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# WTDWTR: What To Do With This Reaction? A New Program in the Field of Computer-Aided Synthesis Design – Application to the Diels–Alder Reaction

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We present WTDWTR (What To Do With This Reaction?), which is a new program in the field of computer-aided organic synthesis. WTDWTR tries to answer the question: what kind of structures can be obtained from a given reaction? We present the results that were obtained for the Diels–Alder reaction of structures that possess four fused rings of size 6, 6, 6 and 5 ("isomers" of the steroidal skeleton) for which WTDWTR generated 590 solutions.


## Introduction

Many programs have been developed in the field of computer-aided organic synthesis. They can be divided into four main categories.[1] The principal program is on the subject of retrosynthesis: starting from the target compound, the program searches its precursors and the process is repeated until it generates commercial or simple starting materials. The second program tries to directly find the starting materials hidden in the target. The third program searches for the key step of the synthetic sequence. Finally, several programs have also been developed to work forward from the starting materials.

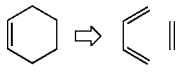
If we consider the syntheses published in the literature, one can remark that a largely used method is to start from a given reaction: the chemist is familiar with a particular reaction (Diels–Alder, radical cascade, [2+2+2], de Mayo, etc.) and he searches for a structure for which it is possible to apply this reaction as the key step in its synthesis. Holowin has been developed to retrosynthetically find the key step of a synthesis.[2]

In 1988, we wrote SCORE (SCOpe of a REaction), a program which tried to follow this approach by generating structures that are able to be formed by a given reaction.[3] SCORE was developed on an old computer without the facilities of the recent ones, so we decided to write a new program inspired by SCORE called WTDWTR. Many improvements have been incorporated. The main ones include graphical description of the reactions, automatic and interactive versions, addition of several rings in one step, perception of symmetry, constraints on the kind of rings (spiro, fused, bridged), automatic drawing of the results, elimination of identical structures, generation of basic skeletons, printing of the results, introduction of heteroatoms and multiple bonds.

Cyclic structures are among the most important ones in organic chemistry. So, the aim of WTDWTR, as it was for its predecessor, is to generate the cyclic structures which correspond to a given reaction. In a first approach only carbocyclic structures are generated.

### Program

To describe the program let us consider the classical Diels–Alder reaction shown in its retrosynthetic form in Scheme 1. To build the different possible cyclic structures in which the reaction is present, the program has to add rings onto the cyclohexene unit. The corresponding precursors are generated in a second step. For example, if WTDWTR has to generate fused structures with a new six-membered ring, it must generate the four structures of Scheme 2 and their precursors. These four structures can then be used to generate a new set of structures with one more ring, and the process can be repeated as many times as necessary.



Scheme 1.

The first part of the program is the input of the starting reaction. The user draws it on the screen using the mouse: the target (on which the rings will be added, for the Diels–Alder reaction it is the cyclohexene ring) and its precursor.

Then, for the generation of the structures, several problems must be solved: (1) Addition of a ring is, in fact, to introduce a chain of atoms between two atoms of the target. So, the first problem is to calculate the number of atoms to add. If the program has a six-membered ring to add be-

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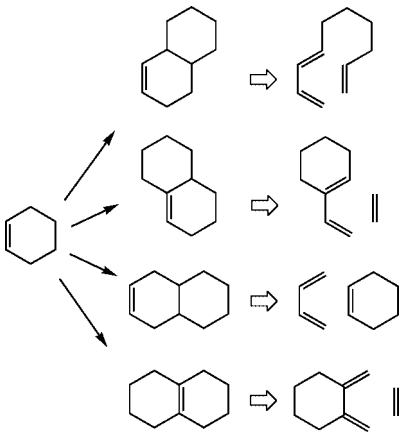


Scheme 2.

tween two atoms which are separated by *n* atoms, it has 6 – (2 + *n*) atoms to introduce in the connectivity tables that are generated. (2) Symmetry is perceived in order to avoid the generation of identical structures. (3) To avoid valence violation, before a ring is added WTDWTR checks the valence of the atoms. (4) To draw the solutions on the screen of the computer, the coordinates of the atoms of the generated structures are calculated by a subroutine already developed in the past.[4] (5) During the process of generation, identical structures may be created. So, when a structure is generated, the program verifies if it is new or not.

