Article

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Functional Group Transformation: An Efficacy-Enhancing Approach in Combinatorial Chemistry

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In combinatorial chemistry, the time-consuming step is optimizing the reaction conditions rather than the actual preparation of the library. We propose a new combinatorial strategy, "functional group transformation", which permits construction of new libraries while making use of much of the chemistry developed for earlier ones. We use some of our current methods for determining chemical diversity to demonstrate that the added diversity of such a transformed library can be as large as that of a library based on totally new chemistry.

Introduction

In recent years, the search for new lead molecules within pharmaceutical research has been radically altered by the introduction of combinatorial technologies. Combinatorial chemistry is generally understood to mean the simultaneous preparation, either in mixtures or as single compounds, of all combinations (called libraries) of certain collections of reagents, or building blocks.

Two lines of methodological support have been developed to maximize the output of these combinatorial efforts. On one hand, the number of different products theoretically accessible by combining all commercially available building blocks of certain types is so overwhelming that a selection has to be made. Under the assumption, basic to medicinal chemistry, that similar compounds will exhibit similar biological activities,[1] methods have been developed that will detect such similarities in the set of compounds theoretically accessible from all combinations of available building blocks (the virtual library). Removal of those compounds that are too close to other members of the library leaves a set which covers as many of the properties present in the virtual library as possible but uses only a small subset of its members. On the other hand, to make as many chemical series accessible as possible, considerable effort has been directed to make existing chemical transformations applicable to a combinatorial setting.[2] Although many reaction types can now be applied with success, it is a general experience that the precise reaction conditions for a certain transformation can differ appreciably from case to case and that a substantial amount of optimization is required before a library can be produced. Indeed, while the actual synthesis of a combinatorial library typically takes days or, at most, weeks, the optimization of the various reaction steps often takes months.

Methods to improve the effectivity of invested time have been described earlier. The concept "libraries from libraries"[3] was introduced to capitalize on the initial effort in preparing a mixture-based library (see Figure 1A). However, most of the examples given are based on a multiple conversion of several identical functionalities (e.g., N-permethylation or reduction of amide bonds). A similar principle can be applied by transforming a single functional group as demonstrated by the Chiron group[4] and has been termed "postsynthesis modification" (Figure 1B). This basic strategy involves introduction of a functional group which is used as the cornerstone for elaboration in a variety of heterocyclic ring systems. Both transformation methods result in compounds with alternative properties.

Our approach is an extension of the Chiron approach. After having established the optimized reaction conditions for a given "virtual library", this first-generation library is brought in production. The benzodiazepine library published by the group of Ellman[5] (see Figure 2A) may serve as an example. A second-generation library is prepared by making use of most of the same building blocks and chemistry already optimized for the first one. However, in one position a functional group is introduced that is suitable for chemical transformation and which should give access to a new region in chemical diversity space. The time spent on the preparation of this second library should be a small fraction of that of the first library. Only the introduction of the functional group and its transformation have to be optimized. In this paper exercise we introduce on the R_1 position of the benzodiazepine an aldehyde moiety, which can be converted to nitrones. By means of a 1,3-dipolar cycloaddition with alkenes or alkynes, isoxazolidine and isoxazoline systems, respectively, can be obtained (see Figure 2B). The functional group transformation aldehyde−nitrone−isoxazolidine on solid support has been demonstrated earlier.[6]

In this paper we will study whether the concept of "functional group transformation" is a valid one with respect to diversity. We will compare the original benzodiazepine library as described by Ellman with the proposed functional group transformed benzodiazepine library.

