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Perspective

Definition of Templates within Combinatorial Libraries

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It is common in the field of combinatorial chemistry to differentiate combinatorial libraries into distinct structural classes. In many cases, combinatorial libraries are divided into subsets, and the concept of "templates" or "core structures" has been frequently used in such contexts. The question of where within a combinatorial library one template (structural class) ends and another begins is frequently a difficult one to define precisely. The answer is important both to the commerce of libraries and to the science of combinatorial chemistry. Such a definition provides the means to decide what is new and what is simply an extension of existing libraries. A template or core structure is frequently taken to mean the common or invariant molecular framework of the structure common to a large portion of the library. This template can be further defined as the common covalently bonded collection of atoms to which defined permutations or structural components are attached or bonded. In the following, we attempt to offer some ideas on one method of deciding what is reasonably defined as a template. Our proposal is an attempt to establish the rules for defining what is a template based on a medicinal chemist's knowledge. They can be considered as the rules upon which a computer-based "expert system" would be constructed. These rules attempt to capture molecular shapes, molecular pharmacophores, substituent orientation, and substituent diversity as the elements that serve to differentiate one template from another. It is first necessary to define more fully the common molecular framework and how one can modify it.

Classification of Various Modifications to a Common Framework

There are two common types of chemical variations that should be considered in the context of a template: structural variations and functional variations. A structural variation would result from changes within the template and lead to a new template. A functional variation would result from changes "around" the template and would not be a change in templates. A functional variation concerns a site within the molecule at which substituent diversification is achieved. At such a substituent diversification position, the variation in the derivatization reagents employed does not create a new structural class. Examples of functional variations include an amine site that is derivatized as a set of amides, sulfonamides, and/or ureas. These add diversity to a template but do not alter it sufficiently to create a new template.

Ring systems, which can be mono-, bi-, poly-, or spirocyclic in nature, constitute a frequently encountered class of templates. While noncyclic systems can be templates, and a substantial number have been produced and effectively employed, noncyclic templates will not be addressed in this discussion. We are electing to restrict ourselves to defining rules for cyclic templates and will address noncyclic templates in a subsequent manuscript. We now consider what modifications to a structure could be considered to constitute a move from one template to another, i.e., a structural variation.

Substituent Orientation and Diversity

As outlined above, the mere introduction of different substituents to a ring structure at a given position is normally considered to diversify the same template framework. Structural variations at a given position (e.g., cyclic vs acyclic) do not define a new template, unless this position incorporates a site which is itself substantially diversified. Alternatively stated, introduction of a bifunctional component defines a new structural class only when it is further derivatized. An example of this would include an amine that is diversified via acylation. If acylation includes use of an amino acid, this does not constitute a new template until the amine of the amino acid is itself acylated or otherwise derivatized into multiple products. Herein, the acylated amino acid series of compounds would be a different template from the original acylated amine template. A second example would be a template which included a substituted benzene ring. If the substituents at a given position included a phenyl (e.g., creating a biphenyl unit), this would become a new template only when the phenyl substituent contained a functional group that was further diversified (a carboxylate that is turned into a series of amides).

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Any change on a given template that alters the orientation of one diversity site relative to another within the template is a structural variation and therefore a template change. Changes in the orientation of two sites of diversification within a template are clearly providing different projections (vectors) in three-dimensional space for these substituents, and this seems more than sufficient to consider them different templates. An example of this would be 2,4-diaminopyridine compared to 2,6-diaminopyridine, wherein the amines are each derivatized by acylation or sulfonylation.

Ring Atom Addition, Subtraction, Replacement, or Interchange

In aromatic systems, the nature of the compound is usually significantly altered by atom addition or subtraction. Thus, quinolines are quite distinct from indoles. Accordingly, atom addition or subtraction within the aromatic portion of the ring would constitute a change in the template.

A significant change is induced by the addition or subtraction of a CH_2 group within a nonaromatic (a completely or partially saturated) ring when this alters the orientation of diversity sites with respect to another diversity site or some functionality within the ring. Thus, a 3-substituted-piperidin-2-one is a different template from a 4-substituted-homopiperidin-2-one. The case is much less clear for a 3-substituted-piperidin-2-one compared to a 3-substituted-homopiperidin-2-one. Again, tetrahydroquinolines are close in character to dihydroindoles and are not clearly a new template, provided the diversity sites lie within the aromatic portion of the molecules and their orientation relative to the heterocyclic nitrogen does not change. If the substitution patterns on the two systems are different in either the saturated or the unsaturated portion of the structure, then it is reasonable to classify the two as different templates. This would classify a 4-substituted-dihydroindole as distinct from a 7-substituted-tetrahydroquinoline but not from a 5-substituted-tetrahydroquinoline.

