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# Effectiveness of retrieval in similarity searches of chemical databases: A review of performance measures

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*This article reviews measures for evaluating the effectiveness of similarity searches in chemical databases, drawing principally upon the many measures that have been described previously for evaluating the performance of text search engines. The use of the various measures is exemplified by fragment-based 2D similarity searches on several databases for which both structural and bioactivity data are available. It is concluded that the cumulative recall and G-H score measures are the most useful of those tested.* © *2000 by Elsevier Science Inc.*

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## INTRODUCTION

The performance of a database retrieval system can be evaluated from two principal viewpoints: the *efficiency* of retrieval is based on the resources, such as computer time and memory, that are required for a search; whereas the *effectiveness* of retrieval is based on the extent to which a search has successfully met a user's information need, as described by the query that has been submitted to the retrieval system. This article discusses criteria for measuring the effectiveness of a chemical similarity search,[1] which involves calculating the similarity of a user-defined target structure with each of the molecules in a database using some quantitative measure of intermolecular structural similarity.[2,3] The resulting similarities are sorted so that the database molecules are ranked in decreasing order of similarity with the target structure (or increasing order of distance from the target structure if a coefficient such as the Euclidean distance is used). A cut-off may be applied to retrieve some fixed number of the top-ranked database structures, the nearest neighbors, or to retrieve all molecules with a similarity greater than (or a distance less than) a threshold value. It is known that structurally similar molecules tend to have the same properties,[2,4] which implies that the nearest neighbors of a target structure with some particular biological activity will be expected to exhibit that activity. Accordingly, the effectiveness of a similarity search for a bioactive target structure can be determined by the extent to which further molecules with that activity occur towards the top of the ranking.

In this article, we discuss several ways in which bioactivity data can be used to measure search effectiveness. The article seeks to provide a tutorial overview of the performance measures that are currently available and thus to alert researchers in the fields of molecular similarity and molecular diversity of the need to use standard methods of experimental reporting to facilitate comparison of different computational procedures. Many of the measures that we consider are based on those that have been developed for quantifying the performance of text-based information retrieval systems,[5–7] and the next section provides a brief introduction to performance evaluation in information retrieval. We then exemplify the use of these measures for evaluating the performance of chemical similarity searches, and the article concludes with a summary of our major findings.

## EFFECTIVENESS OF SEARCHING IN INFORMATION RETRIEVAL SYSTEMS

There is an extensive literature associated with the measurement of retrieval effectiveness in information retrieval systems.[8–11] However, nearly all of these measures can be described in terms of the 2 × 2 contingency table shown in Table 1, where it is assumed that a search has been carried out resulting in the retrieval of $n$ documents (or molecules in the case of a chemical database system): this could either be the $n$ nearest neighbors from a ranking or the $n$ documents that satisfy the logical constraints associated with a Boolean query. Assume that these $n$ documents include $a$ of the $A$ relevant documents in the complete database, which contains a total of

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**Table 1. Contingency table describing the output of a search in terms of records retrieved and records that are relevant**

| | | Relevant | | |
|---|---|---|---|---|
| | | Yes | No | |
| Retrieved | Yes | $a$ | $n-a$ | $n$ |
| | No | $A-a$ | $N-n-A+a$ | $N-n$ |
| | | $A$ | $N-A$ | $N$ |

$N$ documents. Then the *recall*, $R$, is defined to be the fraction of the relevant documents that are retrieved:

$$R = \frac{a}{A},$$

and the *precision*, $P$, is defined to be the fraction of the retrieved documents that are relevant:

$$P = \frac{a}{n}.$$

Any retrieval mechanism seeks to maximize both the recall and the precision of a search so that, in the ideal case, a user would be presented with all of the documents relevant to a query without any additional, irrelevant documents. In practice, it has been found that recall and precision are inversely related to each other, so that an increase in the recall of a search (as may be accomplished, e.g., by going further down a ranking or by including additional OR terms in a Boolean query) generally is accompanied by a decrease in precision, and vice versa.[12]

It is possible to define several other measures from the contingency table. For example, the *fallout*, $F$, is defined to be the fraction of the nonrelevant documents that are retrieved:

$$F = \frac{n - a}{N - A},$$

whereas the *generality*, $G$, characterizes the particular query that is being searched for (rather than the performance of that query) and is defined to be the fraction of the database that is relevant:

$$G = \frac{A}{N}.$$

Further measures based on the table are discussed by Boyce et al.[9] and by Robertson and Sparck Jones[13]; the latter have been used as evaluation criteria for substructural analysis of high-throughput screening data.[14] Their origins in the same basic contingency table mean that the various measures mentioned above are closely related, e.g., Salton and McGill[5] note that:

$$P = \frac{RG}{RG + F(1 - G)}.$$

The need to specify two parameters, typically $R$ and $P$ but occasionally $R$ and $F$, to quantify the effectiveness of a search has led several workers to suggest single-valued measures that combine $R$ and $P$ by some form of averaging procedure. Examples are the measures described by Vickery[15]:

$$\frac{1}{(2/P) + (2/R) - 3},$$

and by Heine[16]:

$$\frac{1}{(1/P) + (1/R) - 1}.$$

van Rijsbergen[17] subsequently described a measure, which he called the *effectiveness* or $E$ measure, that is a generalization of the Vickery and Heine measures and is given by:

$$\frac{1}{\alpha(1/P) + (1 - \alpha)(1/R)},$$

where $\alpha$ ($0 \leq \alpha \leq 1$) is the relative importance assigned by the user to the precision of the search. Setting $\alpha = 0.5$ in the formula yields the measure suggested by Shaw[18]:

$$\frac{1}{(1/2P) + (1/2R)}.$$

Voiskunskii[19] noted that similarity coefficients provide a simple and direct basis for the measurement of retrieval performance and demonstrates the use of the cosine coefficient to obtain the combined measure:

$$\sqrt{PR}$$

Given two objects $X$ and $Y$, containing $x$ and $y$ attributes, respectively, of which $c$ are in common, then the binary form of the cosine coefficient is defined to be[1]:

$$\frac{c}{\sqrt{xy}}.$$

Let $X$ and $Y$ here denote the set of records that are retrieved and the set of relevant records, respectively (so that the attributes here are individual record identifiers); then, using the information in the contingency table (Table 1), the cosine coefficient is given by:

$$\frac{a}{\sqrt{nA}}.$$

Now

$$p = \frac{a}{n} \text{ and } R = \frac{a}{A},$$

from which the cosine coefficient is $\sqrt{PR}$, as noted earlier. Thus, it is possible to define a whole range of different performance measures depending on the similarity coefficient that is used. For example, the Tanimoto and Dice coefficients[1] yield the Heine and Shaw measures, respectively. Voiskunskii[19] argues that the cosine-based measure is superior to all other possible combinations of $P$ and $R$.

Finally, a rather different approach to the measurement of performance is provided by the *normalized recall*.[5] Consider a *cumulative recall* graph, which plots the recall against the number of documents retrieved. The best-possible such graph would be one in which the $A$ relevant documents are at the top of the ranking, i.e., at rank positions 1, 2, 3, ... $A$ (or at rank positions $N-A+1$, $N-A+2$, $N-A+3$, ... $N$ in the case of the worst-possible ranking). In practice, of course, the clustering of

**Table 2. Upper bound values of the various performance measures**

| Measure | $n < A$ | $n = A$ | $n > A$ |
|---|---|---|---|
| Precision-recall | $P = 1, R = \frac{n}{A}$ | $P = R = 1$ | $P = \frac{A}{n}, R = 1$ |
| Vickery | $\frac{n}{2A - n}$ | 1 | $\frac{A}{2n - A}$ |
| van Rijsbergern ($\alpha = 0.5$) | $\frac{2n}{A + n}$ | 1 | $\frac{2A}{A + n}$ |
| Voiskunskii | $\sqrt{\frac{n}{A}}$ | 1 | $\sqrt{\frac{A}{n}}$ |
| G-H score ($\alpha = \beta = 1$) | $\frac{n + A}{2A}$ | 1 | $\frac{n + A}{2n}$ |

the relevant documents is much less pronounced, and the area between the actual and ideal cumulative recall plots can be used as a measure of the effectiveness of the ranking. Let *RANK(I)* denote the rank of the *I*-th relevant document; then the normalized recall is defined to be:

$$1 - \frac{\sum_{I=1}^{A} RANK(I) - \sum_{I=1}^{A} I}{A(N - A)}$$

which Salton and McGill[5] note is equivalent to the area under a recall-fallout curve.

