Chemistry challenges in lead optimization: silicon isosteres in drug discovery

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During the lead optimization phase of drug discovery projects, the factors contributing to subsequent failure might include poor portfolio decision-making and a sub-optimal intellectual property (IP) position. The pharmaceutical industry has an ongoing need for new, safe medicines with a genuine biomedical benefit, a clean IP position and commercial viability. Inherent drug-like properties and chemical tractability are also essential for the smooth development of such agents. The introduction of bioisosteres, to improve the properties of a molecule and obtain new classes of compounds without prior art in the patent literature, is a key strategy used by medicinal chemists during the lead optimization process. Sila-substitution (C/Si exchange) of existing drugs is an approach to search for new drug-like candidates that have beneficial biological properties and a clear IP position. Some of the fundamental differences between carbon and silicon can lead to marked alterations in the physicochemical and biological properties of the silicon-containing analogues and the resulting benefits can be exploited in the drug design process.

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▼ The challenge for medicinal chemists

The pharmaceutical industry is once again facing major challenges. Following the introduction of high-throughput synthesis and screening during the early 1990s, the expected increase in the numbers of robust development candidates and approved drugs from these technologies has not yet been realized. Eighteen new chemical entities and seven new biological entities were introduced onto the market for the first time in 2001. This was the least productive year of the past decade, in which the number of new therapeutic entities ranged from 27 in 1998 to 44 in 1994 [1]. A high attrition rate in development is apparent, the major reasons being poor pharmacokinetics, toxicity and lack of efficacy [2]. During the lead optimization phase of projects additional factors contributing to subsequent failure may include poor portfolio decision-making and a sub-optimal IP. The pharmaceutical industry has an ongoing need, therefore, for new, safe medicines with a genuine biomedical benefit, a clean IP position and commercial viability. Inherent drug-like properties and chemical tractability are also essential. Lead optimization represents the key phase during the discovery process that identifies drug development candidates from biologically active hits. During this phase, scientists need to assess a multitude of chemical and biological parameters on many compounds to choose the best candidate for development. The medicinal chemist, and associated colleagues with expertise in pharmacology and drug metabolism, is involved in a cycle of design, synthesis and assessment of biological activity. During this process, hard and critical decision-making is required to maximize the potential of success.

Novel IP

Most pharmaceutical and biotech companies are using similar chemical libraries for hit identification. These libraries originate either from commercial sources or from 'in-house' synthesis, but in both cases they are likely to utilize similar chemistry that is amenable to high-throughput applications. To achieve 'drug-likeness' at this early stage of the drug discovery process the design strategy for building drug-like chemical libraries [3] is crucial to obtain high quality starting points and is a key determinant to success later on during the lead optimization phase. However, with the current limitations in

1359-6446/03/$ – see front matter PII: S1359-6446(03)02726-0

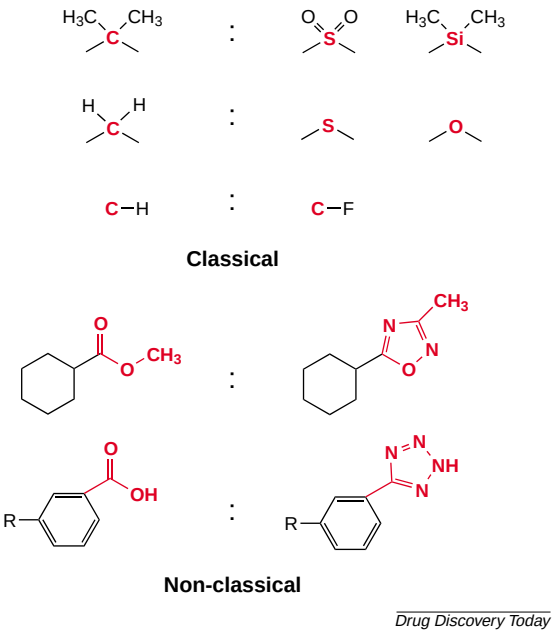

Figure 1. Classical and non-classical bioisosteres. Bioisosteres contain similar molecular shapes and/or similar distributions of electrons.

available starting points, the opportunities for finding novel IP space in combination with drug-like features is becoming increasingly difficult for well-validated drug discovery targets. The challenges for the medicinal chemist during lead optimization to obtain novel and patentable compounds are, therefore, ever increasing. A major hurdle facing researchers is the lack of available experimental data to evaluate the varied questions on diversity. It is of prime importance for medicinal chemists to remember that the principal 'value adding' event that occurs in pharmaceutical R&D is the creation and selection of a novel chemical entity (NCE) that has the right properties to be a successful drug.

