Designing chiral libraries for drug discovery

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Identification of new biological targets combined with combinatorial medicinal chemistry has enormous potential to facilitate the discovery of new therapeutics. However, these new targets might require the use of different or more complex screening libraries. This complexity might be achieved through the use of new templates or the identification of new chemistries. One approach is the use of chiral libraries that have been designed using three-dimensional pharmacophore and shape descriptors to provide maximal structure–activity information after screening. The advantages of using a designed chiral library in primary screening and the information one should obtain are discussed.

Much effort has been devoted to the development of procedures or methods that increase the efficiency of the drug discovery process. All areas of research have been affected by these changes, which include target identification, HTS, combinatorial chemistry, *in vitro* compound profiling and clinical studies[1–7]. One approach that spans all the different disciplines is the use of screening libraries designed to provide information about the target of interest, and to facilitate the secondary profiling and lead optimization process. A computational approach for the design of informative libraries has been developed and then applied to several chiral combinatorial templates. The rationale for the design and use of chiral screening libraries and their potential advantages in today's drug discovery paradigm are outlined.

Current approaches

In an effort to identify higher quality clinical candidates, the pharmaceutical and biotechnology industry has looked for ways to increase the efficiency and breadth of the drug discovery process. One approach has been the use of genomics and proteomics to identify new targets or pathways that can lead to more selective and safer drugs[8,9]. Although successful, it has shifted the discovery bottleneck to other areas of research. For example, the new targets identified now need to be validated and prioritized, assays and screens need to be developed, and leads should be identified that modulate them. In addition, many of these new targets involve complex interactions, which are difficult to modulate with small molecules. To date, more classical compound libraries have demonstrated little success in affecting these types of assays and more complex molecules might be more effective.

Many approaches have been implemented in an effort to increase throughput and eliminate the backlog of targets. These include combinatorial chemistry approaches[10], focused or smart libraries[11] and higher capacity screens[12]. In addition, many groups have begun profiling screening hits more extensively and earlier in the discovery pipeline, in an effort to be more selective with the compounds that move into lead optimization[13]. For example, the use of high-throughput assays for measuring bioavailability, metabolism or toxicity characteristics can prioritize series of compounds that need medicinal chemistry[14,15]. Implementation of high-throughput chemistry and screening has resulted in significantly more compounds being evaluated in a shorter period of time. However, it also means

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that a greater number of compounds need prioritization, analysis and medicinal chemistry resources.

Another approach used to increase throughput has been the pooling (mixing) of compounds and libraries[16,17]. Although popular, the number of laboratories screening mixtures has recently declined, owing to the difficulty in analyzing the biological data and determining the specific compound responsible for the observed activity. In addition, compound mixtures cannot be used to evaluate secondary characteristics such as selectivity, bioavailability or any other *in vitro* secondary profiling measurement, as the results obtained are not interpretable. Recently, the use of single discrete compounds has become the method of choice, particularly as the synthetic techniques for preparing and purifying single compounds in an automated parallel fashion have improved. Furthermore, computational tools for designing libraries and interpreting the results have also improved[18–21].

Chiral drugs

The use of enantiopure drugs has continued to grow in the pharmaceutical industry, as chiral drugs will account for >$100 billion in sales in the year 2000 (Ref. 22). Currently, nearly half of all of the marketed drugs are enantiopure. This is not surprising because most biological processes are stereospecific, and the use of stereospecific compounds enhances the chances of finding potent and safer drugs. However, combinatorial and high-throughput chemistry efforts have continued to focus on achiral molecules. There are two reasons for this:

- Much of the technology to prepare chiral molecules in the quantities and format required for combinatorial chemistry is not widely available
- The significance of addressing stereospecificity in the early stages of drug discovery is not widely appreciated. (This might soon change because the use of mixtures of stereoisomers as drug candidates is not generally accepted and could suggest that the use of libraries of enantiopure compounds earlier in the discovery process is beneficial.)

