Generation of New Synthetic Scaffolds Using Framework Libraries Selected and Refined via Medicinal Chemist Synthetic Expertise

Thomas R. Webb,*,† Ruben E. Venegas,‡ Jian Wang,† and Alain Deschenes§

ChemBridge Research Labs., Inc., ChemBridge Corporation, 16981 Via Tazon, San Diego, California 92127, and Chemical Computing Group, Suite 910-1010 Sherbrooke St. W Montreal, Quebec, Canada H3A 2R7

Received June 4, 2007

With the expansion in the application of library methods in medicinal chemistry and chemical biology there is a growing need for improved technology for the design of novel templates that are well suited for the synthesis of libraries targeted toward specific subsets of protein families. In this report, we delineate an improved stepwise general method that is well suited for this purpose. This process uses virtual framework libraries to identify frameworks that rigidly match specific aspects of a ligand's bioactive conformation. The resulting frameworks can then be ranked and sequentially modified by a combination of computational scripts and human derived expertise, in order to develop rational proposals for new combinatorial templates or new sets of potential ligands.

INTRODUCTION

It often occurs in drug discovery projects that only non-druglike ligand information is available, yet there are few well-accepted methods that generally allow this information to be transferred into a druglike small molecule template.[1] For example, a considerable body of work has been dedicated to the elucidation of the bioactive conformation of peptide ligands, as a starting point in the development of drug lead compounds.[2] The peptide beta-turn has been recognized as one of the important features of many bioactive peptides and as a starting point for template design. A large body successful peptidomimetic[3] work has been directed toward this motif.[4] This vast body of work includes a significant portion of the effort in the discovery of small molecule nonpeptide agonists at G-protein coupled receptors (GPCRs) with peptide ligands[5–11] that has relied on the stepwise modification of peptide analogs containing modified α-amino acids, which, in general, yields compounds with physical properties that may limit their application as orally active and blood−brain barrier penetrating drug leads.[12] An alternate approach is to develop small molecule templates (molecular scaffolds) that mimic the size and shape of the main-chain of peptide beta-turns that can also be combinatorially arrayed with the substituents which, in turn, may mimic the properly spatially oriented interactions of the side-chains of a specific bioactive beta-turn peptide. Despite the need and interest in this problem there have been only a few examples of the use of templates that do not include α-amino acids.[13]

As part of our work on the development of new and practical methods for the design of scaffolds that would be useful to medicinal and combinatorial chemists, we have recently published some of our results toward the development of such an approach.[14–16] As we have previously reported, the starting point in the development of our method were the critical insights reported by Garland and Dean.[17] These authors observed that cluster analysis and recombination of the experimentally observed positioning patterns yielded a triangular consensus positioning of the C-α atoms among the various beta-turn types, and that these triangles could be used as queries to search 3D databases to find existing compounds that match the consensus positioning of the C-α atoms of beta-turns. Using this kind of approach we have found new agonists for the somatostatin receptor[14] as well as agonists for several melanocortin receptor subtypes,[16] which demonstrate the utility of this general type of template and targeted library design method (see Figure 1).

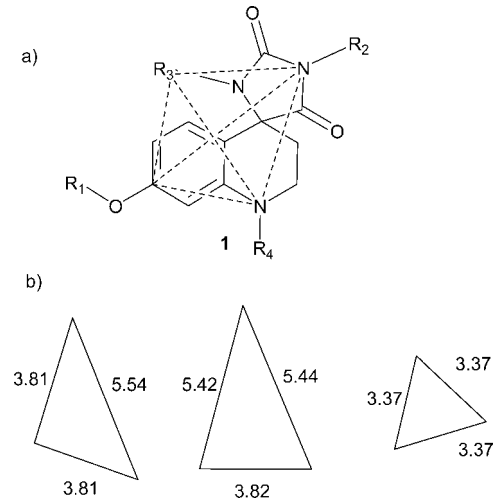

Figure 1. (a) Template **1** shown with dashed bonds to indicate the Garland−Dean triangles (connections of atoms that mimic the C-α atom positions in peptide beta-turns). (b) Three geometries (in angstroms) observed by Garland and Dean.[17]

* Author to whom correspondence should be addressed. Current address: Department of Chemical Biology and Therapeutics, St Jude Children's Research Hospital, MS 1000, 332 North Lauderdale, Memphis, TN 38105. E-mail: thomas.webb@stjude.org.
† ChemBridge Research Labs., Inc.
‡ ChemBridge Corporation.
§ Chemical Computing Group.