It is apparent that the large and successful pharmaceutical companies are those with the greatest number of patent applications. In 2001, GlaxoSmithKline (http://www.gsk.com) was at the top of the 'number of patents filed' rankings with a staggering 1911 qualifying patent documents between 1995 and 2000. Merck and Company (http://www.merck.com) were ranked second place with 1364 [4]. From data collated during 2001, nearly half of the inventions in patent applications originated in the US, about 10% from Japan and Germany and 7.3% from the UK. Heterocyclic compounds, acyclic and carbocyclic entities, which make up the majority of small molecule IP matter, accounted for a mere 14% of all applications, whereas 18% related to microorganisms and enzymes.

What makes a molecule a drug?

The answer to this question relates to a complicated relationship between synthetic tractability, novelty, chemical and metabolic stability, toxicity, specificity and, of course, marketability. The use of sophisticated tools to identify genuine drug-like molecules by the interrogation of databases [5] has suggested that the Comprehensive Medicinal Chemistry (CMC) database of over 7,500 compounds [6] is a good source for the identification of drug-like structures, particularly when compared to the Available Chemicals Directory. Data have also been presented detailing the results of an analysis of approved drugs, demonstrating that 32 scaffolds could account for half of the compounds [7]. Furthermore, a relatively small number of functional groups represent the majority of side-chains found in drugs [8]. It is possible that the chemical space available for small drug-like molecules is less diverse than we originally thought. The strategy of capturing information about existing drugs and their properties to design new entities may, in itself, be rather limiting. By using such an approach in combination with chemistry knowledge, however, provides optimism that new drug-like molecules will still be forthcoming for many years.

Bioisosteres

The strategy outlined above is exemplified by the use of a bioisostere to improve the properties of a molecule and obtain new classes of compounds without prior art in the patent literature. An oxo group to replace a methylene in a chain (a classical bioisostere) or a 1,2,4-oxadiazole group to replace a carboxylic ester moiety (a non-classical biosostere) both exemplify this approach (Fig. 1). Ring-to-ring transformations are among the most common methods of bioisosteric changes used by medicinal chemists, for example the replacement of a carbocyclic or heterocyclic ring system by another heterocyclic ring. Several authors have reviewed this approach extensively [9,10]. Chain-to-chain transformations are also a well-recognized strategy for the medicinal chemist to use. The bioisosteric relationship between amides, ureas, cyanoguanidines and carbamates has been fully explored over the past 30 years. Less common is the use of silicon in medicinal chemistry as an isostere for a fully substituted sp3 carbon (Fig. 2) [11–13].

The use of silicon in medicinal chemistry

Sila-substitution (C/Si exchange) of existing drugs is an approach to search for new drug-like candidates that have beneficial biological properties and a clear IP position. In searching for opportunities to exploit the benefits of silicon in medicinal chemistry, William Bains (cofounder of Amedis Pharmaceuticals) identified the groundbreaking

work of Reinhold Tacke (University of Wuerzburg, Germany), as being central to the company's success. Bains realized that Tacke had pioneered the concept of a 'silicon switch' during the 1970s [14], with a particular focus on the area of muscarinic receptor antagonists [15–17]. To capitalize on this a close collaboration was forged between Amedis and Reinhold Tacke's group. Such a 'silicon switch' could be considered as a classical tetravalent bioisostere; however, until now the potential of exploiting the properties of organosilicon agents has not been fully utilized in drug discovery and development. In 2001, less than 1% of patent applications related to compounds containing phosphorus, silicon and other less common elements in the drug discovery field [4].

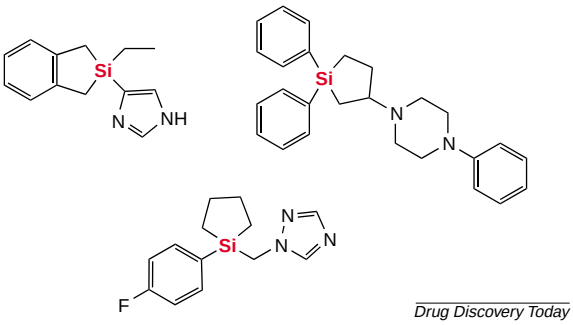

Figure 2. Examples of silicon isosteres of carbon. Drug-like small molecules containing silicon in place of an sp^3 carbon atom are shown.

Properties of silicon in medicinal chemistry

Carbon and silicon both possess four valence electrons (C: $2s^2 2p^2$; Si: $3s^2 3p^2$). Similarities with respect to the chemistry of carbon and silicon may, therefore, be expected, although it is also known that in several aspects the two elements differ substantially from one another. Some of the fundamental differences between carbon and silicon that can lead to marked alterations in the physicochemical and biological properties of the silicon-containing analogues, which can be exploited in the drug design process, are summarized in Table 1.