The advantages of using chiral molecules as drugs is clear, particularly considering the activity and selectivity differences that exist between stereoisomers. There are numerous examples that illustrate the differences in activity between stereoisomers against a given target[23], but much of this information is obtained late in the discovery process or not until the compounds have advanced into clinical trials or are approved[24]. Addressing chirality early in the discovery process has several clear advantages. As already stated, screening mixtures of compounds might often complicate or mask assay results. Screening of mixtures of stereoisomers can present even more problems. Chiral compounds active as a single isomer can exhibit little or no activity as stereomixtures. This could be because the inactive isomer(s) are present in larger quantities or to the opposing effects of the stereoisomers, which effectively cancel each other out. The latter situation, known as a false negative, would occur undetected if mixtures were being screened, wasting potentially valuable leads.

Chiral libraries in drug discovery

In the past, pharmaceutical companies have usually taken great pains to avoid chiral drugs or leads because of the added costs associated with the synthesis and purification of such compounds. This mentality also propagated into combinatorial chemistry approaches, and recent small-molecule libraries have been based on readily available nonchiral heterocyclic molecules. Of note is the fact that the first combinatorial libraries were peptides[25] (and thus chiral, because they were derived from amino acids and contained multiple chiral centers). These chiral libraries were, however, usually prepared as mixtures and the chiral information they contained on screening was not accessible nor generally appreciated. In fact, as 'combinatorial technology' shifted to a more medicinal chemistry focus, the concept of chirality was quickly eliminated. Furthermore, if chiral molecules were synthesized and screened at all, they were typically screened as mixtures of enantiomers or diastereomers, and the active component(s) of the mixtures were identified later. The identification often required much effort, either to separate the enantiomers or to devise a stereospecific synthesis. Many companies have had success by following this approach, but new targets and assays identified through the use of genomics or proteomics might require the use of more complex molecules in screening (and thus the current libraries could have limited use).

The importance of enantiopure libraries or compounds becomes crucial as a lead proceeds through the drug discovery pipeline. Different enantiomers have different solubility properties, bioavailability and protein-binding characteristics. For example, active transport is a stereospecific process, as is conjugation and metabolism by P450 monooxygenases. In addition, there are several examples in the literature illustrating that stereoisomers vary in their toxicity profiles[26]. As compounds proceed into animal and clinical studies, interactions with other drugs become

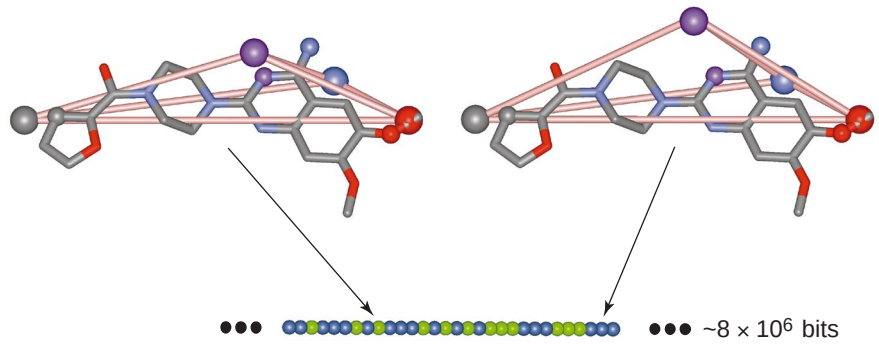

Figure 1. *Construction of the pharmacophore signature. If a conformation of a molecule matches a pharmacophore (left), the bit associated with that pharmacophore (identified by the arrow) is set (green). If all sampled conformations of a molecule are unable to present a pharmacophore (right), the bit associated with that pharmacophore is unset (blue). Each molecule's pharmacophore signature contains several million bits.*

important. For example, the enantiomers of propanolol affect the binding of benzodiazapines differently[27], and therefore could adversely affect the outcome of bioavailability and efficacy studies. In summary, the use of enantiopure compounds will help to minimize surprises that occur during preclinical and clinical development.