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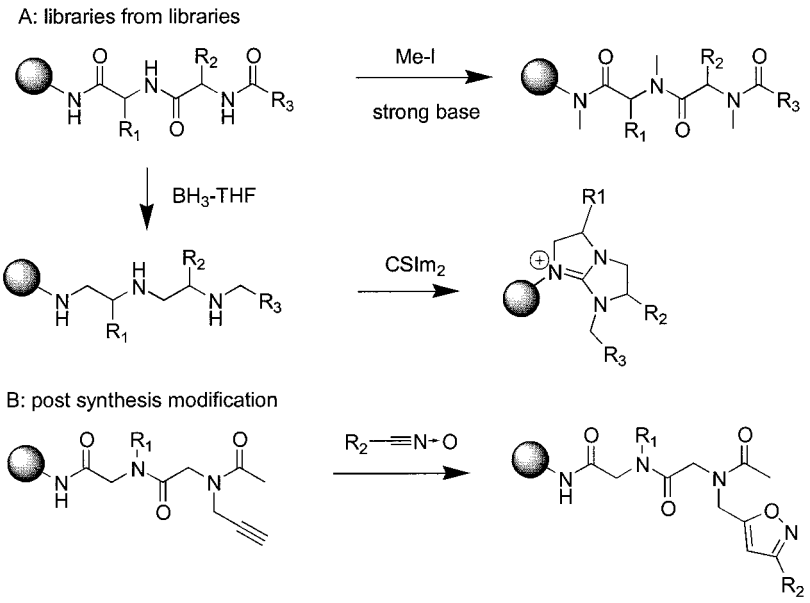


Figure 1. Various methods for expanding on existing libraries.

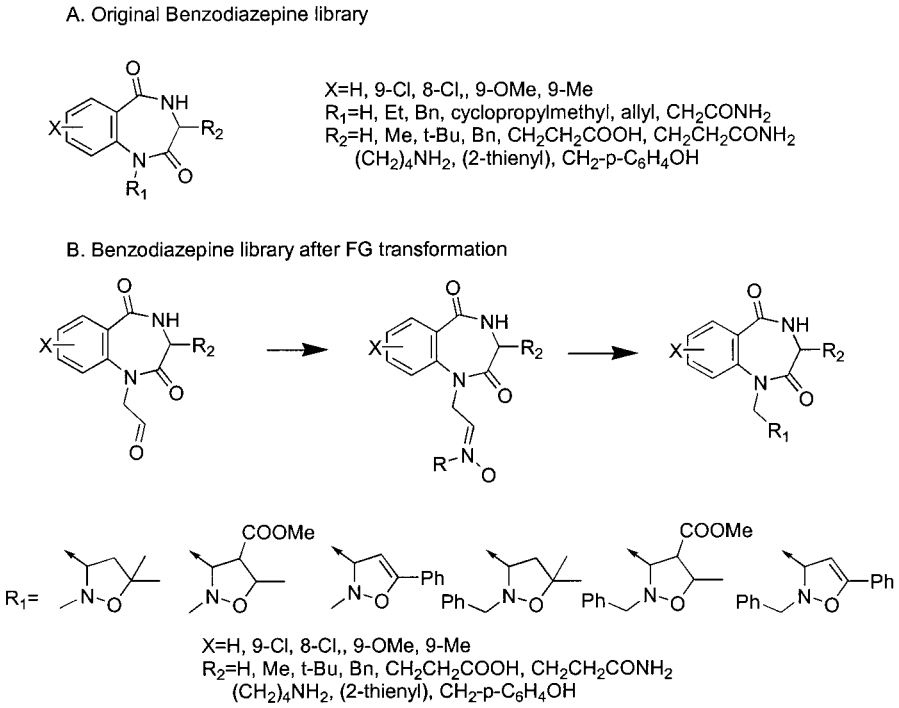


Figure 2. Functional group transformation approach.

Furthermore, we will use diversity methods to assess whether such a transformed library can explore as much new chemical diversity as would preparation of a library representing an entirely new chemical class. Arbitrarily, we chose the β-lactam library (see Figure 3) published by Ruhland[7] as an example of a library derived from a different chemical series.

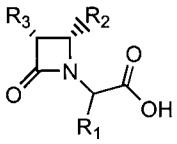
Methods and Results

To test the effect of functional group transformation, we compared the original library of 270 benzodiazepines with its transformed analogue library and with a completely different chemical series, viz., a library of 300 β-lactams.