It will be clear from the above that the measurement of retrieval effectiveness is of central importance in textual information retrieval; however, rather less interest in the evaluation of performance is evident when we consider chemical information systems. This reflects, at least in part, the fact that most early information systems provided facilities only for 2D substructure searching, where the use of the first-stage screening search and the second-stage atom-by-atom search ensured that all queries resulted in perfect recall and perfect precision, respectively. The only performance measure that is widely quoted for substructure searching systems is the *screenout* (the fraction of a database that is eliminated by the initial screen search), and it can be argued that this is really a measure of efficiency, rather than effectiveness; other such measures are much rarer, e.g., that described by Bawden and Fisher.[20]

There is less consensus as to how the results of chemical similarity searches should be reported. For example, the Sheffield group has generally quoted the mean numbers of active compounds identified in some number (e.g., the top 20) of the nearest neighbors, when averaged over a set of searches for bioactive target structures. An example is a study of distance-based measures for 3D similarity searching.[21] Alternatively, the Merck group has used cumulative recall diagrams, from which it is simple to obtain the *enrichment*, i.e., the number of actives retrieved relative to the number that would be retrieved if compounds were picked from the database at random. The use of such diagrams is exemplified by a study of similarity searching using geometric pair descriptors.[22] More recently, Güner and Henry[23] proposed a new combined measure, the *G-H score*, for evaluating the effectiveness of 3D database searches and suggest that it is superior to existing single-variable performance measures. Using the previous notation, the G-H score is defined to be:

$$\frac{\alpha P + \beta R}{2}$$

where $\alpha$ and $\beta$ are weights describing the relative importance of recall and precision. The lower bound for the G-H score is zero; if both weights are set to unity, then the score is simply the mean of recall and precision:

$$\frac{P + R}{2},$$

i.e., the square of the Voiskunskii measure divided by the Shaw measure.

Having introduced the various measures, we conclude this section by noting their upper bound behaviors. As noted previously when discussing normalized recall, the best-possible similarity search is one in which all of the *A* actives are in the first *A* positions in the ranking. From such a perfect ranking, it is possible to calculate an upper bound to the value of the various measures that can be achieved given some number, *n*, of retrieved structures. We will illustrate this by considering precision and recall. Given a perfect ranking, there are three cases to be considered: $n < A$; $n = A$; and $n > A$. When $n < A$, all of the retrieved molecules are active so that $P = 1$; however, there are still other actives that have not yet been retrieved and $R = n/A$. When $n = A$, we have the perfect outcome, in which all of the actives have been retrieved, so that $R = 1$, and none of the inactives have been retrieved, so that $P = 1$ also. When $n > A$, $R = 1$ (as all of the actives have been retrieved) but $P = A/n$, so that the precision steadily decreases in line with the size of the output. Examples of upper bound values are detailed in Table 2.

## EXPERIMENTAL DETAILS

Much of the literature on similarity searching relates to the different measures that can be used to compute the degree of

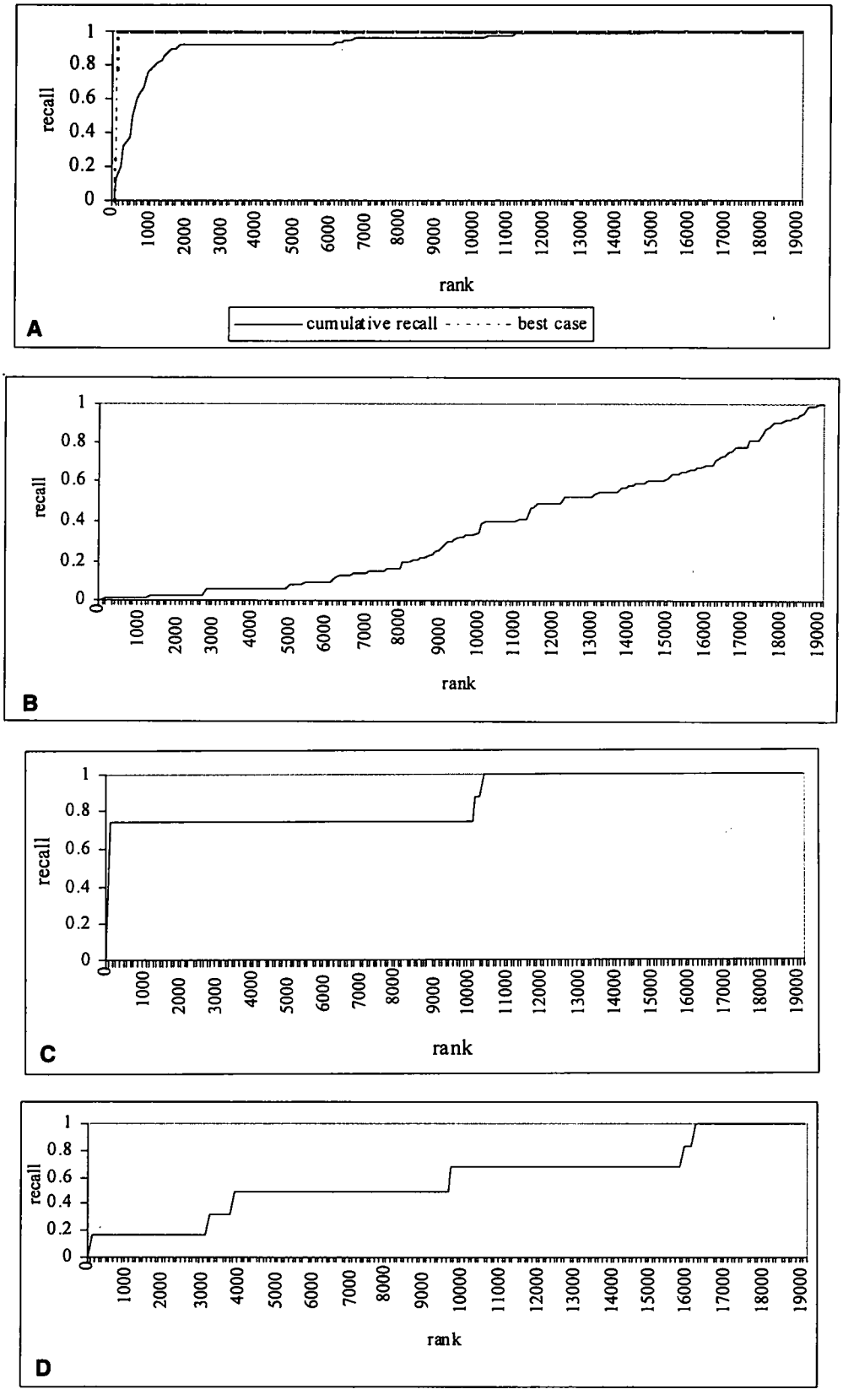



*Figure 1. Cumulative recall for target A (a), target B (b), target C (c), and target D (d).*

resemblance between a target structure and a database structure.[1-3] The most common type of similarity search procedure determines the extent of this resemblance by a comparison of the molecules' fragment bit-strings or fingerprints, with the degree of similarity being a function of the number of bits (and hence 2D substructural fragments) that they have in common.