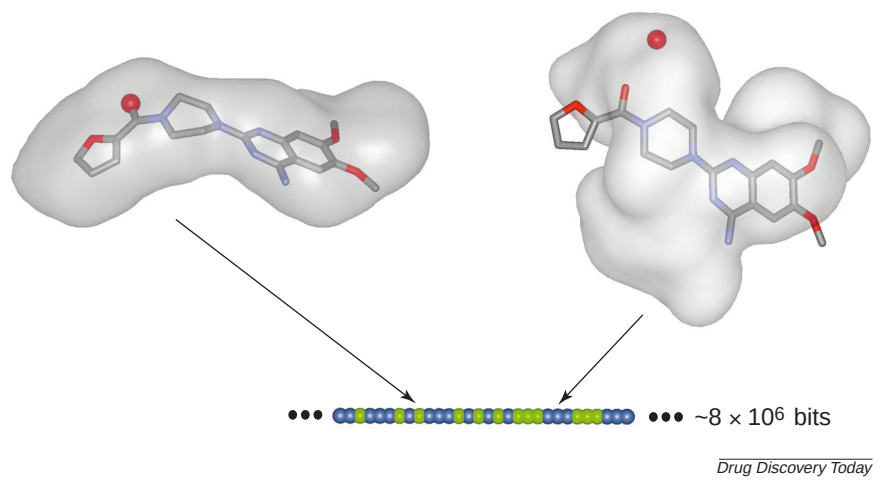

Figure 2. *Construction of the shape–feature signature. If a conformation of a molecule matches a shape and places a chemical feature at a specific location (left), the bit associated with that shape–feature combination (identified by the arrow) is set (green). If all sampled conformations of a molecule are unable to match a shape–feature combination (right), the bit associated with that shape–feature combination is unset (blue). Each molecule's shape–feature signature contains several million bits.*

Chiral library design

Libraries of compounds are most useful when they can be used against all assays and provide information about the assay, target or pathway. Combinatorial libraries built around chiral (or achiral) templates can potentially be quite large, and computational methods are required to select the optimal library for synthesis. The use of information theory provides designed libraries that maximize the three-dimensional (3D) structure–activity information that is obtained when the library is assayed for activity against a target. 3D descriptors are used to encode a bit string that describes each molecule's 3D chemical profile. These bit strings are then used to select the subset of products for which the informational entropy of the bits in the strings is a maximum (Barnum, D.A. *et al.* The design of informative libraries. *American Chemistry Society 215th National Meeting*, 29 March–2 April 1998, Dallas, TX, USA).

The process of library design begins with the computer representation of the proposed combinatorial synthesis, the virtual library. This is constructed from a reaction-based cascade that combines the chiral template with the different reagents and chemical reactions that give rise to the products. The reagent lists are heavily filtered to remove undesirable compounds (e.g. compounds with a high MW or with functional groups that are likely to interfere with the proposed chemical synthesis). In addition, restrictions are placed on the reagent lists to bias the resultant products to be more drug-like[28]. For example, filters are put in place to limit the number of rotatable bonds.

After the virtual library is constructed, a set of representative low-energy conformations is generated for each molecule. These conformations determine what regions of chemical space each molecule can explore. An abstract representation for each conformation of each

molecule is created using topological queries[29,30]. Elements, nuclear coordinates and atomic bond types are mapped to chemical features: hydrogen-bond donors and acceptors, charged groups, hydrophobic groups and aromatic rings. The collection of relative feature positions for each conformation of a molecule is used to construct a 3D descriptor (signature) for the molecule. Two types of molecular descriptors are used in our library design: pharmacophore signatures and shape–feature signatures.

Molecular descriptors

Pharmacophore signatures, which consist of sets of features and their associated interfeature distances, have been described elsewhere[31–34] and will only be summarized here. For each molecular conformer, the distances between all feature pairs are calculated. Distances between features are binned (e.g. interfeature distances of 3.5–5.0 Å would map to a signal distance bin), and all possible combinations of two, three and four features are considered. Each combination maps to a particular bit (or key) in the signature that is set (see Fig. 1). Additional bits are set as each conformer presents the molecule's chemical features in unique positions. All possible two-, three- and four-point pharmacophores that are present in the molecule's conformers are mapped into a single-bit string that identifies pharmacophores that are present in the conformers. Typically, this results in a signature length of ~10 million bits.