The libraries described above were produced by drawing the various building blocks within the ChemDiverse module of Chem-X;[8] the program thereupon automatically assembles all the possible combinations. The SD files for the virtual library can then be written out as input for the various analysis programs. A new 3D database was created from the SD file using the Corina program.[9]

The various analysis programs start with converting the structures to some sort of numerical descriptor. This descriptor, whether a set of numbers or a binary string, can be viewed upon as a coordinate in multidimensional space. Thus, the distance between any pair of molecules can be calculated, and the closest ones are assumed to have very similar properties and hence a high probability of a similar activity.

Clustering. The first descriptor type employed is 2D-substructure fingerprints.[10] This descriptor type has been



R_1 = Me, $(CH_2)_4NH_2$, CH_2COOH, CHOHMe, i-Pr
R_2 = Ph, $CH{=}CPh_2$, cyclohexyl, 2-furyl, 2-thienyl, 2-pyridinyl
R_3 = OPh, $CH{=}CH_2$, $C(Me){=}CH_2$,

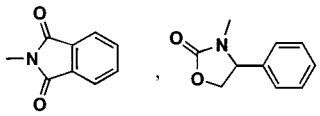


Figure 3. β-Lactam library.

found effective in separating active and inactive compounds,[11] or extracting representative sets of activities from general compound collections.[12] In our implementation of the BCI software,[13] we employ a nonhashed fingerprint of 2465 bits, describing molecules by the presence or absence of a set of (user-defined) substructure fragments; compounds having many fragments in common (and hence, likely to have a similar structure) are then grouped together using the Ward algorithm. As the common core (scaffold) of a combinatorial library contributes a large number of fragments, this method is expected to be somewhat skewed to interlibrary dissimilarity. This is born out in practice: when a combination of the benzodiazepine and β-lactam libraries was clustered, no mixed clusters were produced. This effect was also observed when comparing the transformed with the original benzodiazepine library: when sets containing both libraries were clustered together, no clusters containing members from both starting sets were formed. It is clear that substructure-based clustering is not the method of choice to select between combinatorial libraries. For clustering based on other characteristics, however, see below.

Pharmacophore Comparisons. Pharmacophores are the elements within molecules that are required for direct interaction(s) with the receptor/enzyme, etc. In the standard implementation within the Chem-X programs, these are hydrogen donors/acceptors, (hetero)aromatic rings, and quaternizable nitrogen atoms. Two methods to assess pharmacophore content are implemented. The first one looks at all 10 possible combinations of two pharmacophore points from the four possibilities mentioned above; for each of these combinations, 32 distance bins are provided, making for a pharmacophore fingerprint of 320 bits. To determine these fingerprints, all conformations for every molecule are generated (using a protocol which, for instance, rotates single bonds in 60° increments), and their pharmacophores combined into a single pharmacophore fingerprint for every individual molecule. The resulting distance-based pharmacophore fingerprints can be compared using clustering. As with the clustering based on 2D substructure fingerprints described above, no overlap was found either between the two benzodiazepine libraries or between the original benzodiazepines and the β-lactams. Again, the common substructures within the three libraries generate a sufficient number of specific pharmacophore bits to completely separate the libraries. This is in line with a previous study[12] which indicated the near-equivalence of substructure- and pharmacophore-based fingerprints.

Table 1. Number of Pharmacophores in Each Individual Library[a]

	no. of compounds	no. of pharmaco-phores	avg per compound
original benzodiazepine	270	13873	51.38
transformed benzodiazepine	270	43500	161.11
β-lactam	300	77022	256.74

[a] Note that in reality compounds will have more pharmacophores than the average shown here; however, many of these will be present in more than one (or, in case of scaffold pharmacophores, in all) compound(s) in a library.