Replacement of one ring atom for another can be a matter of degree. Replacement of an oxygen for a sulfur (or vice versa) does not seem sufficient to call a change in template. The interchange of an aromatic or aliphatic carbon for nitrogen brings a substantial modification of properties and will constitute a change in templates, as will a change from oxygen or sulfur to nitrogen. For example, naphthalene and cyclohexane are distinct from quinoline and piperidine, respectively. Multiple replacements will clearly make it reasonable to distinguish two templates as this will alter the molecular pharmacophore (electron densities over the molecular surfaces, dipole moments, hydrogen bonding patterns) even if the molecular shape is unchanged. Examples of this are quinoline compared to 1,2,4-benzotriazine or 1,4-dioxane versus 1,4-dithiane.

Within a saturated ring system, changes in hybridization of a ring atom will result in a change in template. The change from piperidine to 1,2,3,6-tetrahydropyridine is an example of a hybridization change that subtly changes the template. In this example, the change in hybridization has altered the ring conformation which will change the three-dimensional projections of the diversity substituents. The introduction of a carbonyl into a heterocyclic ring affects the conformation and electronic properties of the system as dramatically as addition or subtraction of heteroatoms from a ring. Piperidine compared to 2-piperidinone is a valid distinction between templates. In addition, we suggest that the change obtained by moving from quinoline to 2-quinolinone or 4-quinolinone or a similar change in another ring system is a change in the template. The presence of the carbonyl moiety imparts significant property differences to these ring systems. In this same line of reasoning, *N*-methyl-2-pyridinone is distinct from 2-methoxypyridine and pyridine, which are not different. We are aware that this whole matter is complicated by the phenomenon of tautomerism. Whereas 2-pyridinone exists mainly as the amide form in polar solvents and in the crystalline state (rather than 2-hydroxypyridine which dominates in nonpolar media), the position of the tautomeric equilibrium can be altered drastically by the introduction of substituents.

Changes in Ring Fusion

The fusion of a further ring to the original template would be considered as a move to a new template, if this alters the properties of the original ring. The situation is much less definitive if this fusion does not change the overall properties. Fusion of a benzo-moiety to a piperidine to yield a tetrahydroquinoline is a move to a new template, but a conversion from pyridine to quinoline may not be a template change. The case for creating a new template via fusion of a saturated carbocyclic unit to an existing ring is quite weak. Thus the difference between pyrrolidine and octahydroindole is not significant. These arguments for no change in template are done away with if the fusion disrupts the substitution pattern of the original template or if a new diversity site is added and employed in the portion fused to the original template. In such cases, regardless of the fusion, the templates are different.

Spiro Ring Attachment

The case for considering a spiro ring attachment to an existing template as a change in template can be weak. This is borne out if the added spiro ring is simply a cyclization of two geminal substituents, such as 1,1-dimethyl substituents being converted to a 1,1-spirocyclopropyl moiety. As discussed above for introduction of substituents, if the spiro ring introduced possesses a heteroatom or position that is further derivatized there is a change in templates.

Definition of the Principal Template within a Molecule

Usually, the principal template of a given library is quite evident. It is, however, necessary to define rules for the cases where two or more templates may exist within the same compound in a library. If a single structure within a library has two or more arrays of rings, then we propose that the primary template(s) should be defined following a set of rules that assign values to various molecular features. The product of these values allows (subjectively) each potential template(s) in such a molecule to be ranked, and the principal template identified.

For each of the potential templates the following values should be assigned:

(a) for each heterocyclic ring, a value of 5;

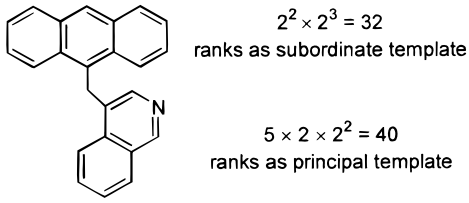
(b) for each ring-fusion bond, a value of 2;

(c) for each ring which contains contiguous cyclic conjugation throughout that ring, a value of 2;

(d) for spiro fusions or for carbocyclic rings possessing a substituent diversity position, a value of 2 (if no diversity position is found, a value of 0).

An example of how this would work is given by Scheme 1.

Scheme 1



Procedure for Deciding Whether Two Compounds Belong to the Same Template or Not

Above, we have addressed in a qualitative fashion the structural features that differentiate templates from each other. Clearly, the question is a matter of degree and many borderline cases do exist. We now propose a set of rules that attempt to quantify the difference between structures.

Comparison of Primary Cores

We now proceed to compare the primary cores for two compounds. The two cores should be overlapped so maximum similarity can be seen. Then the divergences should be counted as follows.