Shape–feature signatures represent where a molecule can place a feature within a set of molecular shapes. Unlike pharmacophore signatures, which consider only features and their related positions, shape–feature signatures consider the steric volume of the molecule. The shape–feature signature space is defined by a shape catalog (a set of shapes that each conformer is compared with, to see if there is a fit) and a set of positions within the shape that might contain a chemical feature. Each such signature is made up of individual elements, which consist of a molecular shape, represented by an approximate steric envelope, and the location of a single chemical feature (e.g. hydrogen-bond acceptor) within the shape. A catalog of shapes is created from the low-energy conformers of all the compounds. Each conformer is processed and, if it does not match any of the existing shapes in the catalog, a new shape is generated. Once the shape catalog is generated, each conformer is revisited and compared with the shapes in the catalog. When a conformer matches a shape, each feature in the conformer maps to a signature bit associated with that shape–feature combination, and the bit or key in the molecular signature is set (see Fig. 2). As in the pharmacophore signatures, all conformers for a molecule contribute to the shape–feature signature.

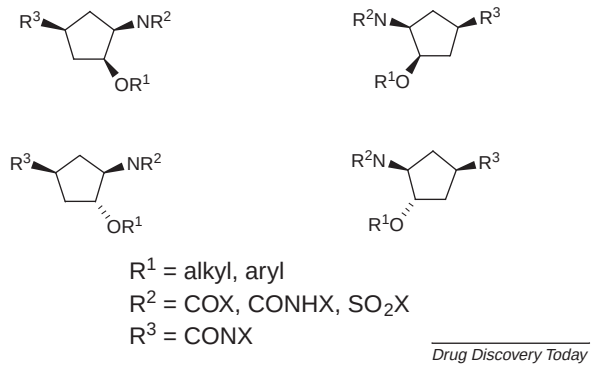

Figure 3. *Products for the four chiral libraries. Four stereoisomers of a cyclopentane-derivative provided the scaffold for the chiral combinatorial libraries. The side-chains chosen for each of the three diversity sites were the same. Synthetic constraints limited the R^1 site to a free hydroxyl group or one of four ethers. For the R^2 site, we selected 16 reagents: five acid chlorides, five isocyanates and six sulfonyl chlorides for amide, urea and sulfonamide bond formation. Sixteen amines were chosen for amide bond formation at R^3, which resulted in 1280 compounds for each chiral library.*

Informative design

Once a set of molecular signatures is complete, a matrix of them is constructed in which each row corresponds to a unique molecule and each column corresponds to a particular descriptor. The subset of the molecules that are used in the combinatorial synthesis is determined by analyzing this matrix. From the M rows (typically hundreds), a subset of N rows (typically tens) is chosen that has the highest informational entropy. Maximizing the informational entropy ensures that assay results for the set of molecules will most efficiently identify which components in the 3D molecular descriptors are correlated with activity.

The design of the chiral screening libraries was based on the diastereomer products shown in Fig. 3 (Chirotech, Cambridge, UK). To maximize the number of possible products obtained from a set of reagents, a matrix synthesis was used (i.e. all combinations of reagents were used in the synthesis of the products). The constraints of matrix synthesis require selection of reagent lists, which can be accomplished by reagent-based analysis or by selection of desirable products, followed by an optimization step that yields a matrix of reagents[35,36]. The design approach was tailored to each of the signature types.

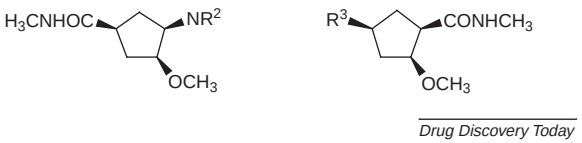

Figure 4. *'Minimal' products used in the creation of the pharmacophore signatures, which are used to select reagents for the R^2 and R^3 diversity sites. Virtual products used to construct signatures for the R^2 reagent selection contained a methyl amide at the R^3 position, whereas the virtual products used to construct signatures for the R^3 reagent selection contained a methyl amide at the R^2 position.*

For pharmacophore signatures, a virtual library of partial products was created by reacting the reagent with a template that had been reacted with minimal reagents at the other diversity sites, as shown in Fig. 4. In selecting the reagents for the R^2 position, the template was first reacted with minimal reagents at R^1 (creating a methyl ether) and R^3 (creating a methyl amide). Thus, for each R^2 reagent, the signature for this minimal product was used to create the molecular signature that was compared with other similarly constructed signatures for the other R^2 reagents. This allowed a greater molecular context in generating pharmacophores than would be possible if signatures were generated for the isolated unreacted R^2 reagents.