Table 2. Numbers of Pharmacophores Gained by Adding New Library (top of column) to Existing Library (left of row)

new library → existing library ↓	original benzo-diazepine	transformed benzo-diazepine	β-lactam
original benzodiazepine		34506	67005
transformed benzodiazepine	4879		49905
β-lactam	3825	16383	

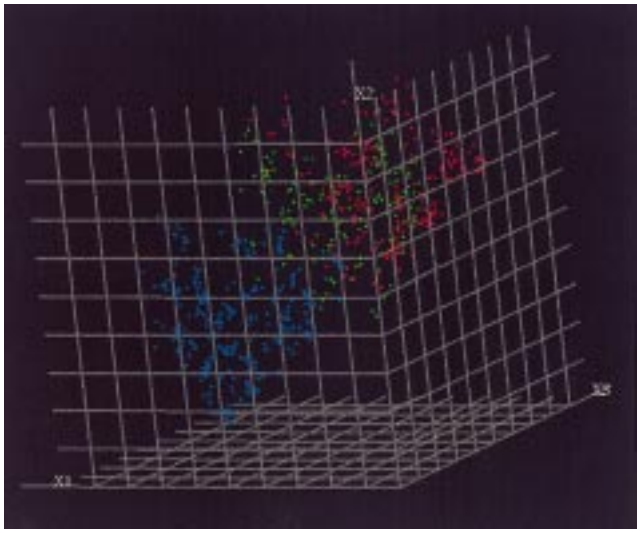


Figure 4. First three principal components of whole-molecule properties of the following libraries: original benzodiazepines (red), modified benzodiazepines (blue), and β-lactams (green). The overlap between the original benzodiazepines and the β-lactams in property space is obvious, while the two benzodiazepine libraries are more or less completely separated.

For a more complete picture of receptor−ligand interaction, three-point pharmacophores are employed. Triangles are made up of combinations of pharmacophores, again with 32 bins for each of the sides (obviously, some of the 32 768 theoretically possible triangular geometries cannot exist in reality because the sum of the two smaller sides is less than the length of the largest side). In this method, seven pharmacophore types are employed (the above four plus acid, base, and lipophilic center); only 44 out of the 84 possible combinations are actually used, while less suitable combinations such as three acid groups are omitted. It is impractical to store the resulting fingerprint of over 650 000 bits for every single molecule (although it can be done, e.g., by reducing the size of the distance bins[14]); therefore, it is

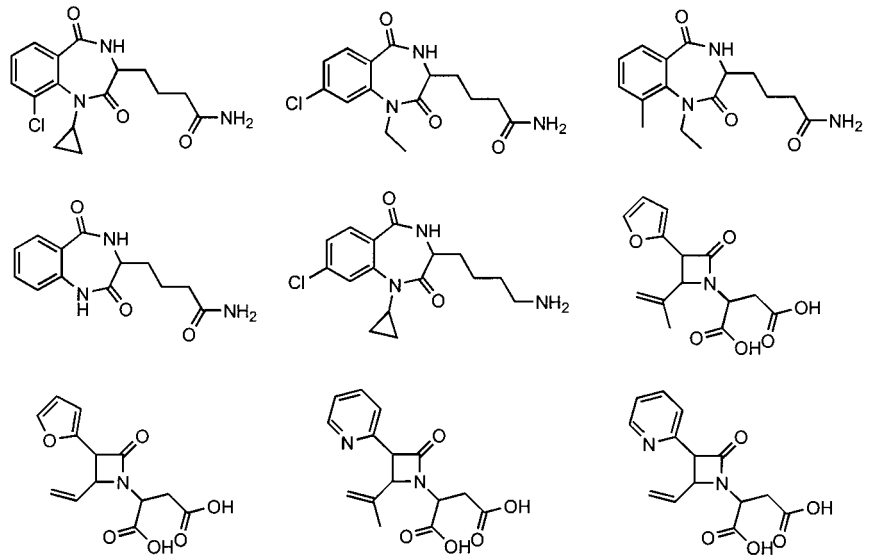


Figure 5. Example of compounds that are close together in property space.

