

# Computer-Assisted Reaction Searching Directed toward the Synthesis of Target Molecules

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As a result of an enormous increase of accessible reaction databases and the introduction of client-server-based database access systems during the past few years, the computer-assisted searching of reaction databases for synthesis planning has become an important part of intense efforts to increase the efficiency and productivity in chemical research. This paper will illustrate effective use of the functionality of MDL's RXL Browser and the concept of retrosynthetic analysis in reaction searching to derive desirable synthesis plans for target molecules.

## INTRODUCTION

The computer-assisted design of chemical synthesis was first demonstrated in 1969 by Corey and Wipke.<sup>1</sup> This approach in synthesis planning was based on Corey's original concept of retrosynthetic analysis.<sup>2</sup> In retrosynthetic analysis the target molecule for chemical synthesis is subjected to a disconnection process which corresponds to the reverse of a synthetic reaction. As a result, a target molecule is transformed to a sequence of simpler precursors in a stepwise manner along a pathway that ultimately leads to simple or commercially available starting materials for chemical synthesis. For a complex target molecule, some precursors may undergo further retrosynthetic analysis. Thus, the repetition of this process eventually will result in a hierarchical synthesis tree for the target molecule.<sup>3</sup> Many systems in computer-assisted design for synthesis planning and reaction prediction have been developed on the basis of this concept during the past 2 decades. Some typical systems include LHASA,<sup>4</sup> SECS,<sup>5</sup> SYNCHM,<sup>6</sup> SYNGEN,<sup>7</sup> LILITH,<sup>8</sup> TRESOR,<sup>9</sup> and SYNTHON.<sup>10</sup> However, none of these systems to date have been widely accepted as a routine and practical tool for synthesis planning. One system that deviates from the retrosynthetic, or synthon, concept is WODCA.<sup>11,12</sup> This system incorporates an algorithm that includes the perception of similarity between the target and starting materials as well as the retrosynthetic steps and reaction prediction steps. A review on computer-assisted planning of organic synthesis has appeared recently.<sup>13</sup>

During the past 10 years another approach to computer-assisted synthesis planning, namely, the computer-assisted searching of reaction databases, has emerged. The early versions of commercially available reaction retrieval systems include REACCS,<sup>14</sup> SYNLIB,<sup>15</sup> and ORAC.<sup>16</sup>

These are structure-based reaction indexing systems that focus on the reaction center.<sup>17</sup> The databases in those systems typically contain literature citations with information on reaction conditions, yields, catalysts, reagents, and references for transformations from reactants to products. The users can apply certain strategies to search reaction databases for the target molecules.<sup>18,19</sup> The number of accessible reaction databases has increased enormously in recent years.<sup>20</sup> The large databases include CASREACT,<sup>21</sup> ChemInform,<sup>22</sup>

ChemReact,<sup>23</sup> and Beilstein CrossFire.<sup>24,25</sup> In addition, more flexible interactive and client-server-based reaction database access systems have been developed recently. One such system, IRDAS,<sup>26</sup> was introduced in 1993 as one of the ISIS applications<sup>27</sup> by MDL Information Systems, Inc. It allows users to access and browse a collection of reaction databases in a networked environment. As a result, the computer-assisted searching of reaction databases has become a more routine approach for synthesis planning in many chemical research laboratories,<sup>13</sup> especially in agrochemical and pharmaceutical industries.

## SEARCHING REACTION DATABASES

The current reaction database access system at American Cyanamid is an enhanced version of IRDAS, named RXL Browser 1.3, recently introduced by MDL. It is intended to provide a more intuitive user interface with the IRDAS functionality. The selection of RXL Browser as our client-server-based access system was a result of the transition from REACCS to IRDAS in 1993. Our global reaction database (globe\_rs.db) comprises a collection of reaction databases from the MDL Reaction Library<sup>28</sup> and ChemSynth.<sup>29</sup> The globe\_rs.db currently contains 667,170 reactions and is updated regularly. Users can access these databases via ISIS/Base on their desktop computers. The databases are installed on an IBM RS/6000 reaction server with ISIS/Host as the search engine. The structure and reaction queries can be built in ISIS/Draw by users and conveniently transferred to ISIS/Base for performing the searches. All of the figures shown in this paper for illustrations are the screen shots of the graphic displays created from ISIS/Draw and ISIS/Base version 2.0 installed under Microsoft Windows 95 in a Dell Optiplex GXMT5166. Unless otherwise stated, all searches were conducted in globe\_rs.db.

The concept of the retrosynthetic analysis<sup>2,3,30</sup> as described above for computer-assisted design in synthesis planning is well-known to organic chemists. This stepwise retrosynthetic disconnection approach can be applied to computer-assisted searching of reaction databases as well. The purpose of this paper is to illustrate with a case study the usefulness of applying the concept of retrosynthetic analysis to reaction searching for synthesis planning. As indicated above, the RXL Browser was the only client-server-based reaction database access system available at American Cyanamid