This minimal product approach is not appropriate for generation of the shape–feature signatures because the minimal template would comprise too much of the steric volume of the minimal product, leading to shapes that are too similar. Therefore, the shape–feature signatures are generated using the isolated reagents. Approximately half of the reagents at each site were chosen using the pharmacophore signatures, and the remainder was chosen using the shape–feature signatures (in the context of the shape–feature signatures of the molecules already chosen).

The final designed library consisted of 1280 compounds per chiral template. Several iterations of design were required because reagents chosen were often unavailable or too expensive. When this occurred, the design process was repeated with the restriction that the reagents chosen in the previous design that were available were forced to be part of the selected reagents in the subsequent design. This permitted replacement of chosen, but unavailable, compounds in the context of those compounds that were available. The process was repeated until the required number of reagents at each diversity site was obtained.

Synthesis of chiral libraries

In general, the synthesis of chiral libraries can proceed from achiral building blocks that can lead to chiral molecules, or they can be prepared from a chiral template that has the desired stereochemistry established. In either case, the design tools just described can be applied. The libraries discussed here were built around chiral templates (see Fig. 3). Thus, the synthetic challenge was to introduce structural variations at the diversity sites on the template while maintaining its chirality.

Figure 5 illustrates the synthetic procedures used for the template shown in Fig. 3. This route was chosen for several reasons:

- It made maximum use of automation to synthesize final products and intermediates.
- It had the ability to use a matrix synthesis approach and suitable monomers were available.
- It minimized the chances of using chemistry that would racemize the chiral centers.

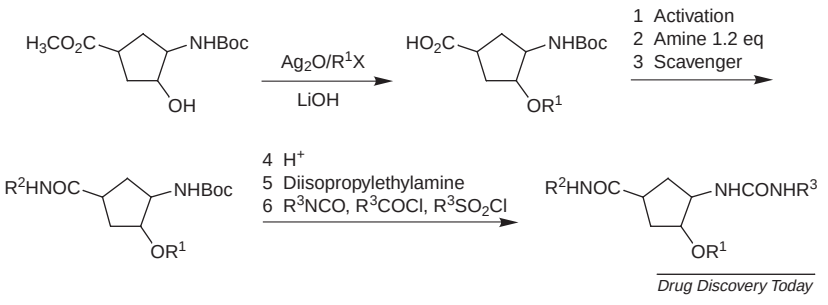

Figure 5. *Synthesis scheme for the four chiral libraries.*

For example, the first step (Fig. 5) involves the formation of the ethers at R^1 using a silver catalyzed reaction. The resulting carboxylic acid ethers are purified by chromatography and fully characterized [liquid chromatography–mass spectrometry (LC–MS) and NMR]. Activation of the resulting acid, followed by treatment with a series of primary amines provides the carboxamides. Excess amine is scavenged using polymer-bound isocyanates and the purity and identity of the 16 amides is monitored by LC–MS. The synthetic

process is performed using a Tecan liquid handler or can be easily carried out manually. Next, the *t*-butylcarbonate protecting group is removed and a series of amides, sulfonamides and ureas are prepared using the Trident Automated Synthesizer (Argonaut, San Carlos, CA, USA). Each compound is then purified by LC–MS and re-analyzed to ensure purity. All of the compounds are re-analyzed using LC–MS after purification to ensure both chemical and stereochemical purity. The intermediates are also purified to homogeneity and analyzed by NMR and LC–MS. The use of a final purification by LC–MS of all the compounds and then reanalysis is a crucial step in that it ensures that the compounds are sufficiently pure to use in not only primary screening but also in secondary assays.