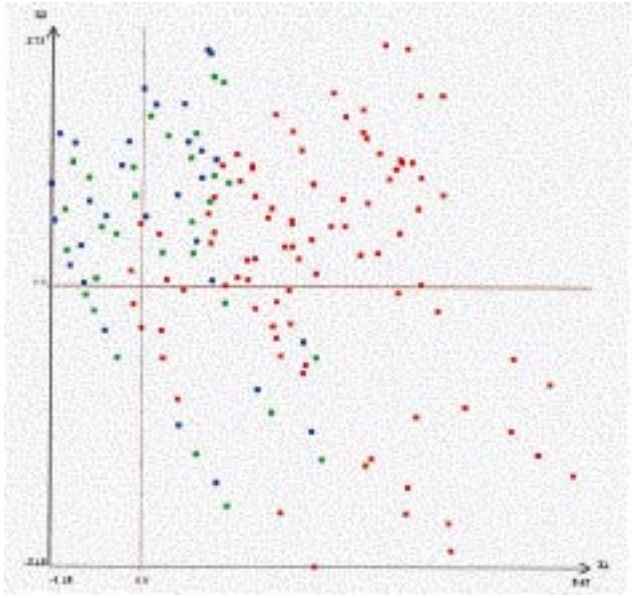


Figure 6. First two principal components for the β-lactam library: (blue) R_3 = vinyl; (green) R_3 = isopropenyl; (red) remaining lactams.

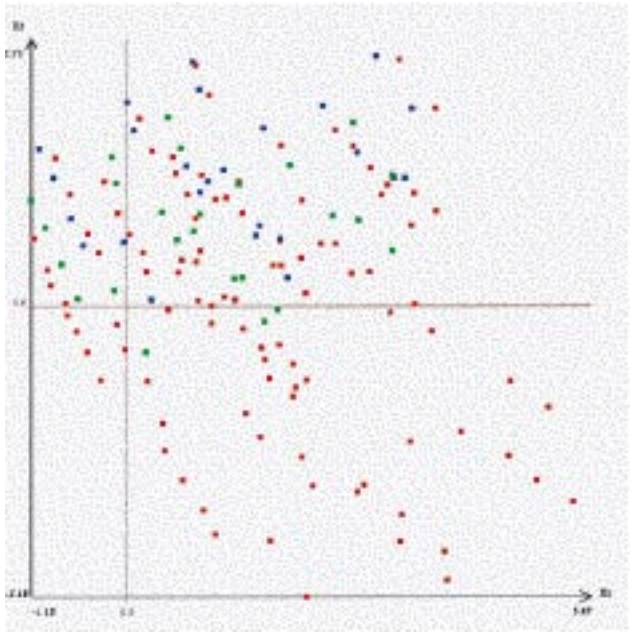


Figure 7. First two principal components for the β-lactam library: (blue) R_2 = furyl; (green) R_2 = thienyl; (red) remaining lactams.

calculated for an entire library, again registering all geometries for all three-pharmacophore element combinations for all conformations for all the molecules in the library. The pharmacophore keys for different libraries can then be compared.

From Table 1, it becomes clear that the original benzodiazepine library as suggested in the literature does not cover a great number of pharmacophores, probably because of the limited variation in the X-substituent and because many of the R_1 and R_2 substituents are alkyl groups, whose lipophilic contributions are hard to pinpoint. The library of modified benzodiazepines clearly spans a much broader range of pharmacophores. The β-lactam library, finally, has the highest pharmacophore content overall.

Table 2 indicates the number of new pharmacophores added to one library when a second library is introduced. This is not simply the difference of the number of pharmacophores listed in Table 1 because the various libraries have a number of pharmacophores in common. Thus, both a library of β-lactams and one of modified benzodiazepines add at least 2.5 times the original number of pharmacophores to the original benzodiazepine library. By this measure, the β-lactam library would seem the better investment, but bearing in mind the likely effort required to develop new chemistry, this might well be offset by the fact that much of the synthetic route to the modified benzodiazepines has already been explored. If anything, this analysis indicates that, from the pharmacophore point of view, it is probably better to go for the modified benzodiazepines directly.

One might expect that, because of their common scaffold, the two benzodiazepine libraries share the larger number of their pharmacophores. What is therefore surprising is the observation that in fact it is the library of β-lactams that has the greater pharmacophore overlap with the original benzodiazepine library.