10.1021/ci7001928 CCC: $40.75
Published on Web 03/13/2008

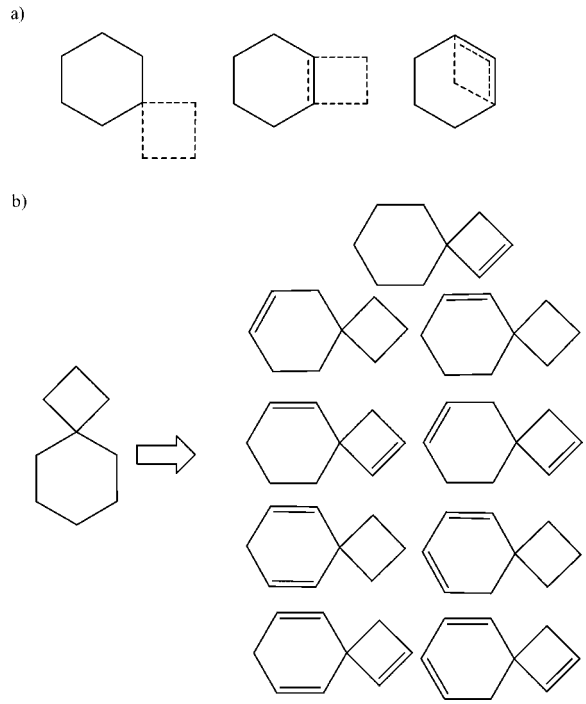

Figure 2. (a) Possible fusions of a cyclobutane layer onto cyclohexane. (b) Some examples of the types of possible unsaturation that we have incorporated into our enumeration scheme. In all cases, methyl groups were also added at all available positions (not shown).

We have previously focused on the extension of the Garland−Dean approach to the *design and synthesis* of novel templates such as **1** (see Figure 1a), which contain multiple substitution points that match several of the Garland−Dean geometries.[14–16] This combination of features is rarely seen in randomly designed diverse libraries.[18] This design paradigm allows for the construction of other templates that, like **1**, are suitable for the exhibition of many of the interesting combinatorial pharmacophoric possibilities that may be observed in bioactive peptides. This original method started with the 3D search of the large ChemBridge internal compound collection (of existing compound structures) to find the initial core molecular frameworks with the correct geometry.

While our initial approach has the advantage that the computational "hit" structures from existing compound collections are compounds that have previously been synthesized and so known synthetic routes exist, this approach suffers from the limitation that many potentially more interesting *new* framework types could not be found when searching this type of database. For this latter reason we have developed an improved and more exhaustive search method based on the enumeration (see Computational Methods) and the computational query of a large library (up to $\sim 10^8$ structures) of rigid virtual frameworks that comprise a large portion of the possible low-molecular weight carbon polycyclic and spirocyclic atomic connections (see Figure 3). In this manuscript, we report an improved and generalized protocol for the generation of new templates using geometric information, *or other similar knowledge-based input* (e.g., pharmacophore information).

