium ions derived from silyl peroxyketals **124**.[96]

Skrydstrup has reported a modular synthetic route to access various substituted azasilaheterocycles that provide silicon derivatives of alkaloid natural products (Scheme 16). The azasilaheterocycles synthesized by this route include a silicon analogue of (+)-coniine and sila analogues for protected variants of nojirimycin and (+)-lentiginosine, a glycosidase inhibitor.[70] The modular synthetic route utilizes the previously developed diastereoselective addition of a lithiated silane (**126**) to a chiral sulfinimine to afford α-silylsulfinamides **127**, which

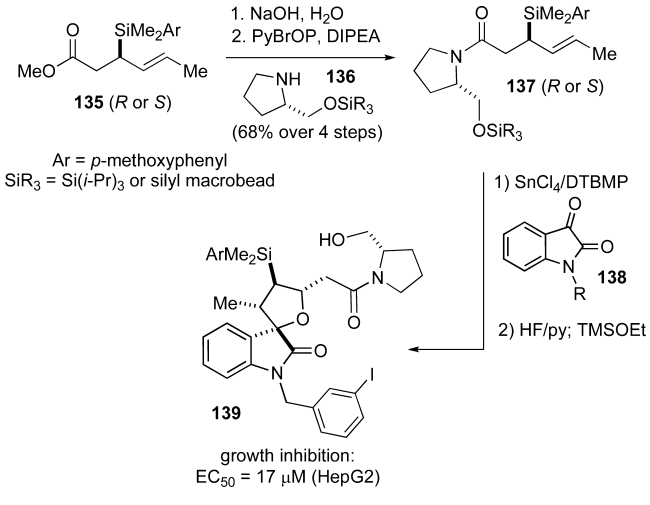
Scheme 16. Skrydstrup's Synthesis of Azasilaheterocycles



can undergo standard synthetic transformations to access various silicon-containing heterocycles such as **128** and **129**. Although the article does not describe any biological testing, previous examples of azasila heterocycles have shown interesting biological activity, and it is expected that these azasilaheterocycles represent examples of new chemical diversity that can be developed for medicinal compounds.

Franz and Schreiber described the first example of a discovery approach to evaluate the biological activity of chiral organosilicon spirocycles such as **139** using high-throughput screening and cellular profiling.[97] The spirocyclic oxindole scaffold was selected because it can be efficiently accessed using an allylsilane−isatin annulation pathway and also provides an attractive target for pharmaceutical lead compounds. Amido- and triazole-functionalized crotylsilanes (e.g., **137**) were utilized to prepare both (*R*)- and (*S*)-enantiomers for the silicon-containing spirooxindoles and to investigate the impact of stereochemical effects (Scheme 17). The silicon−aryl bond is stable under various Lewis acid conditions but can also be cleaved to facilitate formation of a silanol product, or diverse products resulting from metal-catalyzed cross-coupling reactions. From this initial collection, 90 representative sila-spirocycles were profiled in a panel of 41 assays relevant to

Scheme 17. Synthesis of Chiral Organosilicon Spirocycles



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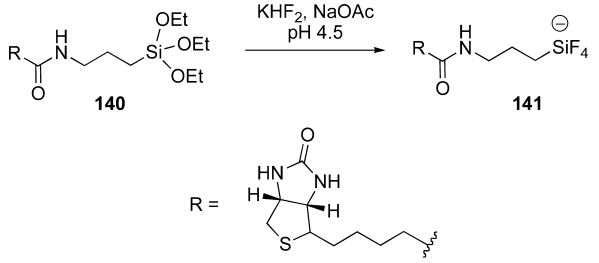
diverse areas of disease biology, and high feature signatures of biological activity were demonstrated based on the functional group and stereochemical diversity of these compounds. As with several cases described in this Perspective, the use of silicon-based reagents provides efficient synthetic routes to access complex heterocycles that may provide new chemical diversity for drug discovery.

7. ORGANOSILICON-BASED FLUORIDE ACCEPTORS FOR IMAGING

Organosilicon compounds are promising for the development of new biological imaging agents because of the efficient fluoride-accepting properties of organosilanes that can be exploited to overcome the challenge of using short-lived ^{18}F isotopes (Scheme 18).[98] Two initial reports highlighted