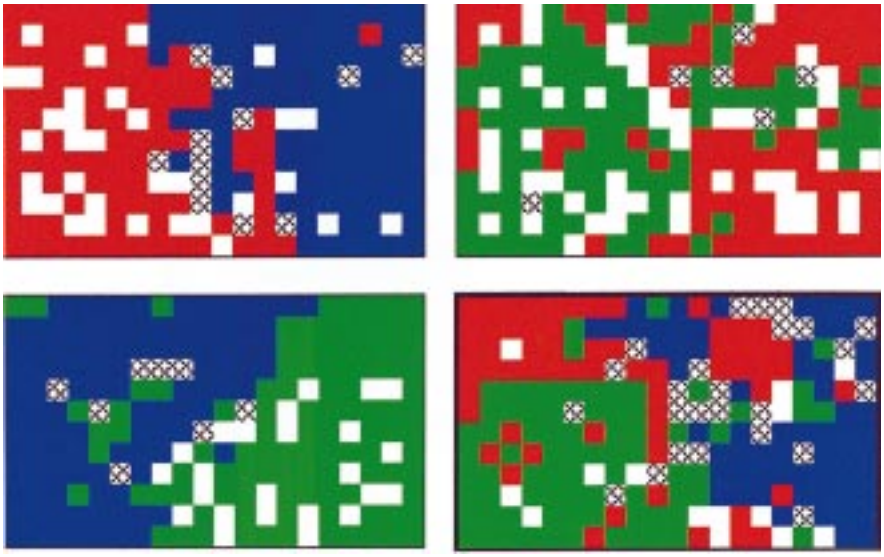


Figure 8. Autocorrelation vectors for original and modified benzodiazepines (top left panel), for original benzodiazepines and β-lactams (top right panel), for modified benzodiazepines and β-lactams (bottom left panel), and for all three libraries (bottom right panel), all projected on a 12 × 20 Kohonen network. Red: cells occupied exclusively by original benzodiazepines. Blue: cells occupied exclusively by modified benzodiazepines. Green: cells occupied exclusively by β-lactams. Hatched cells are occupied by members from more than one library; white cells are empty. In all cases, there is near-complete separation; however, since compounds occupying adjacent cells are still similar, the number of "islands" (cells of one color surrounded by cells of a different color) in the two uppermost panels suggests a larger overlap between the original benzodiazepines and the β-lactams than between the two benzodiazepine libraries.

Although the same pharmacophore may not be exactly equivalent when it is present in two different chemical surroundings, comparing pharmacophore keys is a useful tool to assess complementarity (or otherwise) of combinatorial libraries.

Whole-Molecule Properties. Whereas the methods mentioned before rely on regarding molecules as the sum of fragment properties, the need was also felt to have a method available where molecules are considered as a whole. This method has been developed in-house and briefly works as follows:[15] for every molecule, a number of properties considered to be related to biological activity, such as molecular weight, flexibility, log *P*, and percent hydrophilic surface, are computed. These properties are subjected to principal component analysis; the first 10 principal components explain more than 85% of observed variance, and the first two explain nearly 60%. By inspection of the composition of the principal components, it can be seen that PC1 is mostly connected with size-related descriptors, PC2 mostly with lipophilicity (such as log *P* and donor/acceptor characteristics), and PC3 with shape indicators. These are exactly some of the properties intuitively connected with biological activity. Plotting these principal components either pairwise or with three at a time will give a good impression of how well a certain compound collection covers property space and will also allow comparison of sets with one another.

When the above procedure is carried out for the three libraries, it can be seen (Figure 4) that the modified benzodiazepines cover a set of properties that is almost nonoverlapping with the original benzodiazepines. In contrast, the β-lactams cover the same area in property space as the original benzodiazepine library. The same result is found when other combinations of principal components are inspected. This conclusion is largely in line with the overlap observed in pharmacophore content (vide supra).

In addition, the (principal components of) descriptors can also be used as input for the BCI clustering program, after normalization of the data by standard deviation. In this case, compounds with similar properties are grouped together, rather than those with similar structures.