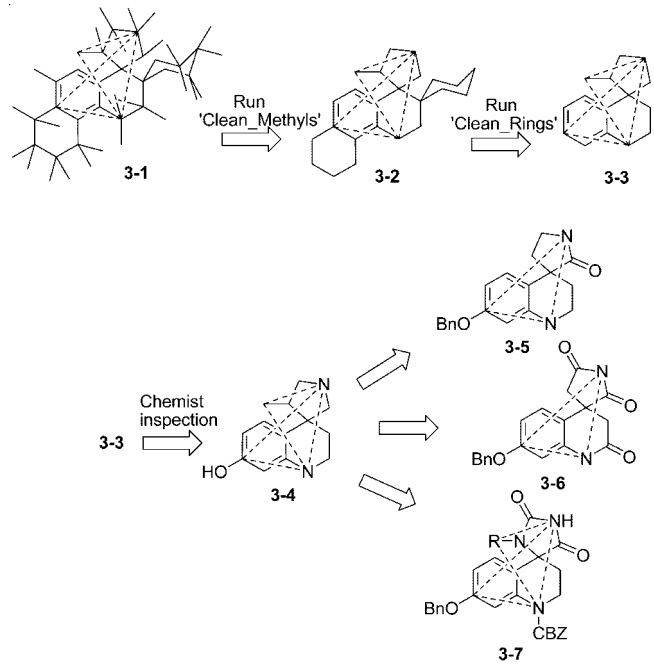

Figure 3. Computational script transformation of a raw framework Garland−Dean match result (**3–1** through **3–3**) and the subsequent steps involved in the conversion of a clean framework such as **3–3** to a virtual template (e.g., **3–4**) a set of potential synthetic targets, such as **3–5**, **3–6**, or **3–7**.

COMPUTATIONAL METHODS

Enumeration of the Virtual Framework Library (VFL). The virtual framework library (VFL) algorithm was written in the scientific vector language (SVL) provided by MOE software.[19] The goal of the algorithm is to fuse rings forming all nonredundant 1-fusion, 1,2-fusion, and 1,2,3-fusion compounds. For the purpose of this description, 1-fusions, 1,2-fusions, and 1,2,3-fusions are defined as two rings that share one, two, or three carbon atoms, respectively, as shown in Figure 2. A 1-fusion is only possible with secondary carbons on the base structure. A 1,2-fusion is possible when each of carbon atoms in the base structure is either secondary or tertiary whereas a 1,2,3-fusion is only possible for secondary or tertiary carbons at the 1 and 3 positions on the base structure.

The algorithm starts with a set of base structures that are to be built upon by fusion with a set of ring fragments. All the base structures were modified by 1-, 1,2-, and 1,2,3-fusions to produce a new set of base structures for input into subsequent cycles of the algorithm (see Figure 2a). Each fully saturated framework was also converted into a set of fully enumerated unsaturated frameworks (see Figure 2b). As the structure generation progresses, temporary files were automatically generated that allow the user to terminate the run at any time without losing previous progress. Structures were stored using MOE's canonical SMILES string representation which allows for the facile removal of duplicates.

The code for the enumeration of the VFL along with a full description of its implementation can be found in Supporting Information Table 1.

Searching the VFL and Application of Cleanup Scripts. The 3D structures of the VFL were generated using Corina with a maximum number of 250 conformations per molecule. The generated 3D conformer was then cleaned up by 100

steps of geometry minimizations using MMFF94x force field as implemented in MOE.[19]

VFL Searches. Searching the VFL involves four steps. First, we need to identify geometric features which are critical for the activity of interest. In this case, we use Garland−Dean queries,[17] or featureless pharmacophores. The application of this latter query method is more general and can be implemented where the original query contains any of 3-point, 4-point, or higher number of features such as hydrogen bond donor and acceptor, aromatic ring, hydrophobic group, anion, cation, etc., that has been derived from a pharmacophore. Second, we converted these features into a hydrophobic (Hyd) feature so that they can "find" a carbon atom in a VFL framework, in the case of aryl (Aro) groups the aromatic carbon that is substituted was retained and used as the Hyd query feature (see examples below). The third step was to search the virtual framework library using MOE. The fourth step of the search was to clean/prune the resulted frameworks and to submit them to a chemist for template design. Following modification of the framework by the chemist, the final step of each iteration cycle was the minimization of the new structural suggestion which was then superposed over the query or the original ligand. Each new template can then be ranked by inspection based on the quality of the atom positioning and the bond vectors. This step can then be reiterated by the chemist to improve either the synthetic appeal or the quality of the fit. See the examples shown in the Results section for additional details.