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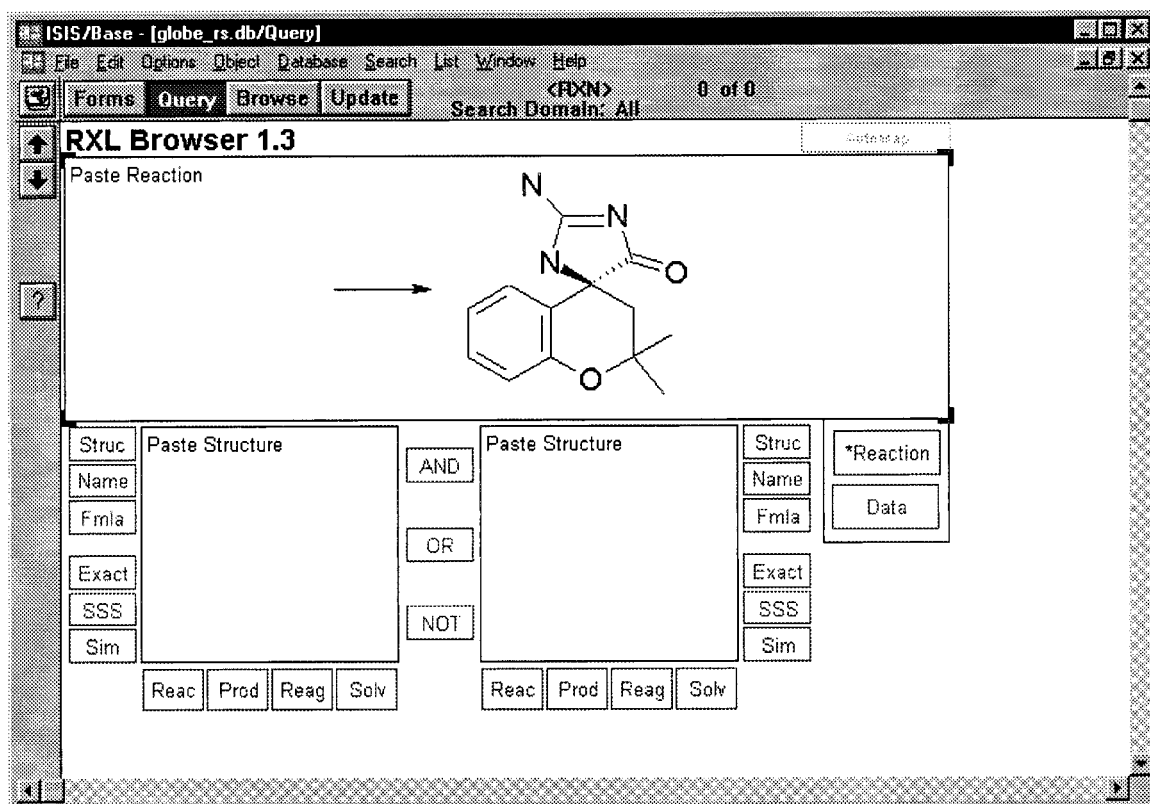
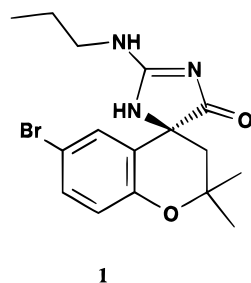


Figure 1. Reaction query in ISIS/Base.

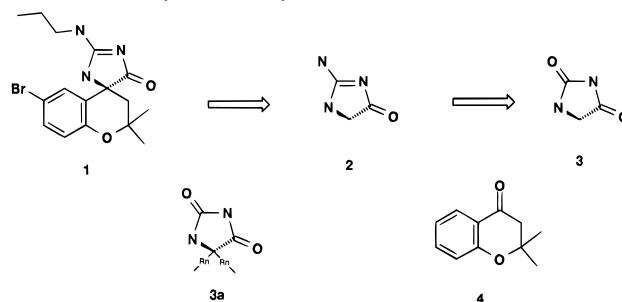
during the course of this study. In order to use a practical example for illustration, we have chosen a recently published chiral spirocyclic benzopyran imidazolone (**1**)<sup>31,32</sup> as the



target molecule. Benzopyrans belong to the chroman family<sup>33</sup> and are important intermediates for agrochemicals<sup>34–36</sup> and pharmaceuticals.<sup>37–39</sup> Considerable interest in the synthesis of chroman derivatives has been generated from their potential and/or observed biological activity. Spirocyclic benzopyran imidazolones have been shown to exert a hypotensive effect and are completely enantioselective in their activity.<sup>31</sup> The enantiomer **1** with *S*-configuration is exceedingly potent as a potassium channel opener.<sup>32</sup> Thus, the design of a reaction pathway directed toward the synthesis of this chiral compound is highly desirable.

As the first step, we wanted to search the preparation of **1** or its analogues from any starting materials and pathways. Thus, a partial reaction query with the root structure of **1** as the product was drawn in ISIS/Draw and then transferred to ISIS/Base (Figure 1). A reaction substructure search (RSS) of this query, however, did not retrieve any hits. Since a direct RSS failed, our search strategy then shifted to Corey's approach of retrosynthetic analysis. As shown in Scheme 1, the spiro molecule **1** may be viewed as being joined by two ring fragments such as 2-aminoimidazolone (**2**) or 2,4-imidazolidinedione (hydantoin, **3**) and 2,2-dimethylchromone (**4**).