In this case, about half the total number of compounds from the β-lactam and the original benzodiazepine libraries end up in mixed clusters (for example, see Figure 5); almost all of the modified benzodiazepines, however, end up in clusters made up exclusively of compounds from this one library.

Finally, of course, descriptors (like the other diversity measures) can be used to gauge the design of the library. Thus, taking the β-lactam library as an example, Figures 6 and 7 nicely show that, between the compound pairs with vinyl and isopropenyl or with the furyl and thienyl substituents, there is no great difference. In fact, these sets each give pairwise the same pattern, the one being slightly offset from the other. In addition, inspection of the pharmacophore keys indicates that these overlap almost completely between the furyl- and thienyl-substituted series, again indicating the redundancy within this library. Thus, the overall diversity coverage of this particular library might have benefited from design with a greater attention to product diversity, which could have lead to a different set of building blocks.

Kohonen Mapping. A receptor and a corresponding ligand recognize each other at their molecular surfaces. The strength of the binding is influenced positively by a good fit of the surfaces and a high complementarity of properties such as electrostatic or lipophilic potential on these surfaces. Therefore, a descriptor that takes into account these factors should be useful for similarity analysis of libraries.

Spatial autocorrelation functions can be used to describe the distribution of the electrostatic potential on molecular surfaces.[16] First, a set of randomly distributed points on the

Table 3. Some Examples of Functional Group Transformation Performed on Solid Support

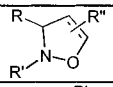
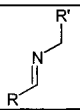
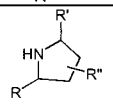
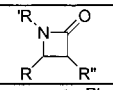
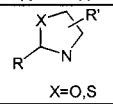
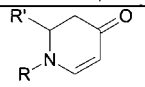
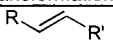
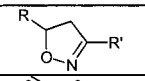
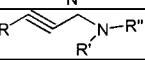
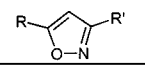
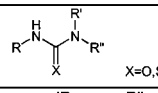
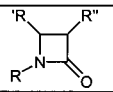
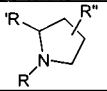
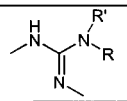
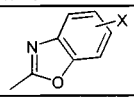
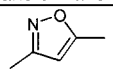
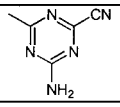
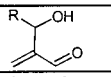
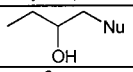
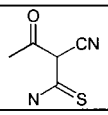
aldehydes			
functional group	**intermediate**	**transformation**	**literature**
			6
	-		20-26
			27
			28-31
			7, 32
	-	 X=O,S	33
			34
alcohols			
functional group	**intermediate**	**transformation**	**literature**
CH_2OH	CH_2X (X=Cl, Br, I, OMs)	CH_2-NHR	25, 35-39
	-	CH_2-O-R	26, 36, 40
alkenes/alkynes			
functional group	**intermediate**	**transformation**	**literature**
		aldehyde functional group transformations	41, 42
		alcohol functional group transformations	42
		carboxylic acid functional group transformations	42
	-		metathesis:43, 44 Heck:45
		epoxide functional group transformations	46-48
		alcohol functional group transformations	49
			50, 51
	-		52
	-		4, 53
amines			
functional group	**intermediate**	**transformation**	**literature**
$R\text{-}NH_2$	-	 X=O,S,NH	urea:54 thiourea:54d guanidine:55
			7, 32
			27-31
	-	$R\text{-}NH\text{-}SO_2R'$	45b, 56