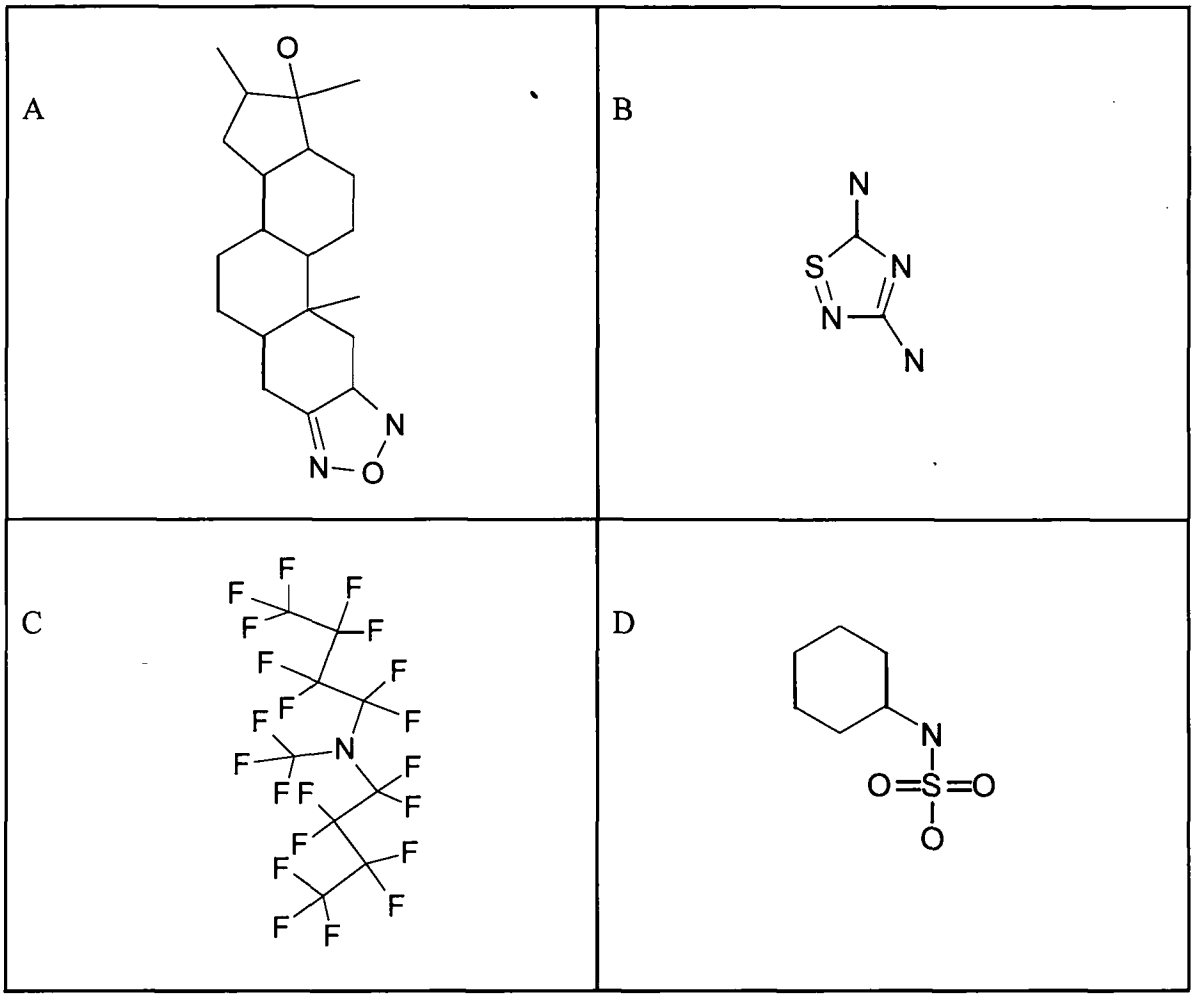



*Figure 2. Target structures A–D used to illustrate the behavior of the various performance measures.*

The experiments reported here have used 2D similarity searching routines based on the Tanimoto coefficient. However, the measures of effectiveness discussed here are applicable to *any* type of similarity measure, subject only to it producing a ranking of a database in order of decreasing similarity with the target structure.

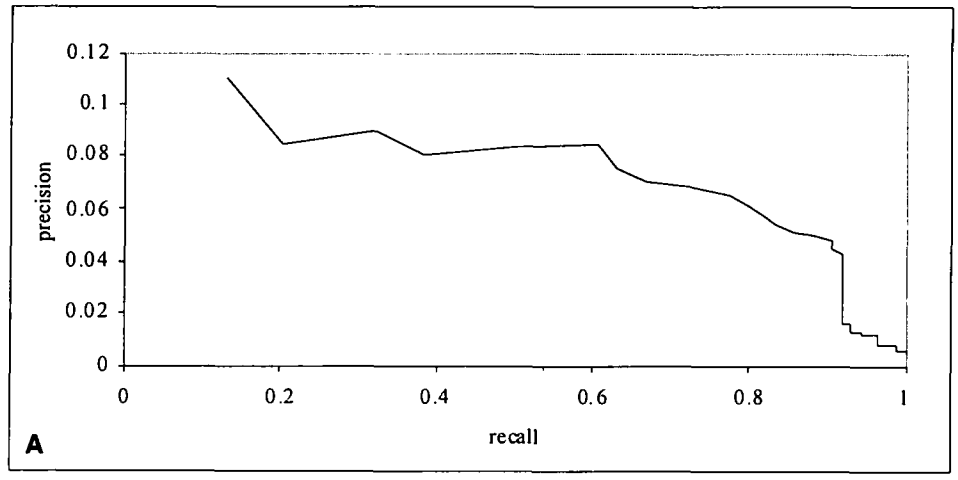
The experiments used a subset of the World Drugs Index (WDI) database.[24] Those structures that did not include activity data were removed, leaving a set of 19,102 unique compounds that were characterized by UNITY 2D fragment bit-strings.[25] This set of structures will be referred to as the *actives database.* Fifty target structures, each associated with a distinct activity class (such as "phytoncide" or "hypotensive"), were chosen from the actives database using a MaxMin diversity selection algorithm[26] to ensure that the targets were structurally heterogeneous. Each member of this *target set* had between 5 and 2,932 associated active structures.

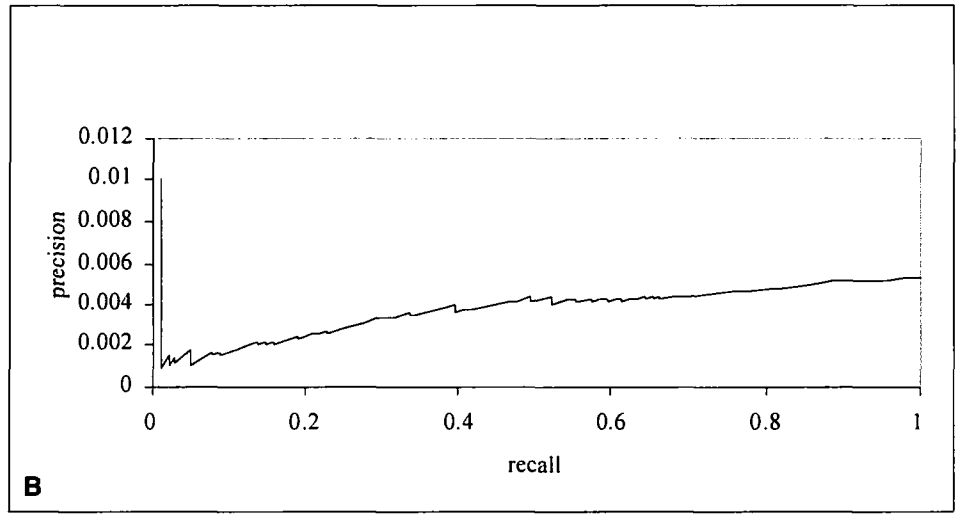
The bit-string of each of the molecules in the target set was used to carry out a similarity search of the actives database, with the structures being ranked in order of decreasing Tanimoto coefficient. Each compound in a ranking was labeled with a "1" where it shared the same activity as the target molecule, and a "0" otherwise, and plots were generated of the values of the various measures at intervals of 100 positions in the ranked list. Note that we have generated plots for the entire ranked dataset to illustrate the behavior of the various measures over the full range of similarity values. In a typical virtual screening application,[27] a searcher is likely to be interested in just the uppermost parts of the ranking. For example, Brown and Martin[28] suggest the retrieval of structures with a Tanimoto similarity of 0.85 or greater, these corresponding to, typically, just the first few structures from the entire ranked list (and thus to points at the extreme left-hand edge of the various plots that are discussed later).

## EXPERIMENTAL RESULTS AND DISCUSSION

### Cumulative Recall

A typical cumulative recall graph is shown in Figure 1a, together with the ideal case, where all of the actives occur at the very top of the ranking. The target illustrated shares its activity with 83 other compounds and shows the best retrieval of the 50 searches carried out, with most of these actives being retrieved within the first 2,000 positions. Figure 1b illustrates an example of poor retrieval in which the shared actives are approximately evenly distributed throughout the rankings, with



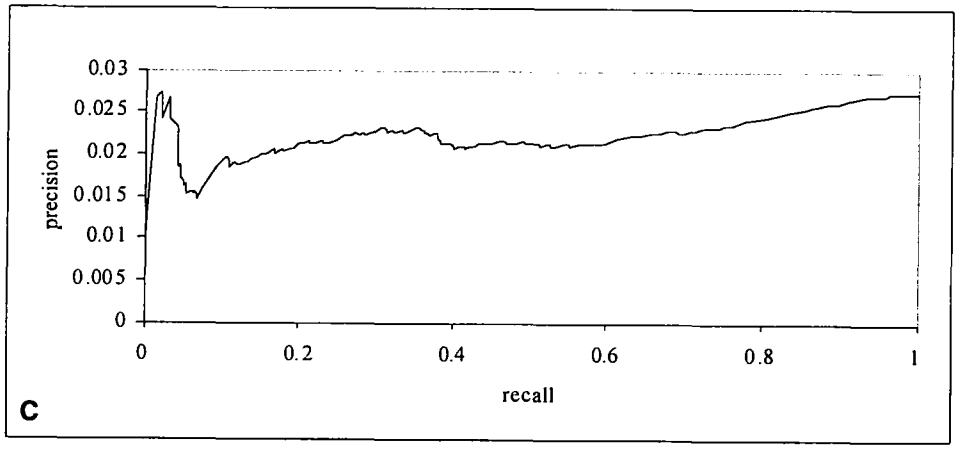




*Figure 3. Precision-recall curve for target A (a), target B (b), and target structure 8067 (c).*

little obvious grouping of them. Figures 1c and d illustrate the stepped cumulative-recall plots that characterize target structures for which there are few other active compounds. The first of these plots illustrates effective searching, with six of the eight actives for this target being near to the top of the ranking, and the other two in the middle of the ranking. The effectiveness of the search in Figure 1d is much lower.