Scheme 1. Retrosynthetic Analysis for **1**



Since the chemistry of hydantoin is known and synthesis of spirohydantoin has been documented,<sup>40</sup> it appeared logical to construct a query that contained **3** as part of the spiro ring substructure (i.e., compound **3a**, Scheme 1) for reaction searching. The strategy involved a substructure search that would retrieve only the reactions containing compound **3a** as a product. To accomplish this goal, we wanted to use a combination search by employing the Boolean A NOT B operation. The RXL Browser has the functionality that allows users to conduct this kind of search. Consequently, a search was performed by highlighting SSS as Product/Not SSS as Reactant in the Paste Structure boxes in ISIS/Base Query mode (Figure 2) for compound **3a** and selecting Search/By Form from the pull-down menu. The result from this search retrieved 44 hits. As indicated in the d1 form of Browse mode (Figure 3), one example (9 of 44) showed a product quite similar to that of the target molecule **1**. The data in d1 form displayed information on reactants, reagents used, conditions, yields, and literature references. The literature reference for hit 9 led to an original publication describing the synthesis of optically active spirohydantoin via asymmetric induction.<sup>41</sup>

As shown in Scheme 2, the spirohydantoin **8** with *R*-configuration was prepared by first treating 2,3-dihydro-

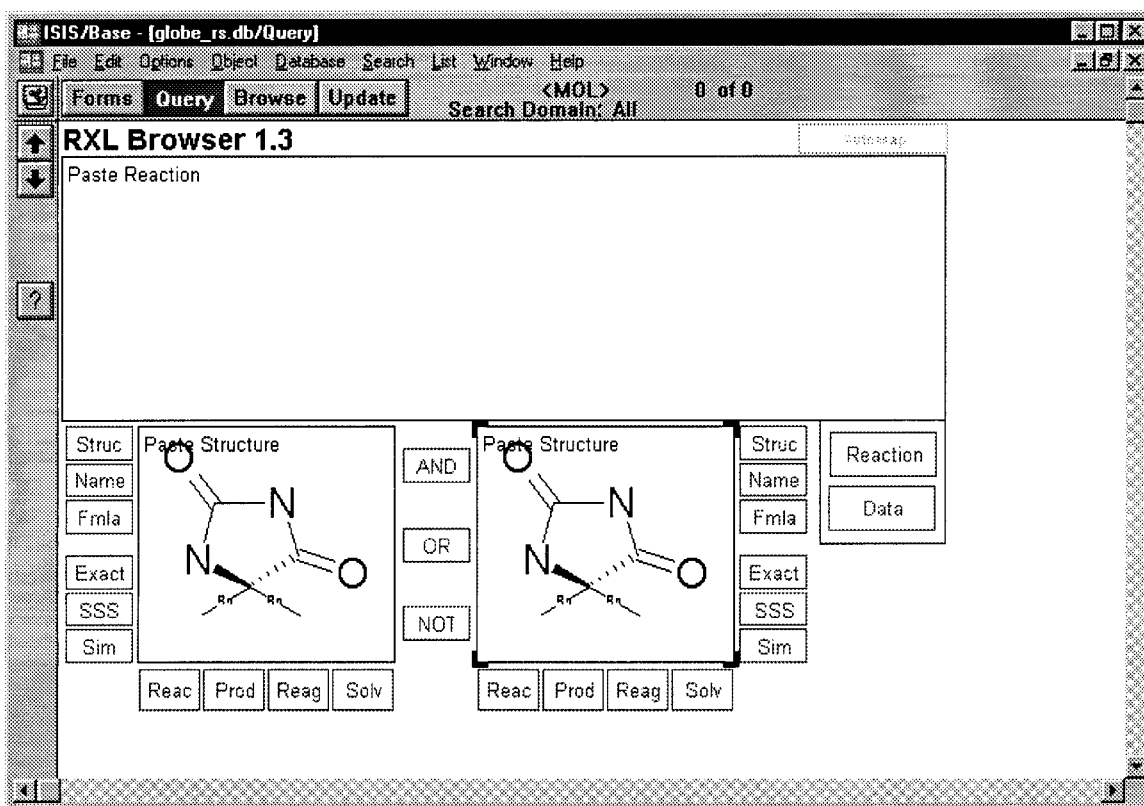


Figure 2. Search SSS as Product/Not SSS as Reactant.