Library characterization

One design goal for the libraries was for the products to have similar physical properties to known drugs. This was the reason for several of the reagent list filters. To verify these drug-like characteristics, the distribution of chemical properties of the libraries was compared with randomly selected compounds from the MDDR (MDL Drug Data Report from MDL Information Systems, San Leandro, CA, USA). The physical property distributions for the drug-like molecules and the chiral libraries were compared, as shown in Figs 6 and 7. The chiral libraries are not significantly different from the sampled MDDR compounds. Similarly, equivalent distributions were obtained for the count of each of the six feature types in each molecule. The number of rotatable bonds was found to be higher in the chiral libraries than in the MDDR compounds. This is actually an advantage, as the compounds in the designed library will be used for primary screening. Many of the compounds in the MDDR are optimized around a particular biological activity and therefore contain fewer rotatable bonds than would be wanted in a screening library.

Three-dimensional similarity

Both descriptors were first verified to be able to resolve chirality differences between diastereomer products. An example is shown in Fig. 8, in which a four-point pharmacophore is matched by only one of the four diastereomer products. Similar discrimination was obtained for the shape–feature descriptors.

One way to assess the effect of the different chiral templates on the four libraries is by direct comparison between diastereomers in the libraries. Each compound in a library has a diastereomer pair in each of the other three libraries, one of which is the compound's enantiomer. Differences between the molecular descriptors of diastereomers result solely from the chirality of the template and indicate how effectively the descriptors distinguish chiral molecules. The

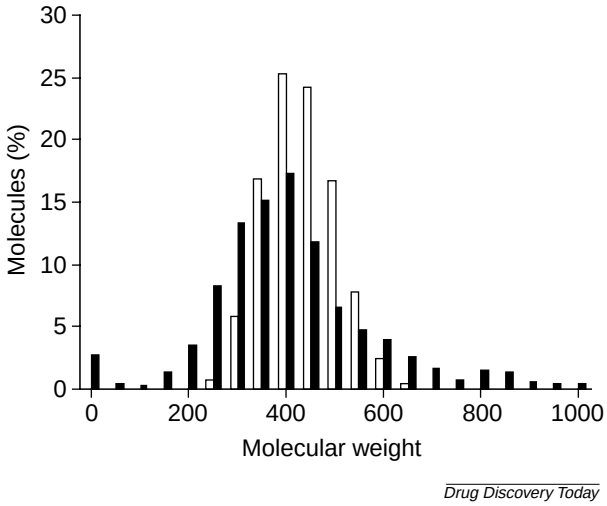

Figure 6. *MW comparison between the first 1280 compound chiral library (open boxes) and randomly selected compounds from the MDDR (MDL Drug Data Report from MDL Information Systems, San Leandro, CA, USA; closed boxes).*

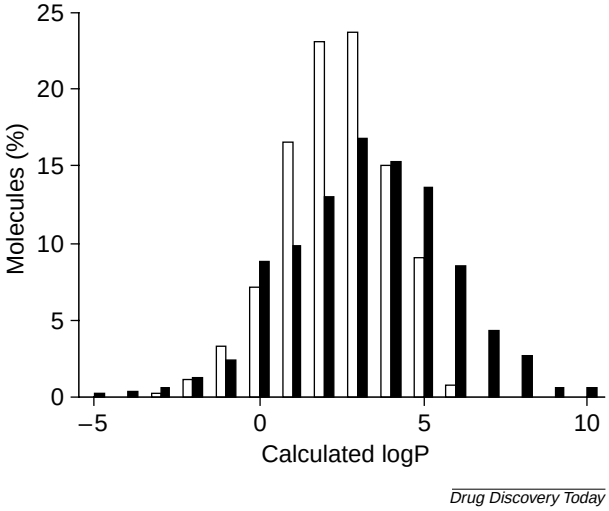

Figure 7. *Calculated logP comparison between the first 1280 compound chiral library and randomly selected compounds from the MDDR (MDL Drug Data Report from MDL Information Systems, San Leandro, CA, USA). LogP values calculated using Molecular Operating Environment (MOE; Chemical Computing Group, Montreal, Canada) software.*