For ease of comparison, these four target structures will be used for most of the illustrations of the other measures: the structures, which are shown in Figure 2, are referred to subsequently as targets A (anabolics), B (blood substitutes), C (antioxidants), and D (sweeteners).

## Precision Recall

Plots of precision against recall are widely used in the information retrieval literature[5,12] and typically involve an inverse relationship, with high values of recall being associated with

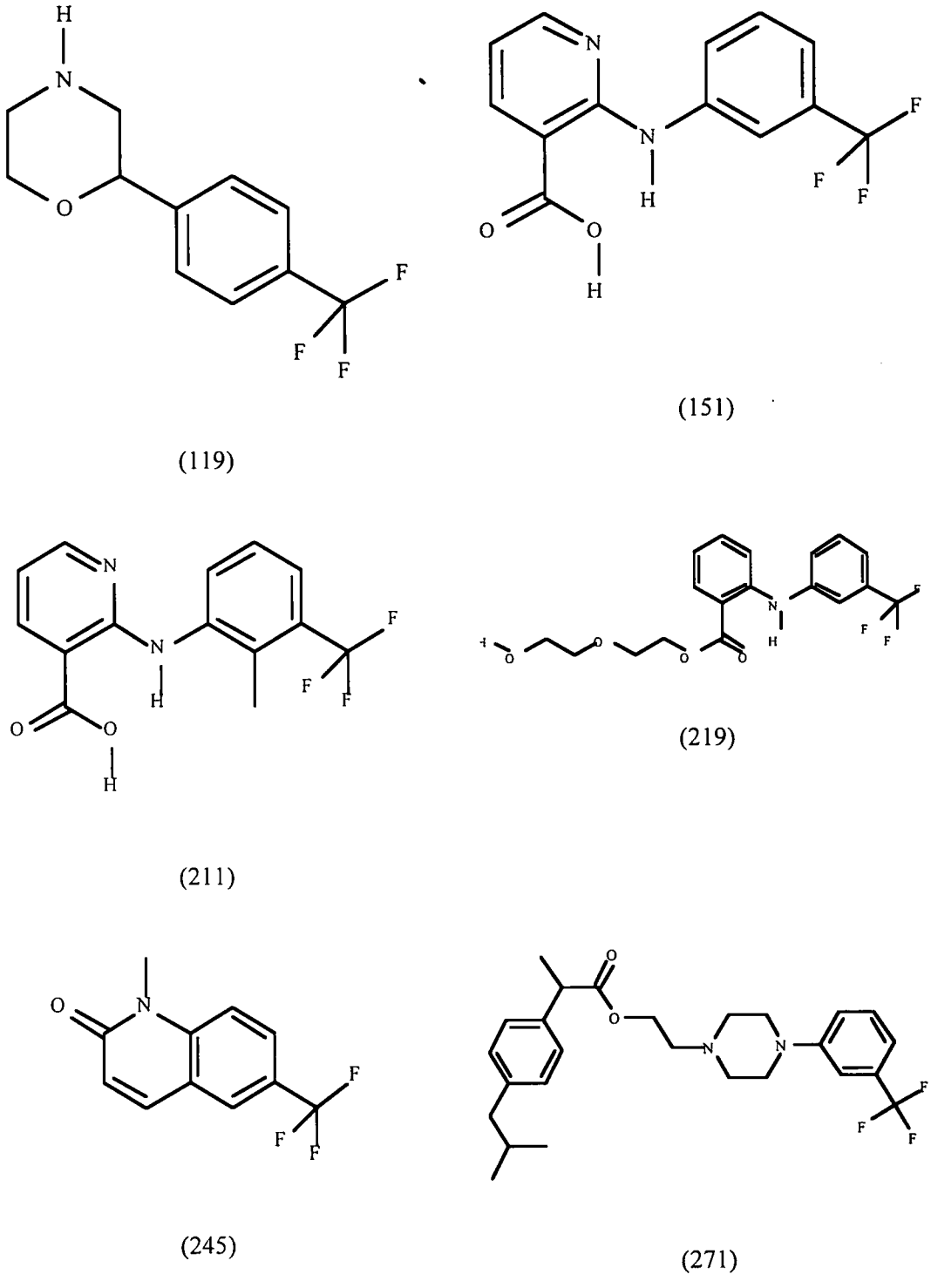
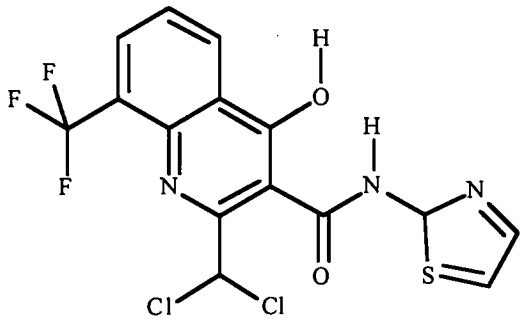



*Figure 4. Retrieval position (in parentheses) of the active structures associated with the two peaks between* n = *100 and* n = *400 in the recall-precision plot for target structure 8067,* $Cl_2FC\text{-}CFCl_2$.

low values of precision and vice versa. Such inverse relationships were encountered only rarely in the individual chemical searches considered here: the plot for target A (Figure 3a) shows some degree of inverse behavior, but this is certainly not the case for target B (Figure 3b). The most common type of plot was one characterized by peaks where the performance is high, indicating that groups of actives are being retrieved together, and troughs where few actives are retrieved, whereas a steady curve would indicate much less grouping of the actives in the ranked list. An extreme example of this behavior is provided by structure 8067, $Cl_2FC\text{-}CFCl_2$, which has a total of 517 other actives. The precision-recall plot for this search is shown in Figure 3c and contains several well-marked peaks. The actives asso-



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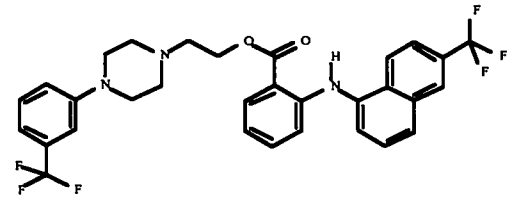

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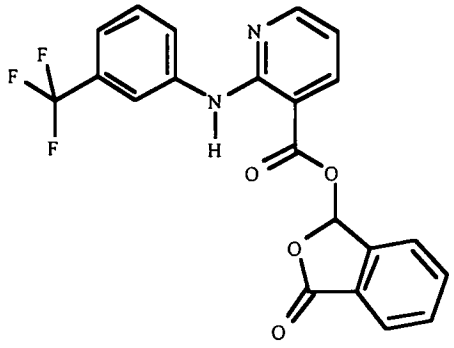

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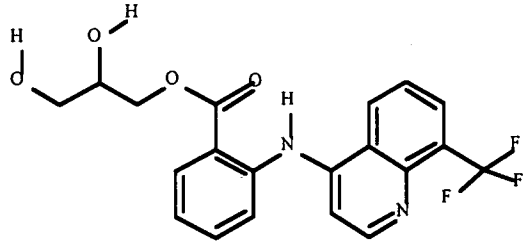


(399)

*Figure 4. Continued.*

ciated with the top two peaks (at around rank positions 100–400) were inspected and were all found to contain a $PhCF_3$ moiety, with many of them also possessing a proximate nitrogen atom (as illustrated in Figure 4). Thus, the peaked behavior observed here appears to arise from the occurrence of large numbers of similar active structures; this is likely to be a frequent occurrence with corporate databases that often contain very large analogue series. The behavior is different from that observed in most text retrieval applications where there is less likelihood of high similarities between the documents that are relevant to a particular query, with the result that precision-recall plots are generally much smoother than those observed here.