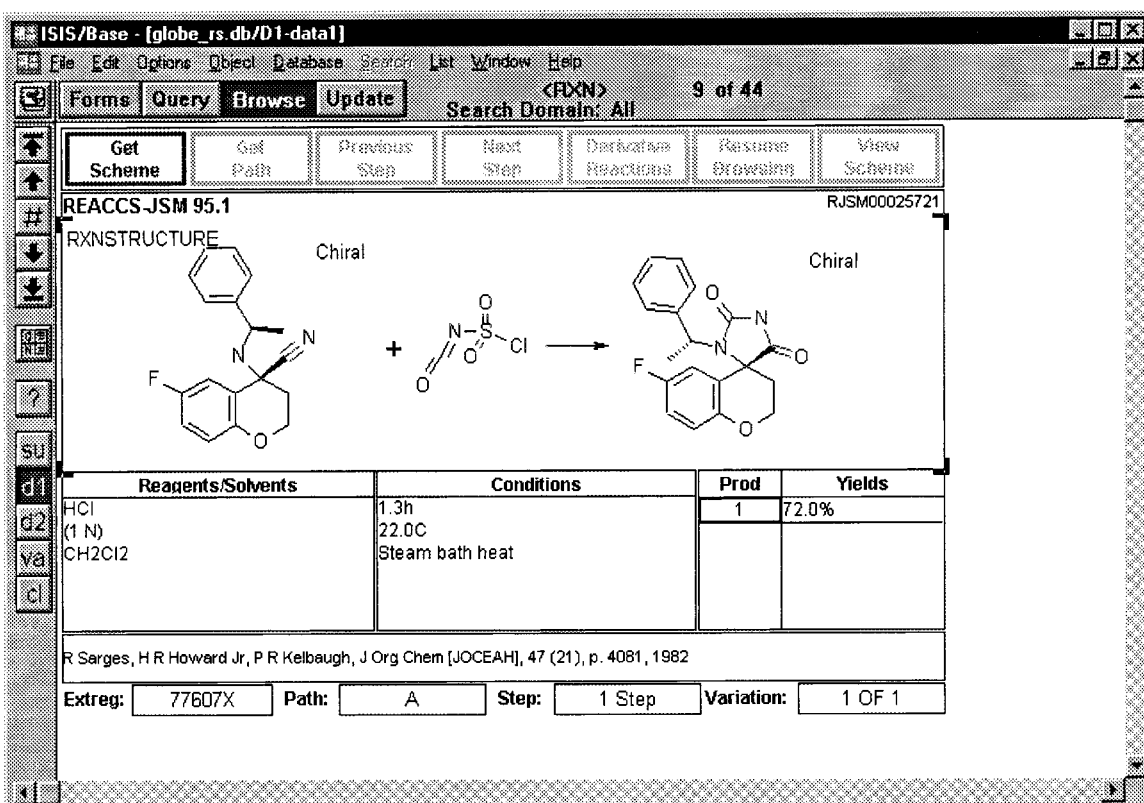
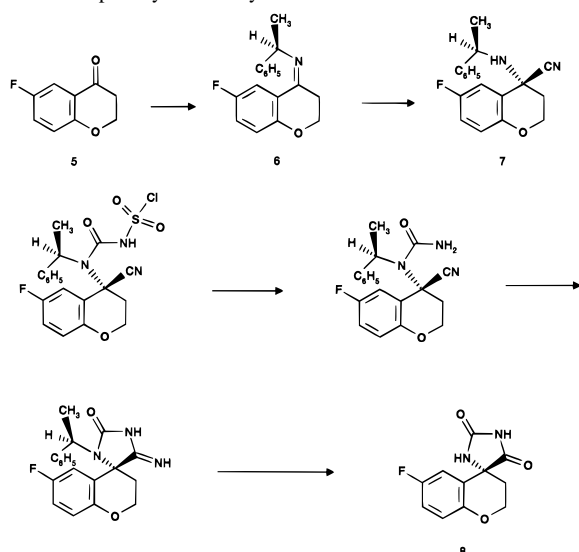


Figure 3. Search hits for spirohydantoin shown in d1 form.

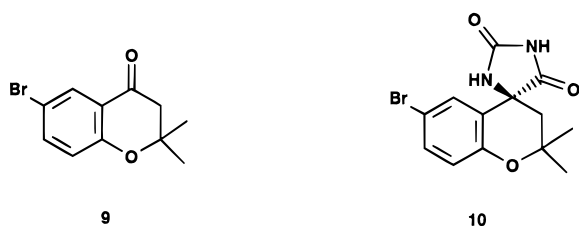
6-fluoro-4*H*-1-benzopyran-4-one (**5**) with (R)-(+)-methylbenzylamine in the presence of TiCl<sub>4</sub> to give imine **6**. Subsequent treatment of compound **6** with HCN in ethanol induced the crystalline and diastomerically pure 4-*R* aminonitrile **7**. This sterically hindered aminonitrile was then reacted with highly reactive chlorosulfonyl isocyanate to give, after hydrolysis, the final product **8** with retention of

the stereo configuration. This final step (i.e., compound **7** to compound **8**) was essentially a modification of the Bucherer–Bergs synthesis.<sup>40</sup>

This literature example retrieved from reaction searches in globe\_rs.db undoubtedly solved the most important synthesis problem for the target molecule **1**. It suggested that the optically active compound **10**, a precursor of

**Scheme 2.** Optically Active Hydantoin Formation

compound **1**, with *S*-configuration could be synthesized in a similar manner using 6-bromo-2,2-dimethyl-4-chromanone (**9**) and (*S*)-(-)- $\alpha$ -methylbenzylamine as the starting materials.