The full code for these scripts is supplied in Supporting Information Table 2.

RESULTS

Design of Templates Using the Garland−Dean Queries. Using the three Garland−Dean queries, the 3D search was implemented as described in the Computational Methods section and the hits were then ranked. The best matches were then subjected to a "chemically intelligent cleanup" process using SVL scripts that we have specifically developed for the molecular operating environment (MOE).[19] For example, the framework **3–1** matches the Garland−Dean triangles (shown in dashed lines, see Figure 3); note that in the case of this particular framework there is more than one possible match. Many initial frameworks matches are found in a search of this type, but only a very small number match at the same framework in more than one possible way, and templates such as these are of special interest.[18] By application of the Clean_methyls script, which removes methyl groups that are not involved in a match, **3–1** is then converted to the simplified framework **3–2**. Application of the Clean_rings script removes rings that are not involved in a match, which then yields the core framework **3–3**.

The subsequent steps rely on the expertise of the chemist to convert a wild-card structure **3–3** into a structure (for example **3–4**) which contains atoms that can allow for the introduction of building blocks at the pseudo-C-α atom positions (see Figure 4), this yields structures that are on a path that can lead to realistic synthetic targets. Heteroatoms were introduced at this stage since such modifications simultaneously make the templates more druglike,[12] improve solubility, add polar surface area and dramatically facilitate both template and final compound synthesis. Further modification of **3–4** by the introduction of functional groups that will allow for the orthogonal introduction of the amino acid side-chain mimicking groups produced numerous new potential templates, a few examples of which are shown in Figure 3 (**3–5**, **3–6**, or **3–7**). Note that the structure **3–7** is a synthon for libraries based on template **1**. The carbon atoms in the VFL can serve as "wildcard" atoms that can be converted to any desired atom type during the subsequent steps, in order to yield a compound that represents a suitable synthetic target.

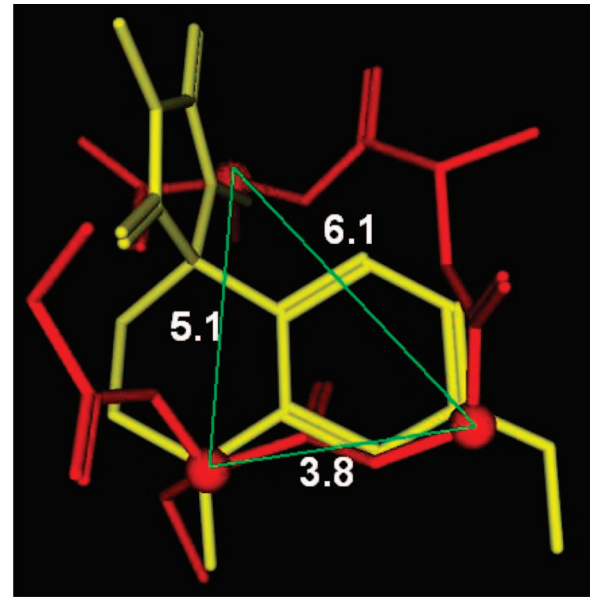

Figure 4. Template **3–4** (red) shown overlaying a peptide beta-turn (yellow). The beta turn structure was taken from a recent independent publication on peptide beta-turn structure.[20]