A. Divergences Consisting of Additional Fused Rings. The values would be as follows:

(a) for each fused ring, a value of 2;

(b) for each fused heterocyclic ring, an additional value of 2;

(c) for each fused ring with complete cyclic conjugation (i.e., no sp^3 hybridized carbon or nitrogen atom), an additional value of 2.

B. Divergences within Individual Rings. The following values would be applied:

(a) for changing the numbers for heteroatoms, a value of 4 (per heteroatom);

(b) for change in the nature of a heteroatoms, a value of 3 (per heteroatom), except oxygen for sulfur or sulfur for oxygen, then a value of 1;

(c) for change in the orientation of the heteroatom, a value of 2 (per change);

(d) for change in ring size, a value of 2 (per atom);

(e) for change in the ring conjugation, a value of 2;

(f) for change in hybridization within a ring, a value of 3.

C. Modifications in the Way in Which Rings Are Connected by Ring Fusion. The following values will be applied for change in the orientation of the ring fusion or connection between two rings:

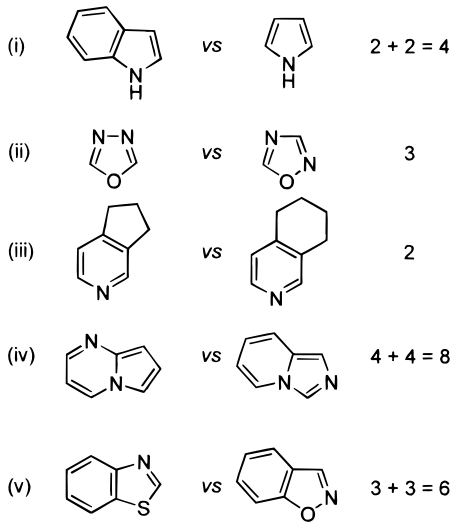
(a) when both rings are heterocyclic, a value of 4;

(b) when one ring is heterocyclic, a value of 3;

(c) when both rings are completely cyclically conjugated, a value of 2;

(d) when both rings are carbocyclic, a value of 1.5.

Scheme 2



Examples of the Comparison of Primary Cores

Examples of the application of the above rules are given for pairs of cores as follows (Scheme 2):

(i) one fused ring (carbocyclic) plus completely conjugated ring, each a value of 2 (Scheme 2, i);

(ii) heteroatom orientation change, a value of 3 (Scheme 2, ii);

(iii) change in the size of a ring by one atom, a value of 2 (Scheme 2, iii);

(iv) change in the number of heteroatoms in a ring—two rings affected, so two values each of 4 (Scheme 2, iv);

(v) change in the orientation of the heteroatom (3) plus change in the nature of a heteroatom (3) (Scheme 2, v).

To decide whether two compounds form part of the same library, the values for their core divergences given in rules A−C above are summed. If the difference in the sums is sufficiently large, then the templates are considered to be different; if not, then the two structures are to be considered to lie within the same template. We propose that for two compounds to be from different templates the difference in the sums of the values listed in rules A−C needs to be at least 5. However, for various specific purposes, a different cutoff value could be employed for the differential needed to distinguish between two templates.

Application of these Suggestions

As mentioned above, application of these rules requires an agreed cutoff limit. If the limit were set as 5, this would

mean that, of the examples above, the first three pairs would in each case be considered to belong to the same libraries. However, pairs (iv) and (v) would in each case be considered to belong to different libraries. Obviously the cutoff limit could be set at any number depending on the situation. Once set, this limit would then allow a rapid decision to be made as to whether or not two structures belong to a same or a different template in any particular case.

Considering another instance for use of these rules, a situation could exist where there are several potential structural variations to be considered and one wishes to define how many templates exist. One can have four structures (A, B, C, and D) which by the above rules, and using an agreed cutoff limit, fall into the following categories. The pair A and B is in the same template as are pairs B and C and C and D. However, A is not within the same template as C or D, and B is not within the template of D. In order to clarify such a position, we believe one must define the "characteristic template" from which all comparisons originate. For example, if B is designated the characteristic template, then A, B, and C would be defined as being within the same template but D would be in a different template. The rules thus allow one to define the starting template as needed and then to define the templates that are related and those that are not.

We view these rules as a first attempt at codifying the definition of what a template is relative to another possible template. We have attempted to apply the medicinal chemistry concepts of molecular shapes, pharmacophores structures, substituent orientation, and substituent diversity as the foundation for rules for differentiating one template from another. We welcome comments and any suggestions that can make these rules more rigorous and less ambiguous or that point out instances where we have not applied the rule appropriately. We are quite aware that there remain many ambiguities and doubtful points and that we have yet to address noncyclic templates.

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