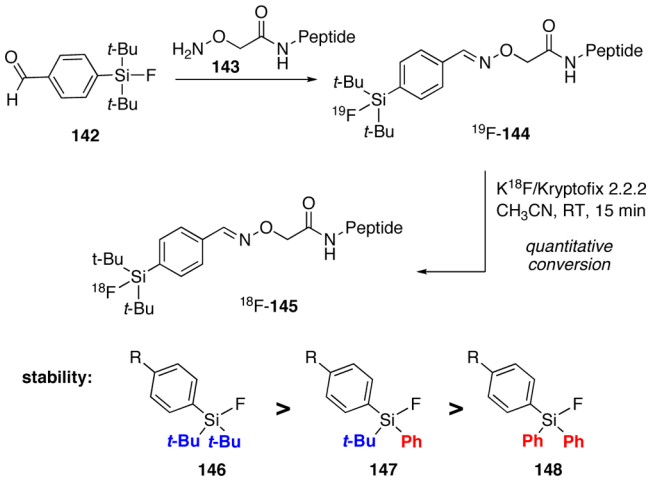
Scheme 18. Synthesis of Tetrafluorosilicate SIFA for ^{18}F Labeling



strategies for the incorporation of organosilicon-based fluoride acceptors (SiFAs).[99,100] Perrin and co-workers first reported the preparation of an (aminopropyl)trimethoxysilane derivative of biotin **140** as a selective SiFA upon the rapid and quantitative formation of the biotin tetrafluorosilicate **141**.[99] Although only currently demonstrated as a proof-of-concept, the authors described that such a biotin reagent will be useful in a variety of applications with avidin-fusion proteins. The kinetic stability of the tetrafluorosilicate imaging agent **141** was measured by incubating the reagent in blood serum and showing that no time-dependent loss of ^{18}F occurs over 60 min. Although the corresponding tetrafluoroboronate derivative was shown to have increased stability relative to the silicate, the alkyltetrafluorosilicate was sufficiently stable with a decomposition rate similar to the rate of ^{18}F decay.

Subsequently, Schirrmacher et al. reported a related strategy for the synthesis of fluorosilyl-containing peptides (**145**) utilizing a chemoselective ligation between an aminoxy-functionalized peptide and organosilicon-functionalized benzaldehyde **142** (Scheme 19).[100] The ^{18}F derivative can be prepared from compound ^{19}F-**145** by a rapid fluoro exchange with a $[^{18}F]F/Kryptofix\ 2.2.2/K^+$ complex. Several silyl derivatives were examined, and a *p*-(di-*tert*-butylfluorosilyl)-benzaldehyde conjugate was chosen based on in vitro and in vivo stability of the F−Si bond toward hydrolysis. While $[^{18}F]$triphenylfluorosilane **148** was unstable in human serum (decomposition/hydrolysis in <10 min), both the mono- and di-*tert*-butylsilane substrates (**146** and **147**) exhibited high stability with no decomposition after 60 min. The in vivo stability of the ^{18}F−Si bond was then measured based on the radioactivity uptake (accumulation of $^{18}F^-$) into bone, and a clear steric trend was observed, indicating superior stability of the di-*tert*-butylsilane substrate (**146**). More recent investigations have now shown that the diisopropyl silylfluoride SiFA

Scheme 19. Synthesis and Stability of Peptide SiFAs for ^{18}F Labeling



cannot be used in nuclear medicine because of its poor hydrolytic stability.[101] Misonidazole analogues have also been prepared with naphthyl substituents on silicon, which have been demonstrated to have enough stability to withstand physiological conditions.[102] Computational models have been developed to examine the relative stability of concentrated SiFAs in acetonitrile/H_2O;[103] however, this does not accurately represent stability in biological conditions.

Incorporating ^{18}F-labeled silicon into bioactive molecules continues to represent a synthetic challenge for ongoing investigation. The two general methods are (1) incorporating ^{19}F into the molecule at an early stage and then utilizing a $^{18}F/^{19}F$ switch strategy in the later stages and (2) using a direct fluorination strategy with a suitable silyl precursor in the late stages of a synthetic route, provided a leaving group on silicon is present (Figure 14). SiFA azide **149** has been synthesized,

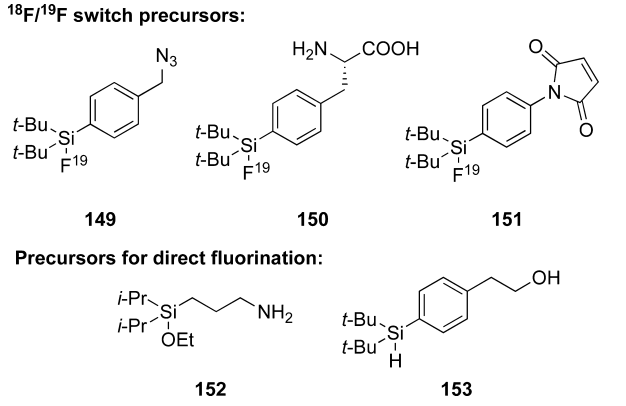


Figure 14. Examples of ^{18}F prosthetic groups and ^{18}F precursors.