## Normalized Recall

It will be realized that cumulative recall and normalized recall are closely related, but they do not result in identical curves because the values for the latter measure take account of the maximum recall that could be achieved (i.e., the upper bound portions of the cumulative recall plots shown in Figure 1). Normalized recall values fall into the range from 1 to 0, with the former representing the case that all the active molecules have been retrieved before any nonactives and the lower the value, the greater the deviation from this ideal behavior. The normalized recall plots for targets A and B are shown in Figure 5. The first portion of Figure 5a illustrates a high level of performance, but then there is a noticeable dip corresponding to a section of the ranking where few actives are being identified, even though there are still many to be retrieved; thereafter, the curve tends to unity. In contrast, the normalized recall plot for target B (Figure 5b) is almost featureless.

## Vickery, Heine, and Shaw Measures

The single-valued measures of Vickery, Heine, and Shaw are very similar in nature and consistently result in highly comparable plots. Hence, we have included only the Vickery plots for targets A and B (in Figures 6a and b, respectively). The first of these, where most of the actives were retrieved near to the top of the ranking, gives a well-marked peak that then drops steadily away as fewer and fewer further actives are identified. Figure 6b again has an initial peak, but the remainder is much more complex, with a large number of small peaks on the main curve as the remaining actives are identified. In general form, this plot is not dissimilar to this target's precision-recall plot (Figure 3b).

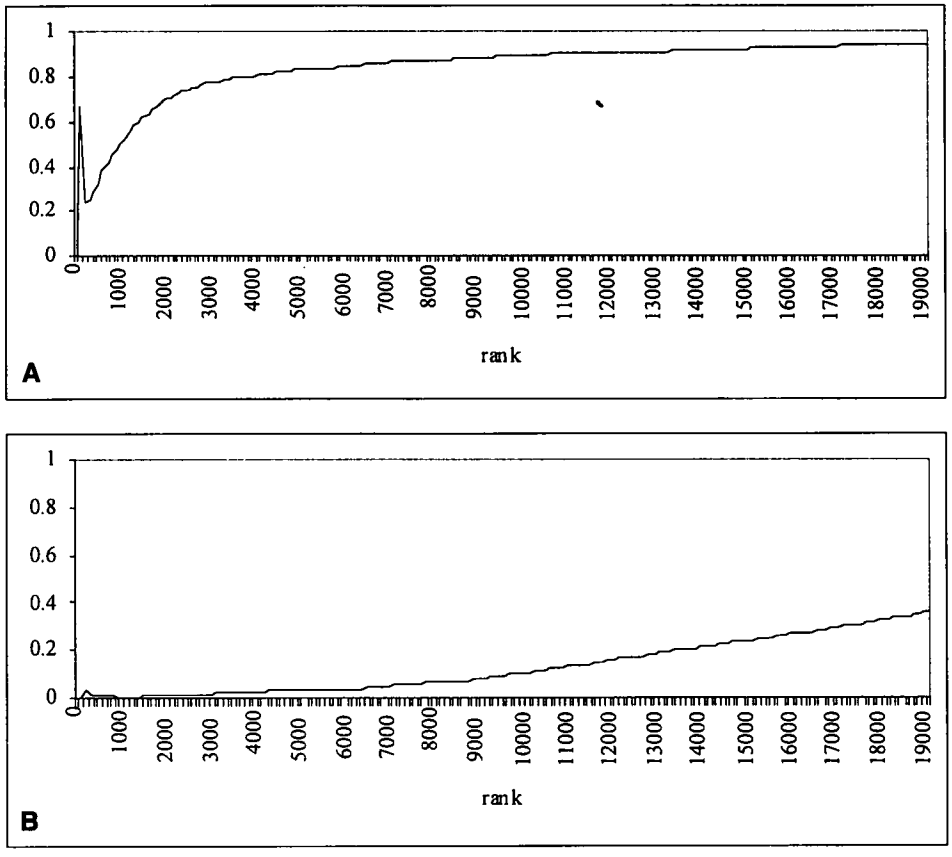



*Figure 5. Normalized recall curve for target A (a) and target B (b).*

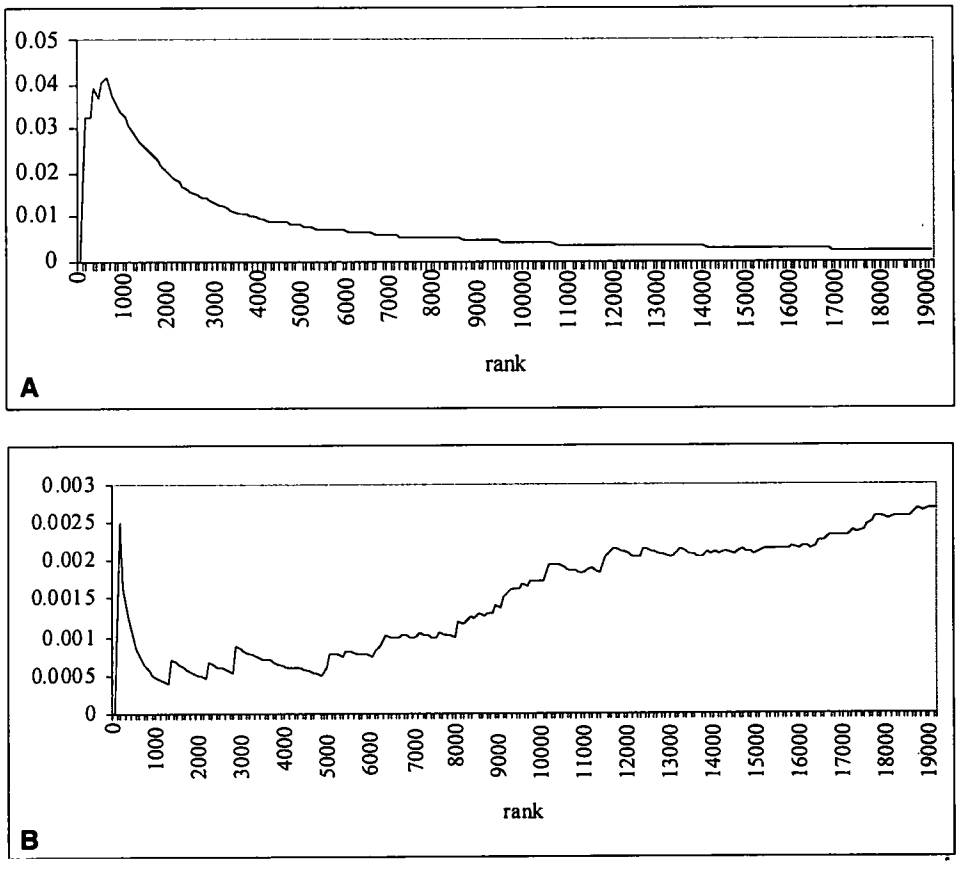
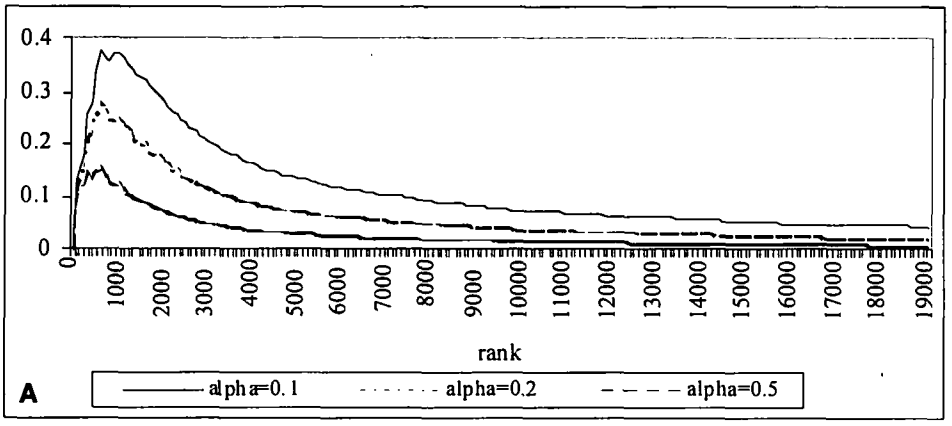
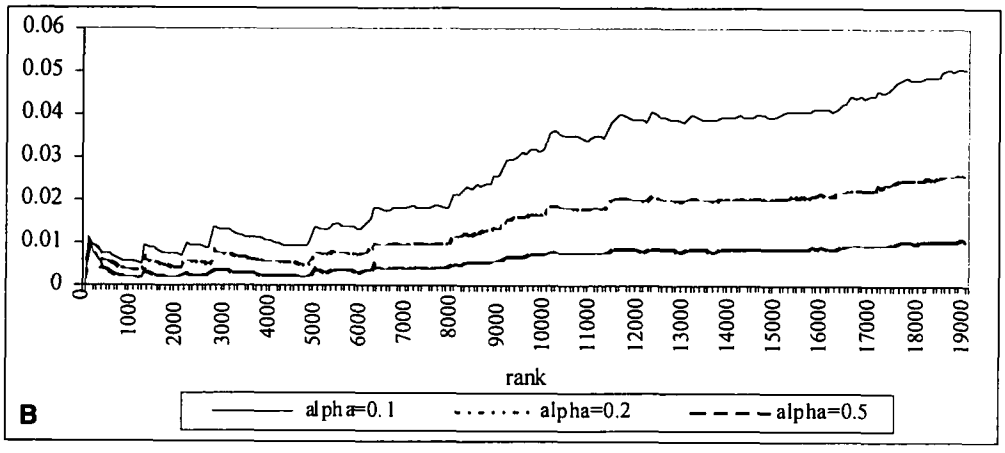
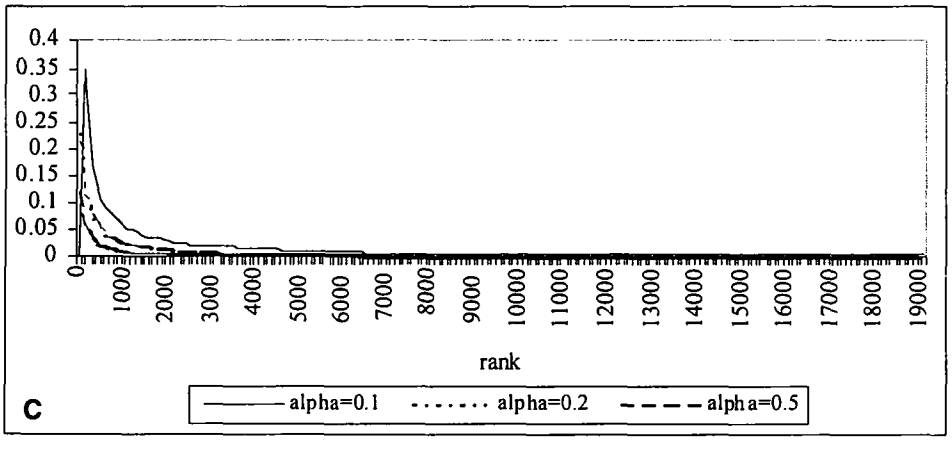