Detailed Example of the Prospective Design of New Templates Using a Pharmacophore. An even broader application of this method is "lead hopping" using a pharmacophore derived from an active small molecule.[21] In order to exemplify application of the VFL method to this more general problem, we will show the steps in the entire process from the query definition, searching, hit validation, and finally the design of some new proposed templates. The first step is to prepare a query. For this example, the query will be derived from Nutlin-3.[22] This molecule is known to potently disrupt the protein–protein interaction between p53 and MDM2.[22] A minimized conformation of Nutlin-3 and the MOE pharmacophore derived from this conformation is displayed in Figure 5a. The features of this pharmacophore were all converted to hydrophobic (Hyd using the PCH pharmacophore scheme in MOE)[19] so that they could find a match at the carbon atoms of a framework in the VFL. The radii of each of the four Hyd features were then adjusted to give a hit frequency that yielded a reasonably sized sample. Figure 5b shows the actual query that was used, which gave a hit frequency of 1.2×10^{-5} hits/framework searched.

The query shown in Figure 5b was then used to search a subset of the VFL of 1 000 000 frameworks. This search yielded the 12 "raw" hit structures shown in Figure 6 with root-mean-square deviation (rmsd) from the query of between 6% and 13%. The hits can be subjected to the Clean_methyls and the Clean_rings scripts at this point. When the "clean" hits were inspected by overlaying the original pharmacophore

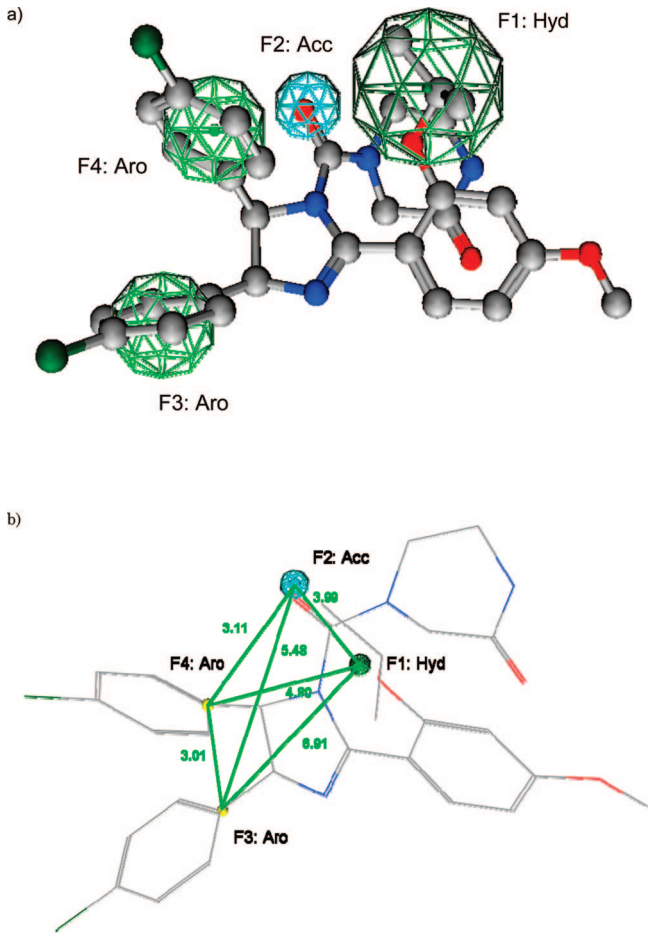

Figure 5. (a) Minimized structure of Nutlin-3[22] with an overlay of the pharmacophore derived from four features; a hydrophobic group (F1:Hyd), a hydrogen bond acceptor group (F2:Acc), and two aryl groups (F3 and F4:Aro). (b) Nutlin-3 rendered as a wireframe overlaid by the "bare" pharmacophore that is used as the VFL query. All features converted to Hyd and the radii were adjusted to F1 0.2, F2 0.3, F3 0.1, and F4: 0.1 Å. The distances are F1 to F2 3.99, F2 to F3 5.48, F3 to F4 3.01, and F4 to F1: 4.80 Å.