Molecular size and shape

Silicon-containing bonds are always longer than the corresponding carbon analogues. The average length of a C-C bond is 1.54 Å, whereas a C-Si bond is 1.87 Å [14]. This difference leads to subtle changes in the size and shape of silicon-containing compounds when compared with carbon (Fig. 3). This can lead to changes in the way that the silicon analogue interacts with specific proteins when compared to its carbon counterpart, with consequential effects on its pharmacology and pharmacodynamic properties, which are both important parameters in drug discovery.

Electronegativity

Carbon and silicon also have differences in their electronegativity. Silicon is the more electropositive element, leading to different bond polarizations of analogous C-element and Si-element bonds. An area in which this has potential benefits for the 'silicon switch' approach is in hydrogen bond strength and acidity. The hydrogen bond strength of the silanol is more favourable as a donor than that of the carbinol [18]. In pharmacophores in which the carbinol functions as a hydrogen bond donor, using a silanol moiety can be beneficial in providing improved potency [19].

Lipophilicity

In general terms, silicon-containing analogues are more lipophilic than their carbon analogues. The consequences of altering the lipophilicity of a molecule can be clearly

Table 1. The properties and potential benefits of silicon in medicinal chemistry.

Property	Difference	Potential benefit
Atomic size	Altered bond lengths and bond angles	Altered *in vitro* potency Modified selectivity Altered rate of metabolism
Electronegativity	Increased H-bond strength and acidity of silanols	Improved potency in pharmacophores where H-bonding is important
Lipophilicity	Increased lipophilicity of silicon compound	Improved *in vivo* half-life Enhanced tissue distribution
Novel chemistry	IP opportunity	Novel compounds exploiting established SAR

Abbreviations: IP, intellectual property; SAR, structure–activity relationship.

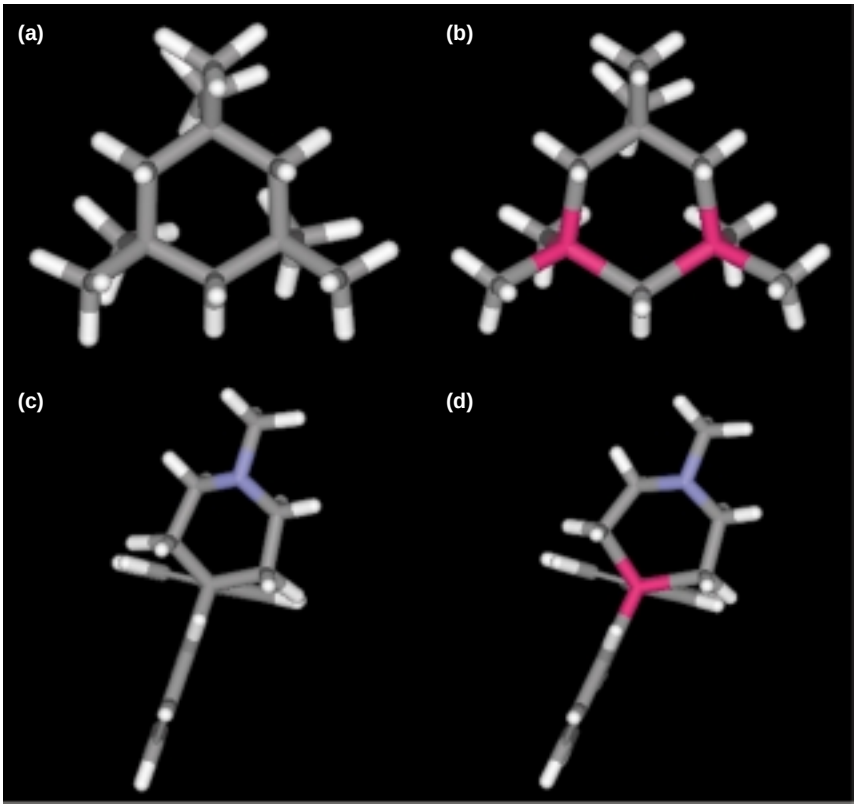

Figure 3. Carbon and silicon switch ring systems based on X-ray crystallography data. The C-Si bond is longer than the C-C bond, leading to a subtle change in molecular shape. The traditional carbon analogues are depicted in (a) and (c) with their respective silicon switch analogues in (b) and (d). Carbon atoms are in grey, nitrogen in blue and silicon in pink.