*Figure 6. Vickery curve for target A (a) and target B (b).*



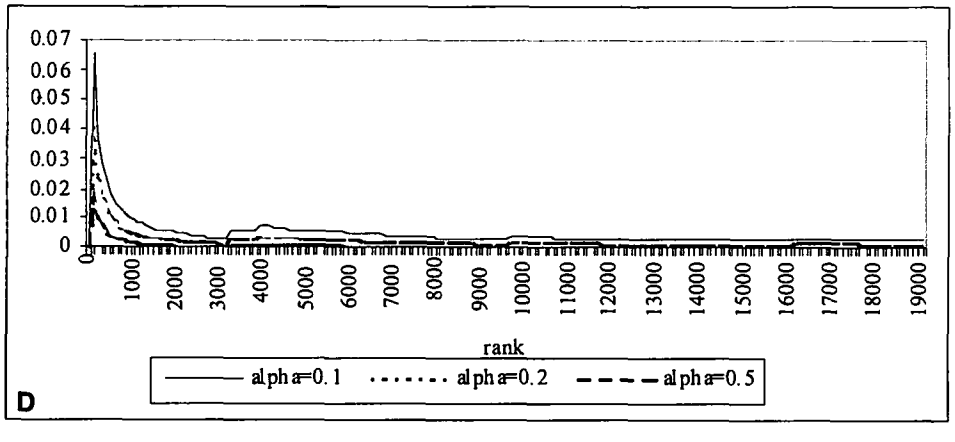
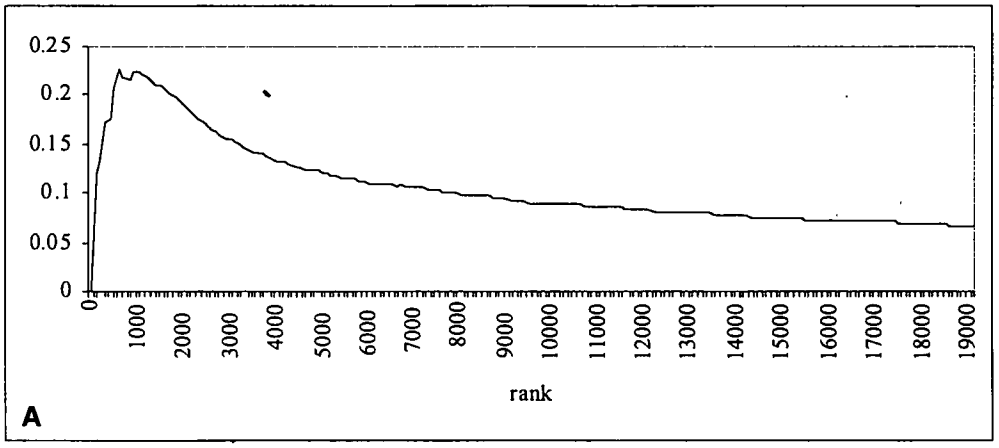
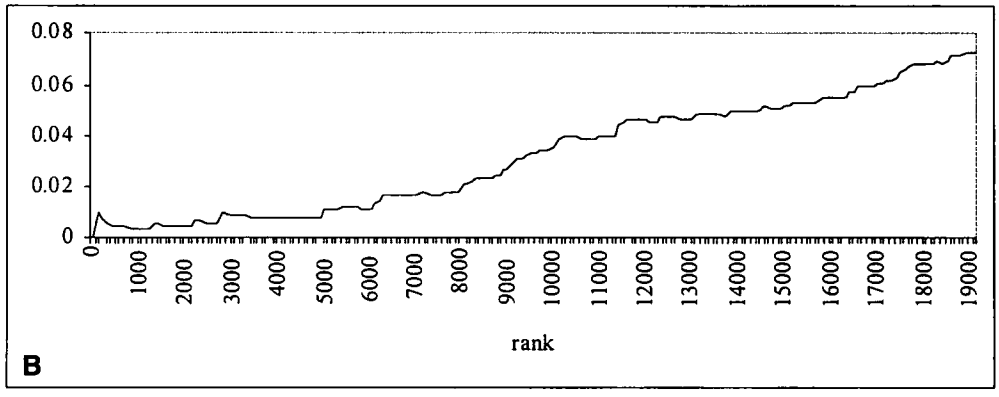
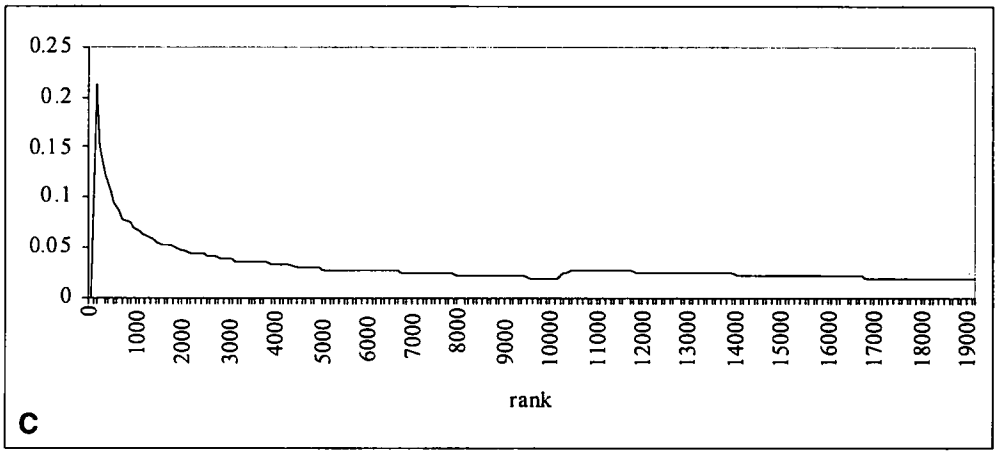




*Figure 7. van Rijsgergen curve for target A (a), target B (b), target C (c), and target D (d).*