(as shown in Figure 5a) over the framework hit, the correct stereochemistry and positioning of the features were added to the hit structure, it can also be seen that several of the hits either do not contain the proper Ar bond angles (**6–4** to **6–8**) or have the features overlapping at centroids of the frameworks (**6–10** to **6–12**). Following elimination of the "bad Ar bond angle" or "centroid" hits, there are five hits which are the result of this process; these are shown in Figure 7.

The next step in the process was the selection of the frameworks for elaboration from inspection of Figure 7 by a synthetic medicinal chemist. This selection will vary depending on the experience and expertise of the particular chemist. In this case four frameworks, **7–1**, **7–2**, **7–3**, and **7–9** were selected for initial elaboration and computational validation. Figure 8 shows four possible heterocyclic templates derived from each of these bare hit frameworks.

The next step is the computational validation of the new template proposals (Figure 8: **8–1**, **8–3**, and **8–9**), which was done by energy minimization (using MMFF94x in MOE)[19] of the new templates followed by inspection of the pharmacophore (or the corresponding conformation of the ligand, in this case Nutlin-3) superposed with the new template. Inspection of the resulting overlay fit for these templates

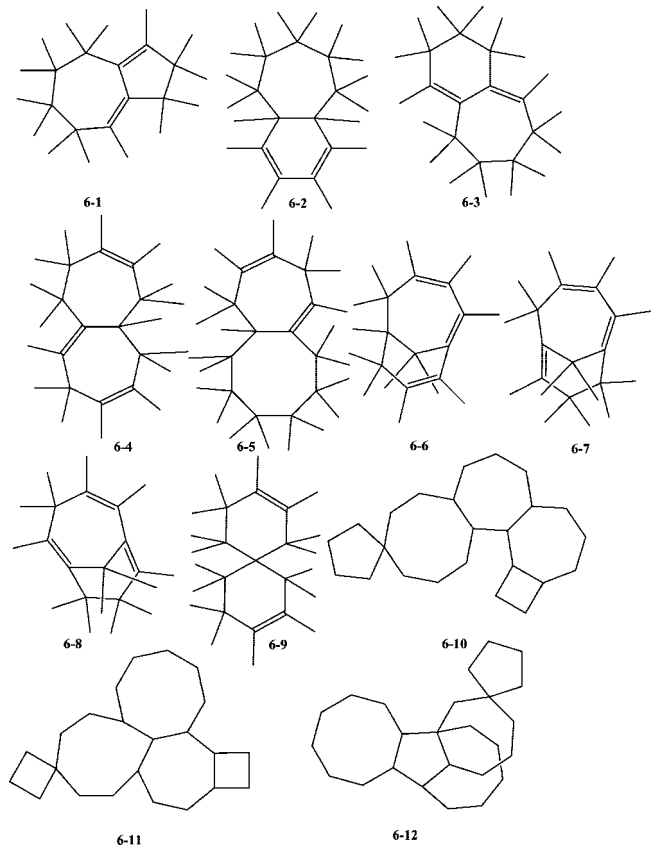

Figure 6. Raw framework hits found using the pharmacophore query from Figure 5b.

shows that the inspection based fit-ranking is **8–9** ∼ **8–2** >> **8–1** > **8–3**. In this case, the most synthetically achievable template appears to be **8–2** since it contains no quaternary carbons and since fewer carbon−carbon bond forming reactions would be required. The superposition of **8–2** with Nutlin-3 (see Figure 9) shows that it is a reasonable starting point for chemistry, or for further iterations of atom type modification and computational validation discussed above, to develop even more refined potential synthetic targets.

For these latter steps, the chemist can be thought of as an intelligent scoring function[23,24] that can select structures possessing desirable physical properties (based on application of medicinal chemistry knowledge) and are achievable synthetic targets (by the employment of synthetic proficiency). The compounds that are selected as synthetic targets may then be checked by a computational chemist to ensure that the modifications introduced during the design process have not excessively distorted the geometry of the template. This design approach makes effective use of computational tools, cheminformatics expertise, and medicinal chemistry know-how for the discovery of these new targeted templates. The final step in this process is the wet laboratory synthetic research and development, which proceeds most efficiently if the chemists that have performed the design are integrally involved in the development of the synthetic protocols for targeting the preparation of the orthogonally protected template core.