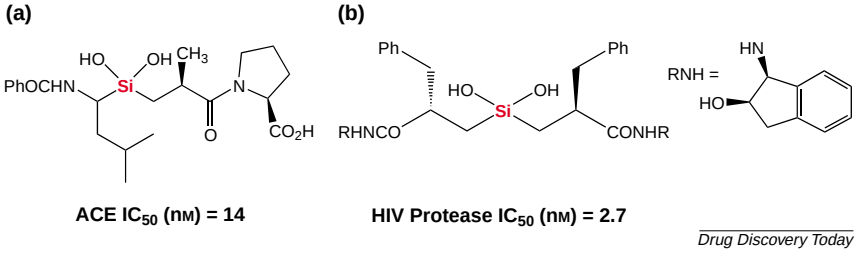

Figure 4. Metallo and aspartyl silicon diol protease inhibitors. The silicon diol moiety provides a novel 'warhead' in protease inhibitor design. Abbreviation: ACE, angiotensin converting enzyme.

seen *in vivo* [20]. A small increase in lipophilicity can markedly increase the volume of distribution of the molecule, reflecting increased tissue penetration. As a consequence the molecule will be less prone to hepatic metabolism and the plasma half-life of the molecule may be improved in situations in which liver metabolism is significant in the carbon compounds.

Novel chemical space

The chemistry of silicon is heavily dominated by the chemistry of single bonds, which has led to its appropriate use as a tetrahedral bioisostere of carbon. The C=O double bond of a ketone is favoured over its hydrated form, whereas formation of a Si=O double bond is disfavoured over its hydrate, the silicon diol. Organosilicon compounds can be synthesized when the carbon counterparts are much more difficult to obtain or do not exist at all under normal conditions. Compounds of this type offer the opportunity to identify compounds with completely novel modes of action, and thus novel IP. An area in which silicon can be effective in this respect is in the design of protease inhibitors and it has been shown that potent and novel aspartyl and metallo protease inhibitors can be identified using this approach (Fig. 4) [21,22]. In the case of aspartyl proteases, the design process was based on the fact that a silicon diol species represents an ideal, nonhydrolysable analogue of the tetrahedral intermediate formed during amide hydrolysis.

Limitations

Although the incorporation of silicon represents an excellent tetrahedral isostere of carbon, it cannot form physiologically stable Si-H compounds. The Si-H bond is not only weaker than the C-H equivalent but also has reversed polarity [Si(δ+)-H(δ–) versus C(δ–)-H(δ+)]. Consequently, the Si-H bond behaves differently from the C-H bond. This is exemplified by the Si-H linkage being easily cleaved by water under non-acidic conditions, forming the corresponding silanol (Si-OH). The following common carbon systems (C=C, C=O) do not have direct sila equivalents. From the lead optimization perspective a potential limitation with using silicon as an isostere is the increase in lipophilicity that silicon brings. Although increasing lipophilicity does have several potential benefits, as discussed earlier, ensuring adequate water solubility in pharmacologically active compounds is a

major challenge for medicinal chemists and increasing a compound's lipophilicity does not help this cause. Constant checks on the overall physicochemical profile of the sila compounds are necessary, in the same manner as with a standard carbon series, while activity and other parameters are optimized.

Toxicology

Organosilicon chemistry can provide a wealth of chemical diversity and biological function for drug discovery, but it has not been exploited to a significant extent within the industry outside synthetic methodology; in part this has been caused by concerns over the potential toxicity of silicon-containing molecules. These concerns arise, in many cases, from an apparent assumption that silicon is 'metallic'. When viewing the trends of the group IV elements of the periodic table, carbon is considered as strictly non-metallic, silicon as essentially non-metallic, germanium as metalloid and both tin and lead as metallic. As electropositive elements go, silicon is one of the least metallic. When considering the available toxicological data on organosilicon compounds it is apparent that the number of toxicological studies is much smaller than the number of pharmacological investigations. Most toxicological data are LD_{50} values and the range of values and associated toxicities is the same for the silicon-containing compound and its carbon analogue. In a literature review from 1971 [23], the authors stated 'evidence is also now available to establish that organosilicon compounds *per se*, are not toxic'. A more recent perspective (Bains, W *et al*, unpublished) covers 74 compound families, which will be published in late 2003. This review concludes that silicon conveys no systematic toxic liability on chemically stable molecules.

No silicon-containing drug has been approved by the regulatory authorities in the USA or Europe to date, but seven organosilicon compounds have been in human clinical trials, and an eighth, flusilazole, is extensively marketed as an agrochemical and as such has been considered in terms of its potential effects on human exposure. Evaluation of the available clinical and toxicological data on these compounds support the hypothesis that silicon is not inherently toxic and recorded adverse events are predominantly mechanism based.