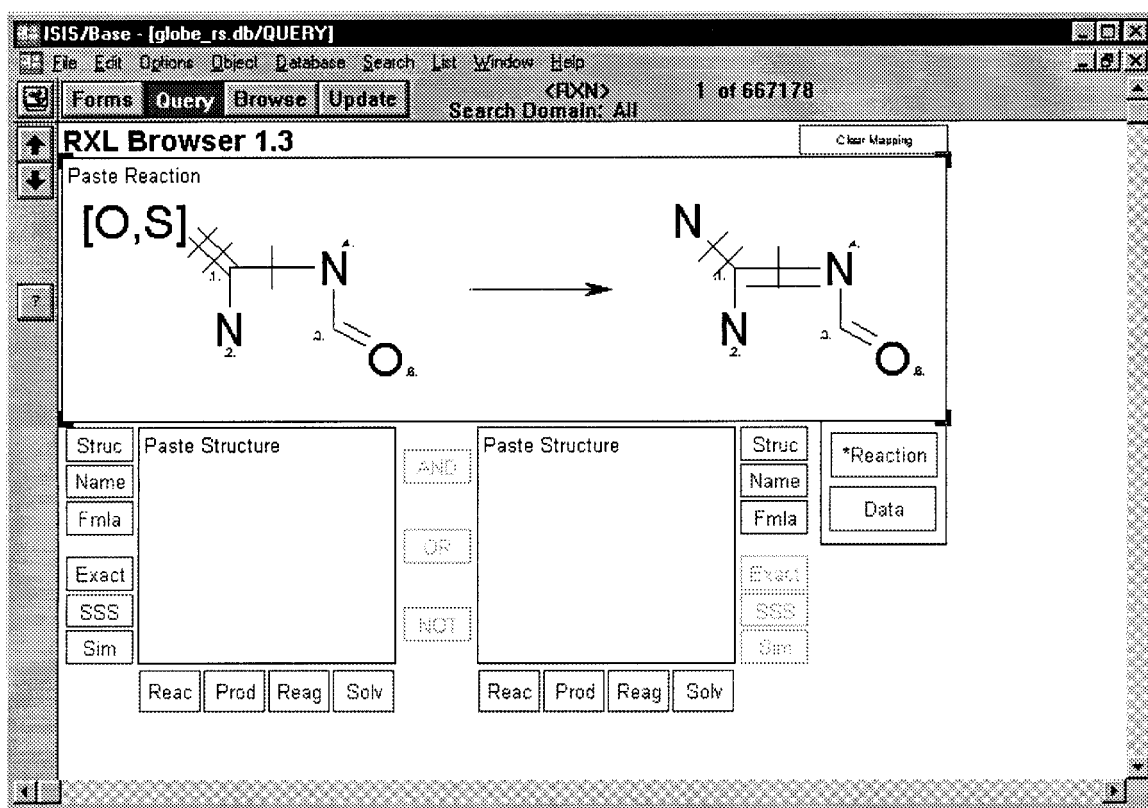
The next step was to find the formation of the 2-aminoimidazolone fragment **2** via hydantoin **3**. Since this step primarily involved the conversion of an urea to a guanidine

moiety, a more general reaction query such as the one shown in Figure 4 was employed. An RSS of this query resulted in 19 hits. One example showed a mild and efficient method for the preparation of guanilidines from thioureas (Figure 5). The thiourea generally can be synthesized from urea using Lawesson's reagent.<sup>42</sup>

In the last step a substructure search (SSS) for 2,2-dimethyl-4-chromone (**4**), an analogue of compound **9**, was conducted and obtained 121 hits. One literature reference<sup>43</sup> suggested that compound **9** could be conveniently prepared from 5'-bromo-2'-hydroxyacetophenone. To search for the readily available starting materials, an exact structure search was conducted in the ACDXSCl database (acdxscl.db). This is an in-house chemical inventory database management system that combines the information from MDL's Available Chemicals Directory (ACD)<sup>44</sup> and our XSCL sample collection of available reagents. The result revealed that 5'-bromo-2'-hydroxyacetophenone is commercially available from Aldrich (Figure 6).<sup>45</sup>

On the basis of the search results described above, we have derived a complete synthesis plan for the target molecule **1**, which is shown in Scheme 3. The key to this synthesis is that the reaction of 6-bromo-2,2-dimethyl-4-chromanone (**9**) with the optically active (*S*)-(-)- $\alpha$ -methylbenzylamine in the presence of  $\text{TiCl}_4$  will give ketimine **11**, which is followed by the treatment with  $\text{HCN}$  to yield enantiomerically pure benzopyran **12**. The sterically hindered aminonitrile is then reacted with highly reactive chlorosulfonyl isocyanate via a modified Bucherer-Bergs reaction to afford the optically active spirocyclic benzopyran imidazolidinedione **10**. Finally, the desired target compound **1** is synthesized from compound **10** via thiourea **13**.

A laboratory synthesis of compound **1** was reported by Gadwood and co-workers at Upjohn.<sup>32</sup> The major difference is that they used molecular resolution to achieve the