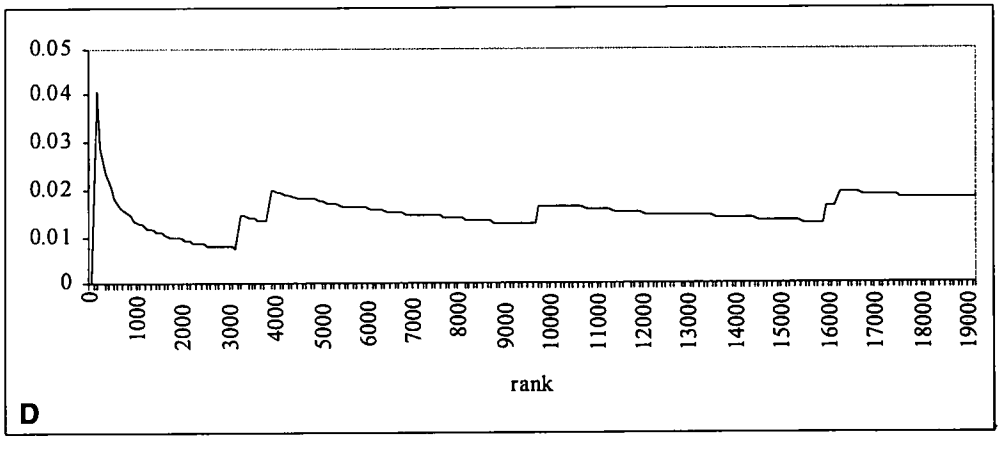




*Figure 8. Voiskunskii curve for target A (a), target B (b), target C (c), and target D (d).*

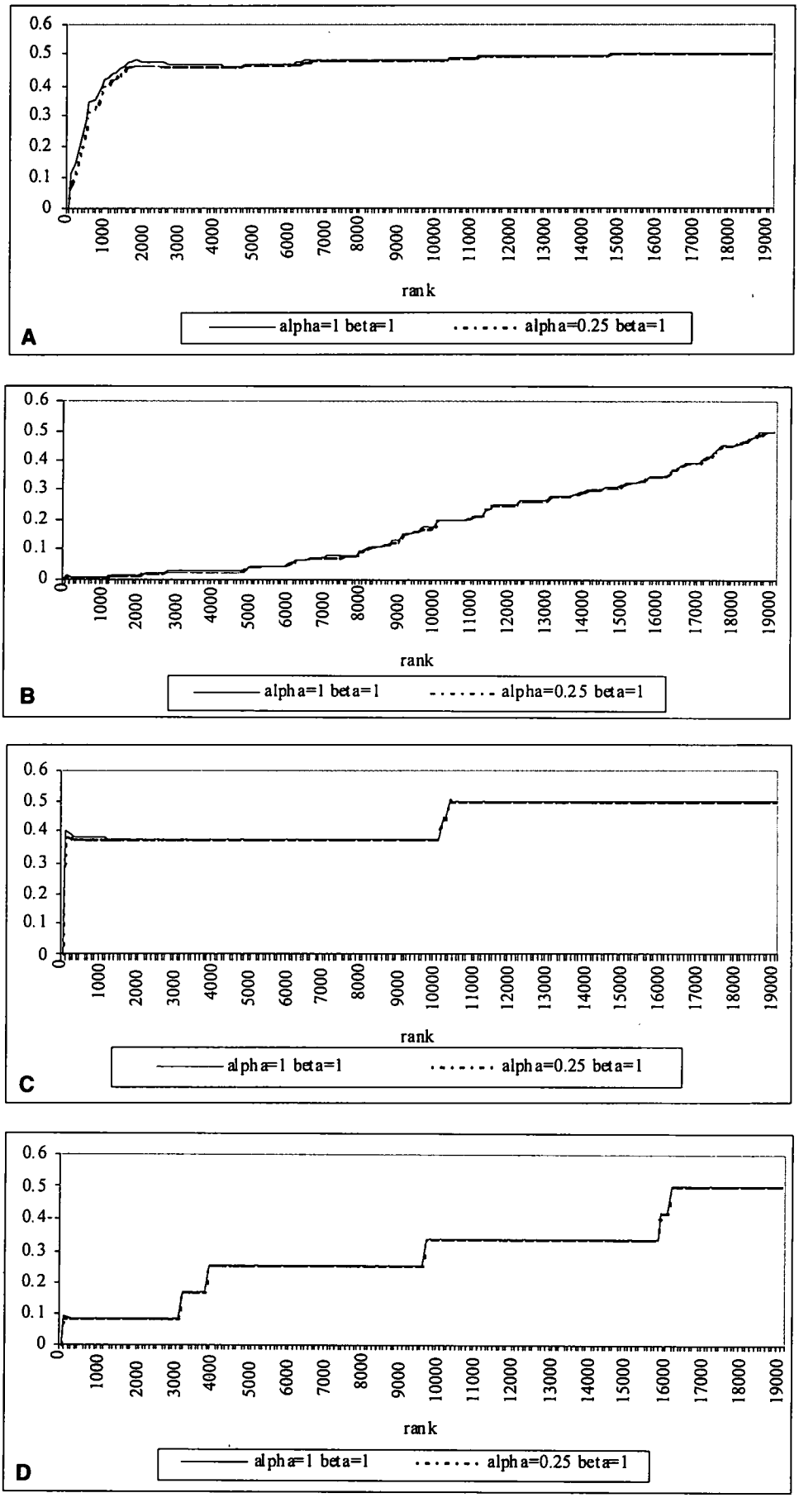
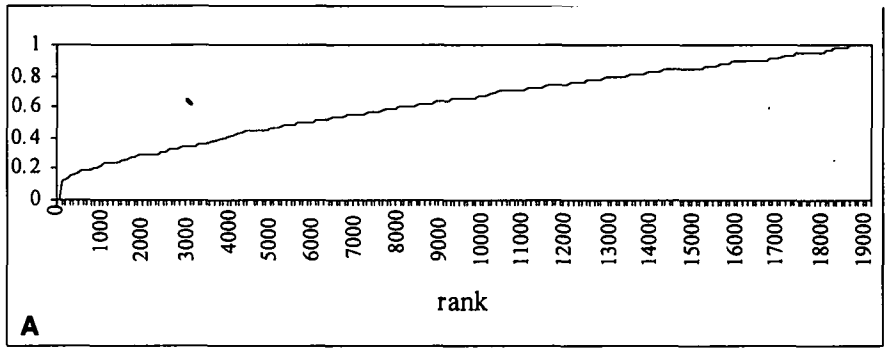
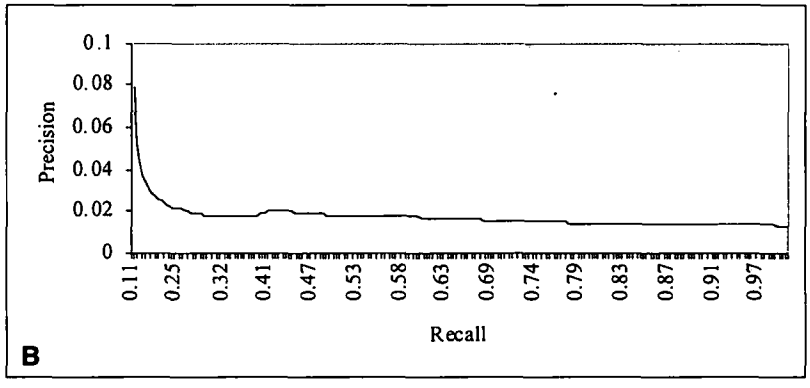
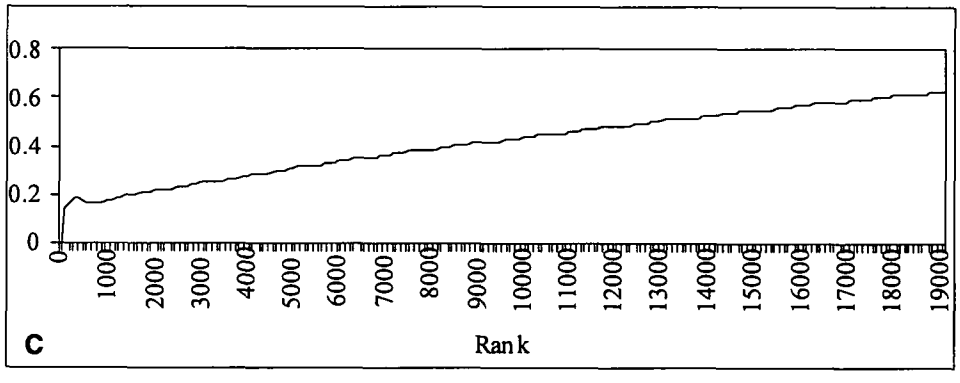