Clinical studies

Organosilicon compounds that have progressed into clinical studies include silperisone, [24] a neuromuscular antagonist for treating muscle spasm, and zifrosilone, [25] a neostigmine analogue functioning as an acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. Zifrosilone was well tolerated in human volunteers after oral

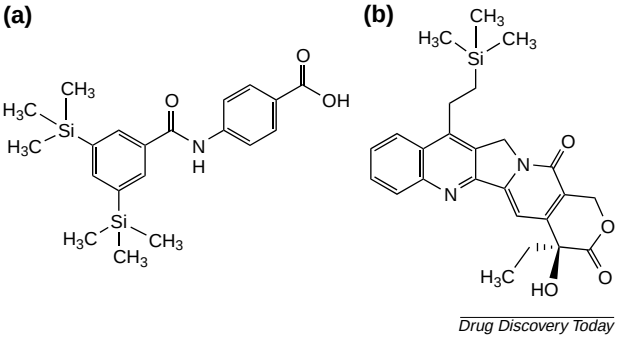

Figure 5. TAC101 **(a)** and BNP1350 **(b)** are in clinical development for the treatment of cancer.

administration and cholinergic side effects were minimal or absent when compared with nonselective cholinesterase inhibitors such as tacrine or physostigmine. It was reported to also inhibit red blood cell acetylcholinesterase activity in a dose-dependent manner [26] and development of this Merrell Dow (http://www.dow.com) compound was subsequently halted. Taiho Pharmaceuticals (http://www.taiho.co.jp) progressed Am555S/TAC101 (Fig. 5), an orally active agonist of the α and β subtypes of the retinoic acid receptor, into Phase I clinical trials for the treatment of lung cancer [27] after promising results in animal models of tumour growth and metastasis. Following oral administration to patients, the most frequent toxicity problems were myalgia/arthralgia, triglyceridaemia and fatigue. No dose-limiting toxicities were observed within the first 4 weeks of treatment, although some patients experienced venous thrombolytic events. The musculoskeletal toxicity and hyperglyceridaemia were side effects that had not been unexpected because they are characteristic of previously studied retinoids [28].

Certain phenyl-containing polysiloxanes have been shown to display oestrogenic activity. *Cis*-2,6-diphenylhexamethylcyclotetrasiloxane (cisobitan) has been shown to possess the greatest biological activity, with a hormonal agonist activity that is equivalent to that of oestradiol but with a low acute toxicity (LD_{50} >5,000mg/kg). It has been shown that the phenyl group is essential for activity and the compound has been patented as an antifertility agent. Owing to its antigonadotrophic properties, cisobitan has been examined for the treatment of human prostate cancer. Toxicity tests lasting 1–6 months undertaken in rats, dogs and monkeys have shown that the observed effects were similar to those of oestrogens in most respects, although the compound had less thrombogenic toxicity [29]. In patients, no side effects were observed that were not present in other oestrogen treatment groups, except

dizziness and diarrhoea [30]. Increases in acid and alkaline phosphatase activity were noticed but no other overt problems or signs of liver toxicity were found, even when treatment was continued for periods of up to six months [31]. Currently, the most clinically advanced compound is BioNumerik's (http://www.bionumerik.com) BNP1350 karenitecin compound (Fig. 5), a fourth generation compound from a novel class of camptothecin analogues. Unlike water-soluble camptothecins, compounds of the karenitecin series, including the silicon-containing BNP1350, appear to be substantially less sensitive to common tumour-mediated drug resistance mechanisms. Studies in rats and dogs have shown that reversible myelosuppression, predominantly neutropenia, is the most likely dose-limiting toxicity that may be expected in humans. Gastrointestinal effects, such as mucositis and diarrhoea, were also observed. None of these side effects observed in animals are unexpected from the known pharmacology of this class of compound. BNP1350 has successfully completed several phase I clinical trials [32] and is currently being investigated in several phase II clinical trials, including recurrent malignant brain tumours and non-small cell lung cancer.

Concluding remarks

The use of isosteres in medicinal chemistry is a key tool in enabling the introduction of new drug-like chemical space into the drug discovery and development process. As the advantages of introducing silicon into drug-like molecules during the lead optimization phase become more widely appreciated, (for example, novel IP, increased lipophilicity, altered efficacy, improved selectivity and pharmacokinetic profiles) the likelihood is that more silicon-containing drug candidates will progress through lead optimization and into the clinic in the near future.

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