**Figure 4.** Reaction query of guanilidine from urea or thiourea.

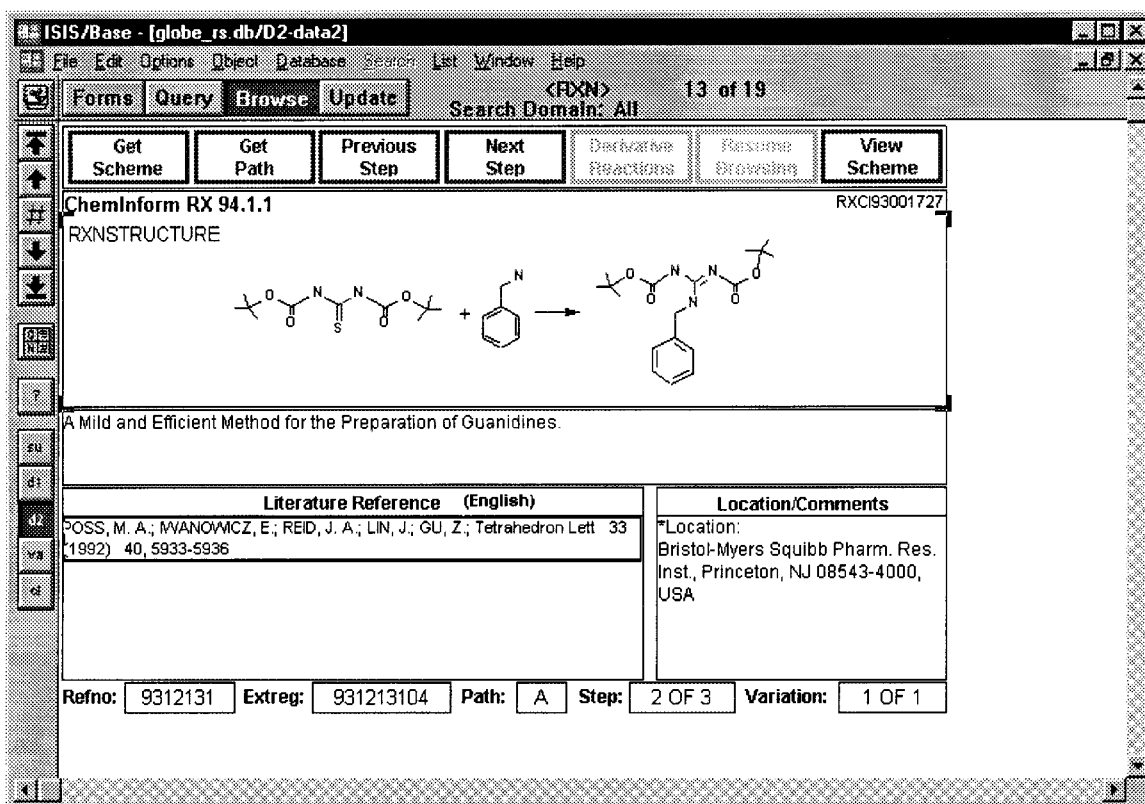


Figure 5. Search hits for guanilidine shown in d2 form.

ACD 95.2a CAS# 1450-75-5 MF: C<sub>8</sub>H<sub>7</sub>BrO<sub>2</sub> MW: 215.0480

MFCD00191850 Name: 5'-BROMO-2'-HYDROXYACETOPHENONE

Information

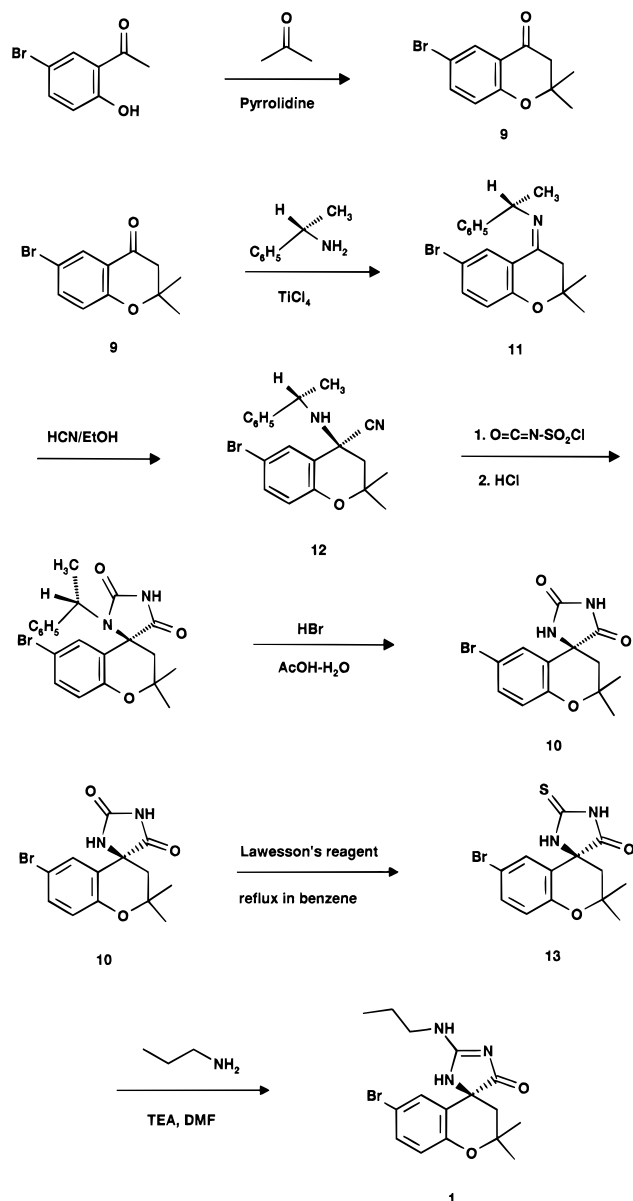
Supplier	Catalog #	Amount Units	Currency	Price	Purity
ALDRICH	9502				
ALDRICH	9502				
	5'-BROMO-2'-HYDROXYACETOPHENONE				
	1450-75-5				
F	38,340-6	10 G	USD	14.00	98%

Figure 6. Search suppliers in ACDXSCL database.