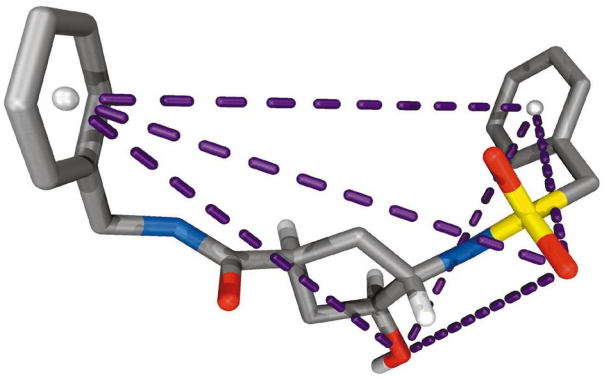

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Figure 8. *A pharmacophore (consisting of two aromatic rings, a hydrogen-bond donor and a hydrogen-bond acceptor) and one of the chiral products that can match it (and whose signature, therefore, has the bit associated with this pharmacophore set). The three diastereomers of this compound (each in one of the other three libraries) are unable to adopt a conformation that matches this pharmacophore.*

pharmacophore descriptors for each compound in the first chiral library were compared with the signatures of its diastereomers in the other three libraries, and the resulting distributions of Tanimoto dissimilarity are shown in Fig. 9.

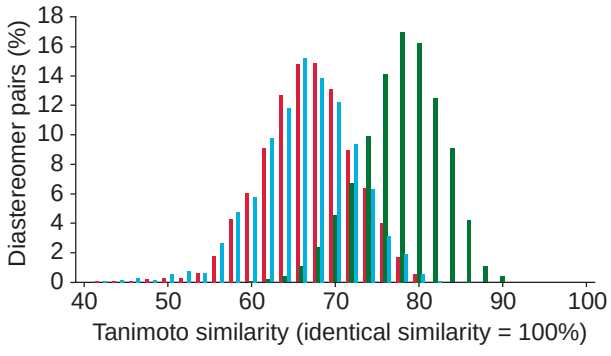

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Figure 9. *Similarity comparison using pharmacophore descriptors. The distribution is shown of pairwise Tanimoto similarities between the pharmacophore signature of each compound in the first chiral library and the signatures of its three diastereomers in the other chiral libraries. The green distribution is the pairwise comparison between enantiomers (i.e. the enantiomer is more similar than the other diastereomers).*

It is interesting to note that, in general, a compound's enantiomer is more similar than the other two diastereomers.

An analogous comparison between diastereomer pairs using shape–feature signatures is shown in Fig. 10. The Tanimoto similarity between all diastereomer pairs is extraordinarily low. This is especially remarkable considering that any 2D similarity measure would consider all pairs to be 100% identical.

Conclusions

We have reviewed the importance of chirality in drug activity and in the discovery and development of drug candidates. We have also described the procedure through which chirality can be incorporated into the earliest stages of lead discovery in the design and synthesis of general screening libraries. The chiral nature of these libraries and the purity are crucial in that these features provide vital information about a target and enable the lead optimization process to begin immediately on completion of screening. The type of design tools that address the issue of chirality is also of great interest. As shown in Figs 8–10, 3D descriptors can distinguish between the different diastereomers. 2D descriptors, which consider only molecular connectivity and ignore chirality, would be inadequate for this task. Indeed, all diastereomers would be identical in this description.

However, because bits in the pharmacophore signature are determined by feature types and interfeature distances, many pharmacophores are achiral, and if they are matched by one molecule, they will probably be matched by its diastereomers (an exception would be if the conformational model were altered by the changing chirality, a situation not possible for enantiomer pairs, but possible for other diastereomers). Furthermore, even though a pharmacophore might be chiral, pairs of chiral products might achieve this with a different part of the molecule or with a different conformation. If this is the case, the ability of that pharmacophore to distinguish between the chiral products is lost.