DISCUSSION

The type of approach that we report here is meant to facilitate the utilization of a computationally derived small

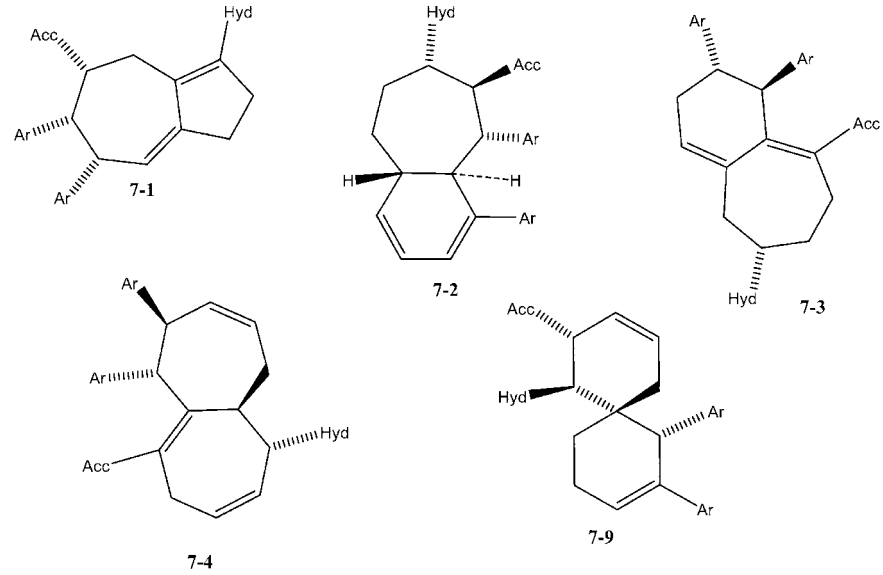

Figure 7. "Triaged" hit frameworks showing stereochemistry and the correctly positioned features from inspection of the pharmacophore from Figure 5a.

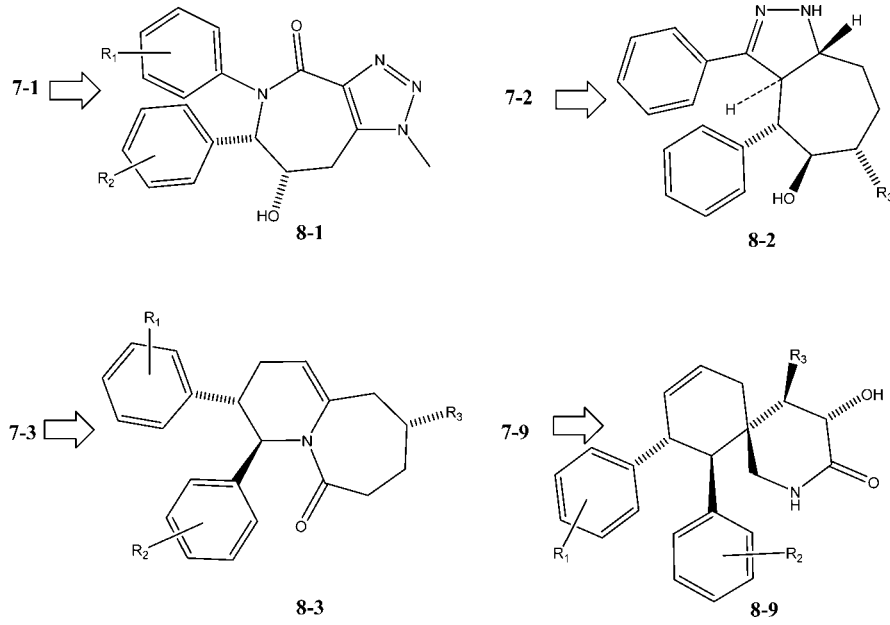

Figure 8. Some of the selected hits and some proposed "final" synthetic targets.