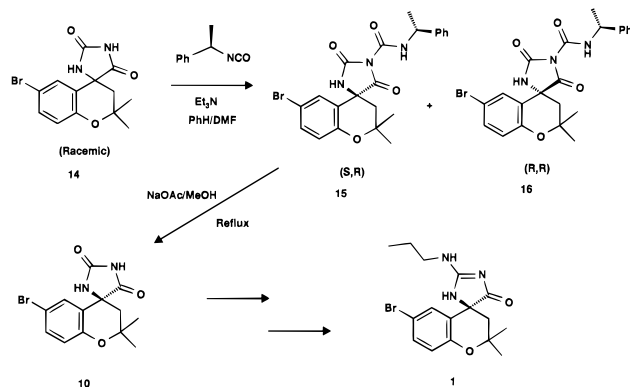
enantiomerically pure compound **1**. They also employed general conditions of the Bucherer–Bergs synthesis (i.e., potassium cyanide and ammonium carbonate)<sup>33</sup> for benzopyranone **9** to afford racemic spirohydantoin **14**. Reaction of compound **14** with *R*- $\alpha$ -methylbenzylisocyanate in the presence of triethylamine afforded two diastereomeric adducts **15** (*S,R*) and **16** (*R,R*), which were then separated by

medium-pressure chromatography. Treatment of compound **15** with NaOAc in methanol under reflux gave compound **10**. The final product **1** was then prepared from compound **10** via thiourea, similar to the conditions described in Scheme 3.

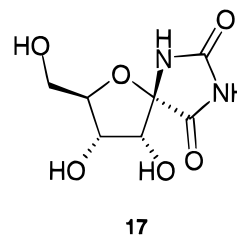
As we can see, the reaction sequences and conditions outlined in the synthesis plan for compound **1** derived from

**Scheme 3.** Synthesis Plan for **1** Derived from Reaction Searching

reaction searching in this case study are surprisingly similar to the laboratory synthesis reported by the Upjohn chemists. This clearly illustrates the power and effectiveness of applying the concept of retrosynthetic analysis to computer-assisted reaction searching. The synthesis plan for compound **1** was not executed in our laboratories. However, some of the key steps in this plan were utilized to perform the synthesis of structurally similar compounds with agrochemical interests.



Two features in RXL Browser are potentially useful for reaction searching. The users can turn on Cluster Browsing so that reactions retrieved from a search are preclassified by reaction types. The reaction types are classified with cluster values of Broad, Medium, and Narrow based on the chemical changes that occur in the reaction centers and in the atoms that surround the reaction centers.<sup>46</sup> Another feature is the ability to display an entire synthetic scheme by retrieving an image of the ChemInform<sup>22</sup> publication if the search hit is coming from ChemInform RX.<sup>28,47,48</sup> This information is very useful for synthetic chemists who want to learn more about the scope and limitations of the synthesis for a known compound. For example, (+)-hydantocidin **17** is a natural spironucleoside isolated from the fermentation broth of *Streptomyces hygroscopicus* that exhibits potent herbicidal activity.<sup>49,50</sup>



Compound **17** has been synthesized and reported in the literature.<sup>51–53</sup> A Current Mol. Search/Flexmatch in globe\_r-s.db and subsequent clustering of the search result (Cluster Value: Medium) showed that there were six hits within three clusters. This suggested that there might be three different methods reported for the synthesis of compound **17** (Figure 7). Since all of these hits came from ChemInform RX, by clicking View Scheme button, the entire reaction schemes and abstracts for the synthesis of compound **17** could be retrieved. This process allowed us to easily compare the scope and limitations of each pathway (or method) for synthesizing the same compound. For instance, the reaction scheme shown below is a printout of the ReView (no. 9448025) form produced by clicking the View Scheme button in RXL Browser. It illustrates a simpler and more efficient synthesis<sup>53</sup> of (+)-hydantocidin among those retrieved from ChemInform RX.

**Stereoselective Bromination of  $\beta$ -Ribofuranosyl Amide. Enantioselective Synthesis of (+)-Hydantocidin.** The synthesis of hydantocidin (**VIII**), a potent herbicidal natural product, is accomplished by the stereoselective NBS-bromination of the  $\beta$ -D-ribofuranosyl amide (**I**), subsequent spirocyclization about the anomeric position and final deprotection. (work by Harrington and Jung<sup>53</sup> at American Cyanamid).

It should be pointed out that clustering of search results based on the reaction types as described above is not always useful, particularly in substructure searches (i.e., SSS or RSS). In these cases, the number of hits can be large, and it may take a significant amount of additional processing time before the user can review the search results. Occasionally, the number of clusters is so large that it does not provide any additional useful information. In this author's view, clustering of the reaction query results based on the traditional perception of reaction types such as substitution, addition, elimination, rearrangement, oxidation, reduction, free radical, and photochemical would be more useful to synthetic organic chemists. Implementation of such a feature