labeled, and shown to be a viable synthetic route to access more diverse arrays of bioactive compounds through well-developed "click" chemistry.[101,104] Di-*tert*-butylfluorosilyl-substituted phenylalanine **150** has been synthesized in both racemic and enantiopure forms and shown to withstand harsh conditions associated with solid-phase peptide synthesis.[105] The ^{18}F-malemido derivative **151** has been employed in the synthesis of labeled rat serum albumin.[106] In general, it appears that the efficiency of the $^{18}F/^{19}F$ exchange process depends on the functional groups present, where the inclusion of amine and

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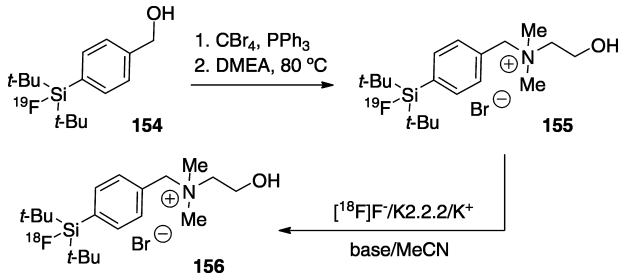
isothiocyanate functionalities has been identified to promote reactivity. Rather than utilizing a $^{18}F/^{19}F$ switch in the synthesis, direct fluorination has also demonstrated promise in labeling complex bioactive molecules using precursors such as silyl ether **152** and silane **153**.[107,108]

Increasing steric hindrance and size of silyl groups often has the undesired effect of increasing lipophilicity to an extent that lowers the bioavailability and utility of SIFA molecules. To reduce overall lipophilicity, Schirrmacher investigated the incorporation of a hydrophilic cationic tertiary ammonium salt linker into SiFA **156** (Scheme 20).[109] This linker strategy

Scheme 20. Hydrophilic SiFA-Based Prosthetic Groups for ^{18}F Labeling



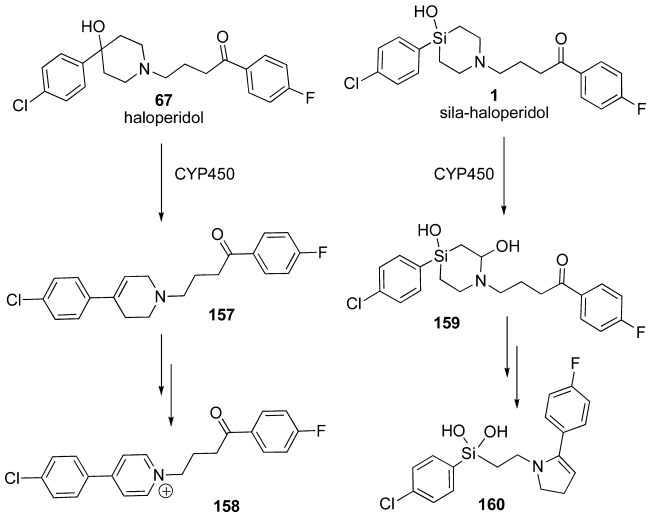
was found to reduce lipophilicity 8-fold, extending the limits of potential applications. The SiFA cations demonstrated high stability in human blood serum upon incubation at 37 °C for 2 h, the typical length of in vivo PET studies. The authors indicate that future endeavors are aimed at incorporating this hydrophilic linker into a more diverse pool of derivatives. Schirrmacher has also demonstrated that hydrophilic moieties such as carbohydrates and polyethylene glycol spacers can also be introduced into SiFA molecules to greatly reduce lipophilicity (log D = 0.96−1.59).[110]

8. METABOLISM OF ORGANOSILICON MOLECULES

The initial interest in the metabolism of organosilicon molecules stems from the reports on the stability of silicones in the environment.[111] The metabolism of organosilanes has been studied and in many cases shown to follow standard metabolic and clearance pathways expected for related carbon analogues.[112,113] Similar metabolic rates and standard oxidation products have been identified where oxidation typically occurs at carbons adjacent to silicon, including some eventual cleavage of the Si−C bonds. In the case of siloxanes, oxidation products including silanols are observed. It is particularly notable that there are also instances where distinct differences in metabolism are observed based on the stability and bonding preferences for some silyl groups.