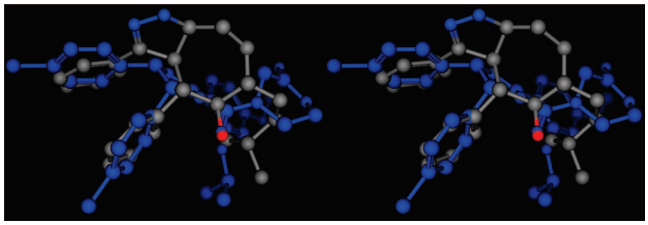

Figure 9. Left−right stereoview of a superposition of **8–2** and Nutlin-3 (Nutlin-3 is shown in blue). All four pharmacophore features were used for the superposition.

molecule design approach by synthetic/medicinal chemists. Recently others have recognized the benefit of chemist-directed computational evolution of template ideas.[23,24] Using this type of approach IJzerman and co-workers have spearheaded the development of a new software tool.[23,24] IJzerman's "Molecular Evoluator" starts from an existing structure or template submitted by the chemist, which are used to "seed" the generation of sets of modified template "suggestions" to assist in the brainstorming of new template ideas. In this case the expertise of the chemist is the primary "scoring function" that is used for selection.

In contrast to this approach, our method uses knowledge about the ligand's known geometric constraints, or the ligand pharmacophore, to guide the selection of bare molecular frameworks that closely match the geometry of the query, as starting points for template design. Our approach is similar in that it uses human expertise to guide the design, selection and refinement of possible new templates. Virtual libraries have recently been described that are conceptually similar to our virtual framework library (VFL) in the context of vector based searching.[25] All of these approaches are complementary.

In our approach, a chemist can use an overlay of the query geometry or pharmacophore features on top of the hit frameworks to select the most "attractive" frameworks, "prune" out unnecessary atoms, modify atom types, and

finally use synthetic insights to design a potential synthetic target. Also, in contrast to the previous virtual framework databases that were developed for the use of CAVEAT vector based searches,[25] our enumeration technique allows for the building of more framework chemistry-space with a larger library and we adorn the frameworks with exocyclic methyl groups. The exocyclic methyl "antenna" groups can "pick up" useful non-ring-constrained feature positions as seen in the examples discussed above. In contrast to other approaches discussed above, we have not developed new software but instead we present here a database enumeration code, applicable scripts, and protocols for their application using existing software tools.[19]

CONCLUSIONS

We present here, for the first time, details of an improved process for our previously reported design paradigm[11] and an extension to the more general application of template design based on ligand derived pharmacophores. The specific steps in this process have been exemplified by both a retrospective design of the previously described template **1**, and other structurally related "virtual templates", and by a proposal for a set of new templates derived from a possible pharmacophore for Nutlin-3,[22] from a database that can exhaustively cover "framework space". The stepwise automated cleanup steps leading to frameworks such as those described above are general and suitable for the discovery of numerous structural solutions that meet the Garland−Dean, pharmacophore geometry, or other template molecular-recognition criteria. Each blank framework can then be elaborated to yield a large number of potential synthetic targets that can be implicitly or explicitly scored "on the fly" by medicinal and synthetic chemists to explore a large amount of high quality virtual template chemistry space. Each elaborated library derived from these templates in turn represents another mushrooming of the available combinatorial space for in vitro screening. The application of this improved and generalized method to other target families should allow for the facilitation of the discovery of other hits (molecular starting points for medicinal chemistry optimization) as well as new small molecule tool compounds (for use in the elucidation of biological or biochemical mechanisms) for other protein families. Progress on the further development of this technique will be reported in due course.

Supporting Information Available: The full code for the generation of the fragment libraries and all scripts described in this manuscript are available free of charge via the Internet at http://pubs.acs.org.

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CI7001928