The ability of shape–feature descriptors to distinguish between diastereomers results from the inherent chirality of shapes. Only symmetric shapes are achiral, and once a feature position is considered within that shape, it is highly unlikely that the combination would be achiral. Moreover, shape–feature signatures for the products consider the entire product, not just a substructure, as with pharmacophore signatures, which makes it less likely that a shape matched by a chiral compound could be matched by its diastereomer.

An increasingly common consideration in library design is the desire to make drug-like molecules, as measured by

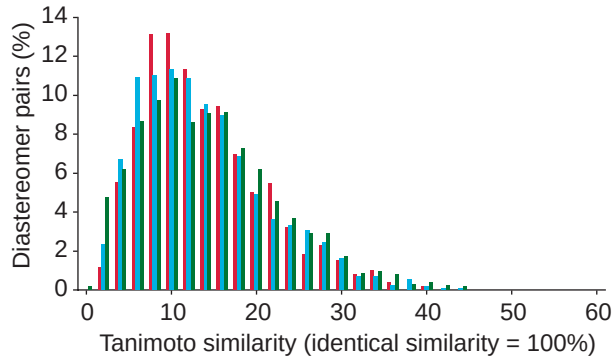

Figure 10. *Similarity comparison using shape–feature descriptors. The distribution is shown of pairwise Tanimoto similarities between the shape–feature signature of each compound in the first chiral library and the signatures of its three diastereomers in the other chiral libraries. All diastereomer pairs have low similarity using this measure.*

physical properties such as MW, octanol–water partition coefficient and hydrogen-bond count. It is hoped that by considering these characteristics early, struggles further down the drug-development pipeline will be minimized. We adopt a similar view with respect to chirality. In fact, if statistical studies of known drugs are used to guide synthesis of screening libraries, it could be argued that chirality is as important a consideration as the other criteria proposed by Lipinski *et al.*[28] The counter-argument to this type of logic is that compounds in screening libraries are not drugs, and putting in too much bias towards the characteristics of drug molecules compromises the ability to find a lead candidate.

The other big advantage of designed chiral libraries is their impact on structure–activity relationships obtained from screening such libraries against a target. If only certain diastereomers return as hits, those models common to the inactive diastereomers can be quickly ruled out. Incorporating this discrimination into an activity model (e.g. a receptor-site model or pharmacophore hypothesis) should result in a higher quality model than could be obtained from screening achiral molecules. This should greatly speed up the process of interpreting assay results and the design of daughter screening libraries to follow up a hit.

A disadvantage of using chiral libraries for screening is the cost. For example, several additional analytical determinations must be carried out to ensure no racemization of the chiral centers, and the time needed to develop and automate the chemistry is also increased in some cases. In addition to the synthesis being more difficult, the analysis of the libraries not only for chemical purity but stereochemical purity is more crucial. However, the time saved in analyzing and understanding the assay data and starting lead optimization might more than compensate for the increased synthetic difficulty.

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Collaboration in the cancer therapeutic area...

Oxigene (Stockholm, Sweden) and **Techniclone** (Tustin, CA, USA) have formed a joint venture, Arcus Therapeutics, which will merge the vascular targeting technologies of the two parent companies for the development of novel cancer therapeutic agents. Oxigene will licence its next generation of tubulin-binding compounds specifically for use in combination with Techniclone's Vascular Targeting Agent (VTA) technology. VTA technology is based on targeting molecules that are thought to bind selectively to vascular endo-thelial cells in tumour blood vessels. These molecules can be linked to different types of effector molecules which, after binding to the tumour vessels, trigger a thrombotic cascade and form a fibrin plug within the vessels, thereby destroying the tumour vessels, and hence the tumour. This technology is currently in preclinical development, and is anticipated to enter clinical trials within the next two years.

Under the terms of the joint venture, Techniclone will supply its intellectual property and the expertise of Dr Thorpe (inventor of VTA and Professor of Pharmacology, University of Texas Southwestern Medical Center, TX, USA) and his most promising lead compounds. Meanwhile, Oxigene will provide its expertise in preclinical and clinical development as well as its tubulin-binding compounds.