The metabolism of silahaloperidol (**1**) has been studied and represents a particularly notable case where the incorporation of silicon significantly alters the metabolic fate compared to haloperidol, thus avoiding the formation of a neurotoxic pyridinium metabolite (**158**).[1,38,64,65,114] These ESI-MS studies provide some of the most detailed studies for the metabolism of organosilicon compounds. Because haloperidol metabolites produce severe side effects, controlling the metabolism can have significant advantages. Silanol analogues avoid common elimination pathways and undergo an alternative metabolic pathway (Scheme 21). The strength of the silicon−oxygen bond and the thermodynamic instability and reactivity of the Si═C bond prevent formation of a silylpyridinium metabolite

Scheme 21. Comparison of Metabolic Pathways for Haloperidol and Sila-haloperidol



(the silicon analogue of **158**).[11] Sila-haloperidol instead undergoes oxidation at the carbon α to the nitrogen to afford **159**, followed by ring-opening to eventually form silanediol metabolite **160**. Another significant difference observed for the metabolism of sila-halperidol was a lack of glucuronide formation. The authors propose two explanations for the absence of glucuronidation: (1) the SiOC glucuronide conjugate forms but is hydrolytically sensitive and undergoes hydrolysis to favor the silanol; (2) the silanol is a poor substrate for the UDP-glucuronsyltransferase. Because glucuronidation can lead to high clearance of a drug in phase II metabolism, the authors propose that the incorporation of a silanol may be a useful strategy to avoid this problem while balancing hydrophobicity and hydrophilicity. Further evaluation is needed to explain the absence of glucuronidation; however, the effect on glucuronidation contributes an additional example where different metabolic pathways for organosilicon molecules may provide a distinct advantage to minimize the formation of undesired metabolic byproducts.

9. SUMMARY

This Perspective highlighted recent approaches and creative strategies utilizing the properties and applications of silicon for medicinal chemistry. Many examples, ranging from amino acid derivatives to inhibitor design, demonstrate that the incorporation of silyl groups provides a general strategy to increase size and lipophilicity for drug design. The most common strategies involve structural modifications of an aryl core, the incorporation of a silyl group using standard amidation methods, and silicon isosteres such as silanols. While standard chemical reactions are generally employed for the synthesis of organosilicon molecules, there are also unique synthetic strategies available for organosilicon molecules that have the advantage of being easier to synthesize compared to some carbon analogues and therefore can allow access to new scaffolds. Applications also extend beyond the realm of small molecule therapeutics where organosilicon molecules have applications for PET imaging, new controlled drug release strategies, and structural probes for the direct detection of drug−protein binding interactions. Although still a growing area in medicinal chemistry, the incorporation of silicon will

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continue to provide a new source of chemical diversity and the inspiration to solve a range of problems related to drug design.

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Notes

The authors declare no competing financial interest.

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Annaliese K. Franz received her Ph.D. in Organic Chemistry from University of California—Irvine with Keith A. Woerpel and then conducted postdoctoral studies at Harvard University, Cambridge, MA, with Stuart L. Schreiber. She is currently an Assistant Professor at University of California—Davis, where her group develops new enantioselective methods, catalysts, and biological probes based on the unique properties of silicon-based reagents and organosilicon molecules.

Sean O. Wilson attended The George Washington University, Washington, DC, where he graduated in 2009 with a B.S. in Chemistry and B.A. in Psychology. He went on to graduate school at the University of California—Davis where he is currently pursuing a Ph.D. in Chemistry with Prof. Annaliese Franz. His research focuses on the synthesis of chiral organic silanols and silanediols, the study of their hydrogen-bonding properties, and application as asymmetric organocatalysts.

ABBREVIATIONS USED

ACE, angiotensin-converting enzyme inhibitors; BMS, borane dimethyl sulfide; CLSM, confocal laser scanning microscopy; *E. coli*, *Escherichia coli*; FPSQ, fluorinated polysilsesquioxane; FTMS, (trifluoropropyl)trimethoxysilane; GI_{50}, inhibition of cell growth (the concentration needed to reduce the growth of treated cells to half that of untreated cells); MLC, minimal lethal concentration; Mont, montmorillonite; NACA, *N*-acetylcysteineamide; NFGAIL, residues 22−27 of the human islet amyloid polypeptide; *P. falciparum*, *Plasmodium falciparum*; PPII, polyproline II; RAR, retinoic acid receptor; RXR, retinoid X receptor; SiFA, organosilicon-based fluoride acceptor; SRB, sulforhodamine B; TEM, transmission electron microscopy; TMOP, 2,4,6-trimethoxyphenyl; TrpV1, transient receptor potential cation channel subfamily V member 1; VR1, vanilloid receptor 1

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