*Figure 9. G-H score curve for target A (a), target B (b), target C (c), and target D (d).*



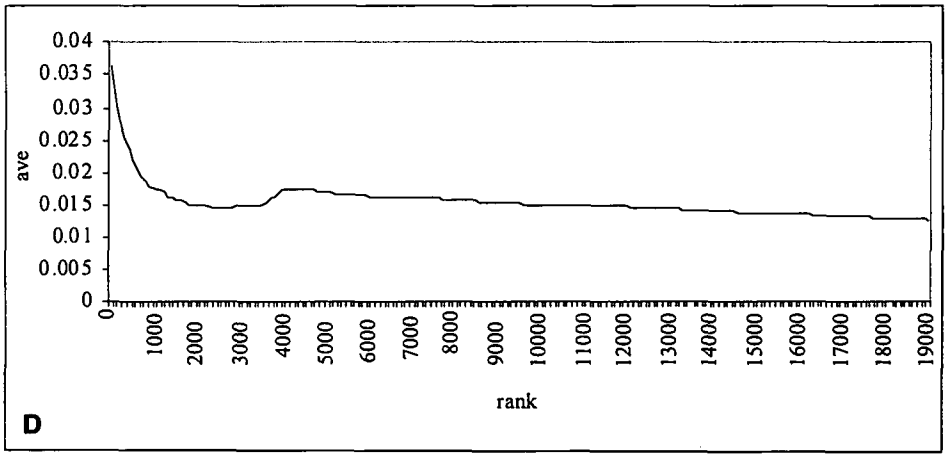




*Figure 10. (a) Averaged cumulative recall. (b) Averaged precision recall. (c) Averaged normalized recall. (d) Averaged Vickery measure. (e) Averaged van Rijsbergen measure ($\alpha$ = 0.2). (f) Averaged Voiskunskii measure. (g) Averaged G-H score measure, ($\alpha$ = 1, $\beta$ = 1).*

## van Rijsbergen Measure

The graphs for the van Rijsbergen measure for targets A–D are shown in Figure 7. The formula for the van Rijsbergen measure differs only slightly from the Vickery, Heine, and Shaw, the extent of the difference depending on the value chosen for $\alpha$, a user-defined parameter that defines the relative contribution of precision and recall to the overall score (with a high $\alpha$ value

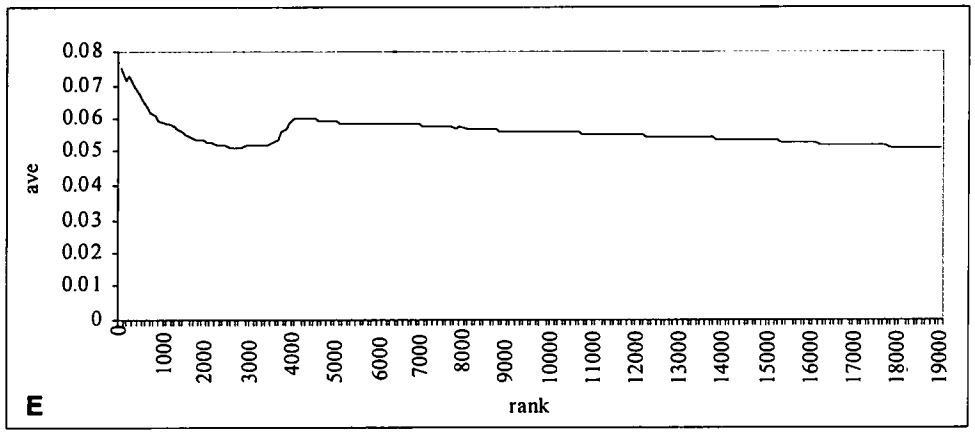



*Figure 10. Continued*

reflecting an emphasis on precision rather than recall). The low values of precision in targets C and D result in near-featureless curves when $\alpha = 0.5$; with lower values for $\alpha$, the plots obtained are similar to those obtained for the Vickery measure in Figure 6.

## Voiskunskii

The form of the measure proposed by Voiskunskii is significantly different from the measures discussed earlier, but the plots that are obtained (Figure 8) are similar in outline to many of those shown previously, although there are some differences. For example, the plot for target D reflects the progressive identification of each of the six actives for this target more obviously than in the corresponding Vickery plot.

## G-H Score

The final measure used to analyze the data is the G-H score of Güner and Henry.[23] The precise form of the plots resulting from use of this measure again depend on the values of user-defined parameters ($\alpha$ and $\beta$ here), but comparably shaped curves are obtained for a wide range of combinations of values, some of which are illustrated in Figure 9. It will be seen that the effect of the parameter values on the plot shapes seems to diminish for small numbers of active structures (as exemplified in Figures 9c and d).

It will be seen that all of the G-H score plots tend to a limiting value of 0.5. For simplicity, assume, without loss of generality, that $\alpha = \beta = 1$, so that the measure is given by:

$$\frac{P + R}{2}$$

As $n \rightarrow N$, i.e., when very many molecules have been retrieved, $a \rightarrow A$, and hence the precision and recall are given by $P = A/N$ and $R = 1$, respectively. Thus, the score at the $n$-th rank position, $GH_n$, is given by:

$$GH_n \rightarrow \frac{\frac{A}{N} + 1}{2}, \; i.e., \; \frac{A + N}{2N}.$$

Now $N >> A$, i.e., the total file size, is much greater than the number of actives for the chosen target structure, and, hence:

$$GH_n \rightarrow 1/2,$$

which is what is observed in practice in Figure 9. By similar arguments, the Vickery, van Rijsbergen (with $\alpha = 0.5$), and Voiskunskii measures tend to $A/2N$, $2A/N$, and $\sqrt{(A/N)}$, respectively (all of which are close to zero as $N >> A$).

In general, the G-H score plots are very similar to the cumulative recall plots. We noted previously that there are close relationships between several of the measures considered here, and it is simple to demonstrate such a relationship for this pair of measures. Consider the case when $n$ molecules have been retrieved, $a$ of which are active. Then the cumulative recall at this point, $CR_n$, is given by:

$$CR_n = \frac{a}{A}$$

and the corresponding G-H score (again assuming $\alpha = \beta = 1$) by:

$$GH_n = \frac{\frac{a}{n} + \frac{a}{A}}{2}.$$

Taking the ratio of these two measures and simplifying, we obtain:

$$\frac{CR_n}{GH_n} = \frac{2n}{A + n}$$

$A$ will be small for most target structures; hence, the ratio will tend to the constant value of 2 as $n$ increases, i.e., as more and more structures are retrieved. Thus, the G-H score can best be considered as a more flexible form of the cumulative recall measure, with the flexibility being provided by the user's ability to specify values for the parameters $\alpha$ and $\beta$. This is, of course, also the aim of the van Rijsbergen measure, and the other related measures (Heine, Vickery, and Shaw) all involve the adoption of an implicit weighting of precision as against recall; however, the cumulative recall and G-H score plots we have obtained seem,

to us at least, to be intuitively more comprehensible than those resulting from the other measures.

### Average Plots

The final set of plots (Figure 10) represent mean values calculated across the entire set of 50 targets. For the van Rijsbergen measure, $\alpha$ was set to 0.2, while $\alpha$ and $\beta$ were both set to 1 for the G-H score. The plots demonstrate the high degree of commonality among the Vickery, van Rijsbergen, and Voiskunskii measures. There are no obvious peaks due to the averaging, but all three show the same characteristics with a pronounced trough, followed by a noticeable improvement in performance at about rank 4,000 that is rather less evident in the G-H score plot, although even here a slight bump is observed in the plot. There does not seem to be any obvious reason for this behavior; hence, we assume that it is specific to this set of structures and targets. The G-H score plot is very similar to the cumulative recall and normalized recall plots; however, as noted previously, the last of these can give very different types of curve for individual searches. The averaged precision-recall plot shows the inverse relationship that characterizes such plots in the textual information retrieval (with the exception of the initial peak at low recall); however, this measure also can give very different types of curve (as demonstrated by Figure 3).

## CONCLUSION

In this article, we illustrated the use of a range of measures for evaluating the effectiveness of retrieval in bit-string similarity searches of 2D chemical databases. Our investigations show that there is little to distinguish among the single-valued measures of van Rijsbergen, Vickery, Heine, Shaw, and Voiskunskii, and that there are close similarities between the cumulative recall and G-H score measures. We believe that the plots resulting from the latter measures are easier to interpret and, hence, recommend their adoption for reporting the results of chemical similarity searching experiments.

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