Table 3 (Continued)

azides			
functional group	**intermediate**	**transformation**	**literature**
N_3	-N=P / -N=C=N-		55b
	NH_2	amine functional group transformations	57-59
carboxylic acids/esters			
functional group	**intermediate**	**transformation**	**literature**
-COOH	-		60
	$COCN_2$	CH_2CO-	61
COOEt	-	COR	62
nitriles			
functional group	**intermediate**	**transformation**	**literature**
CN	CH_2NH_2	amine functional group transformations	63
	-		64
	-		65
nitro			
functional group	**intermediate**	**transformation**	**literature**
CH_2-NO_2			66
miscellaneous			
functional group	**intermediate**	**transformation**	**literature**
	-		67
	-		48
			68

molecular surface has to be generated in order to determine the autocorrelation descriptor. Then, all distances between the surface points are calculated and sorted into predefined intervals [d_l, d_u]. Finally, the spatial autocorrelation coefficient $A(d_l, d_u)$ of the molecular electrostatic potential (MEP) is calculated by applying the following formula

$$A(d_l, d_u) = {}^1/_L \sum_{ij} p_i p_j \qquad d_l < d_{ij} < d_u$$

where p_i and p_j are the electrostatic potential values at points i and j, respectively, d_{ij} is the distance between the points i and j, and L is the total number of distances in the interval [d_l, d_u]. The autocorrelation coefficient represents a measure whether the MEPs at points that are between d_l and d_u apart from each other are correlated. For a series of distance intervals with different upper and lower bounds, d_u and d_l, a vector of autocorrelation coefficients is obtained that describes the distribution of the MEP on the molecular surface.

The similarity of compounds that are described by autocorrelation vectors can be visualized with Kohonen neural networks or Kohonen maps. Such a map consists of an rectangular arrangement of neurons. In a training procedure, each structure is assigned to a neuron on the basis of its

autocorrelation vector so that similar compounds are mapped into the same neuron and molecules that are slightly more different in adjacent neurons. Ideally, different parts of the grid end up being occupied by different classes of molecules. This method has been shown[17] to be quite successful in separating molecules according to activity.

Some examples are given in Figure 8. The various libraries are color-coded, whereas cells that are occupied by members of more than one library are hatched. Broadly speaking, the libraries examined occupy separated areas (which indicates that they are different with regard to the charge characteristics of the surface of the molecules contained in them) with only limited overlap. There is no overlap at all between when (original) benzodiazepines and β-lactams are compared, but the overlap between the original and transformed benzodiazepines is also only marginal.

Discussion

In the paper chemistry exercise described herein we demonstrated the potential of functional group transformations as an efficacy-enhancing approach in combinatorial chemistry and that as much new chemical diversity can potentially be generated with a transformed library as with an entirely new chemical series. Over the past five years, solid-phase organic synthesis has attracted substantial attention both from industry and from academia. This resulted into a fair collection of chemical transformations performed on solid support which can be applied in the concept of functional group transformation. In Table 3 some examples are listed. All of these chemistries have been used in practice, and all of them are amenable to the concept of functional group transformation. Of course, there is no guarantee that the additional diversity generated by this approach will, for every functional group transformation listed in Table 3, be as large as the example presented in this paper.[18]

One of the dangers of this concept is that huge molecules can easily be generated (two scaffolds attached to each other with several side chains) which exceed the proposed criteria for molecular weight of not more than 500 (Lipinski's "rule of five"[19]). However, for hit finding libraries the "rule of five" should be not used as an absolute criterion. Besides, the weight contribution of the R groups can be used as an additional criterion for building block selection to keep the overall molecular weight within the desired boundaries.

Conclusions

A number of methods are available to examine overlap between collections of molecules including combinatorial libraries. There is no single method which will give the definitive answer; however, when the methods are used in conjunction, a balanced view can be obtained.

Thus, we see that libraries overlap to some extent, but it is not necessarily the case that libraries based on the same scaffold (but with different forms of substituents, i.e., transformed libraries) are more similar than two libraries based on different scaffolds. Therefore, the strategy of preparing transformed libraries can lead to molecules probing new areas of chemical diversity space while hopefully incorporating previously explored chemistry, thus making the process of preparing combinatorial libraries more efficient. On the other hand, overlap in just one or two aspects while the remaining ones are suitably different need not be a reason not to prepare a library: similar pharmacophores expressed by molecules with different structures, or similar pharmacophores expressed by molecules with a different range of properties, may still add considerably to the available diversity.

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