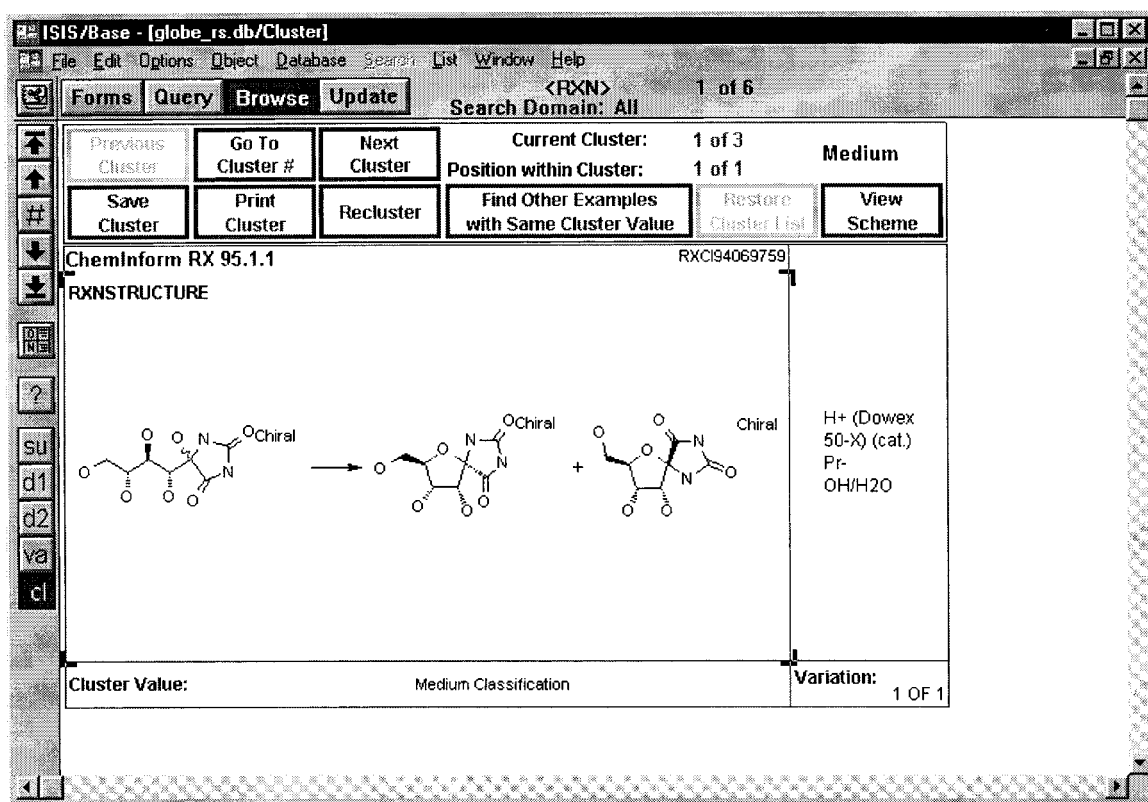
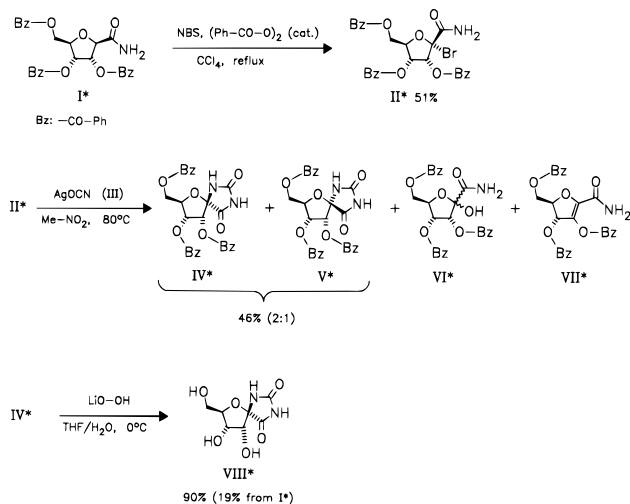


Figure 7. Cluster of the search result shown in c1 form.



in RXL Browser would undoubtedly enhance the power of this already very useful reaction database access system.

### CONCLUSION

This paper is intended to illustrate how we have successfully applied Corey's concept of retrosynthetic analysis to computer-assisted reaction searching directed toward the synthesis of target molecules. This process, coupled with our perception of reaction similarity and effective use of appropriate functionality in the RXL Browser, has resulted in a sequence of precursors along the reaction pathway that led to the selection of commercially available starting materials for chemical synthesis.

The results of this case study suggest that effective use of computer-assisted reaction searching for synthesis planning by chemists can result in an increase in efficiency and productivity in chemical research. There are other commercially available reaction database access systems designed

for chemists as the end-users.<sup>54-56</sup> Recently, we have implemented the CrossFireplusReactions<sup>54</sup> at American Cyanamid. This is a new client-server-based CrossFire System introduced in 1996 for accessing the Beilstein database by Beilstein Information Systems, Inc. This new addition will provide our users the ability to choose from two different database access systems for reaction searching. Any comparison regarding the features and performance of the RXL Browser and CrossFireplusReactions is beyond the scope of this paper. However, it should be pointed out that regardless of which access system is used, the system should be flexible and intuitive enough to allow chemists to conduct reaction searches interactively. At the same time, it should enable them to modify and execute search strategies based on their chemical knowledge and functionality in the system. Furthermore, the system should be able to interface with other computer applications. With the continued increase in the size of commercial reaction databases and improvement of the access systems, computer-assisted searching of reaction databases for synthesis planning has undoubtedly become an important part of chemical research for lead discovery and process improvement in agrochemical and pharmaceutical laboratories.

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