The program is automatic: the user selects a reaction, a file where to save the results, then he indicates the number of rings to be added and the size of each ring. At this step, a new option is available. The user may select the kind of structures that are generated – fused, spiro or bridged – and the number of rings of each category. He may specify, for instance, that he wants only fused structures, or structures with fused rings, one bridge and no spiro rings. All combinations are possible. Let us take the example of the synthesis, by the Diels–Alder reaction, of structures related to the steroid skeleton. Because there is already the six-membered ring of the cyclohexene, the chemist indicates that there are 3 rings to add, two of size 6 and one of size 5, and that only fused structures are desired. When the rings to add are of different sizes, a new problem arises. It is necessary to add the rings in all combinations in order to be sure to create all of the solutions. For the previous example, the program will successively try the three following combinations: +6, +6, +5, then +6, +5, +6 and finally +5, +6, +6. Identical generated structures are discarded as indicated above in (5).

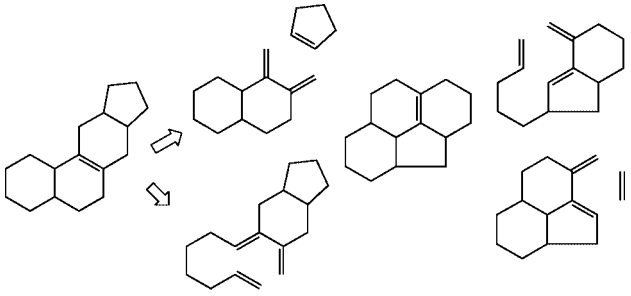
When all of the combinations have been done and all of the solutions have been found, WTDWTR ranks them according to their skeletons. This option facilitates the visualisation of the results because the structures with the same skeletons are grouped together.

When the program is finished, several options are available such as visualisation of the structures, the removal of the structures from the files and the option to print the solutions.

WTDWTR was developed in Visual Basic for PC compatible microcomputers.

## Results

The program has been tested on many reactions. We present here the results obtained for the Diels–Alder reaction applied to the synthesis of "analogues" of steroids as described above: two 6- and one 5-membered rings are added onto the starting cyclohexane ring.. Because the steroid skeleton is made up of fused rings, we asked the program to generate only these kinds of structures. WTDWTR generated 553 structures and 590 solutions. There are more solutions than structures because several of the structures possess two precursor units (Scheme 3).



Scheme 3.

Because all of the structures possess a double bond, we wrote an option to remove it, which generates only 48 saturated skeletons. This result confirms the one obtained with GASP, a computer program that generates structures having a given number of rings whose size is fixed by the chemist.[5] These 48 structures are gathered in Figures 1 to 3.

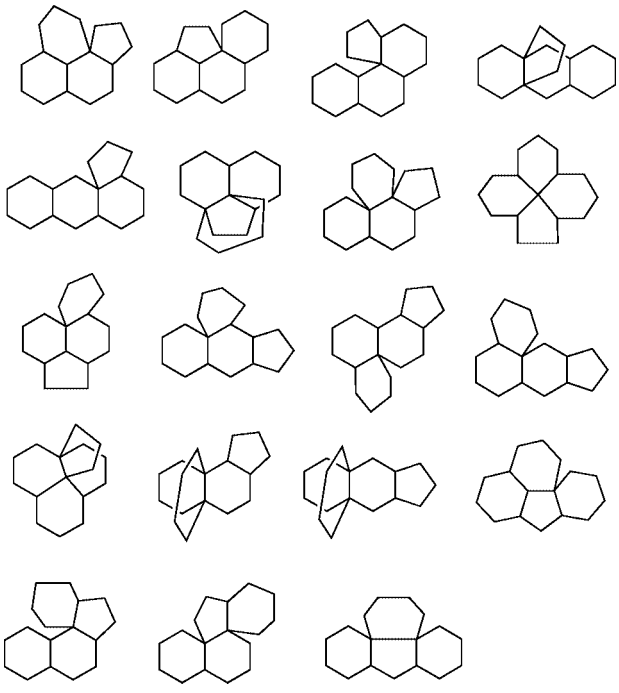


Figure 1. Fused structures not found in the Beilstein database.

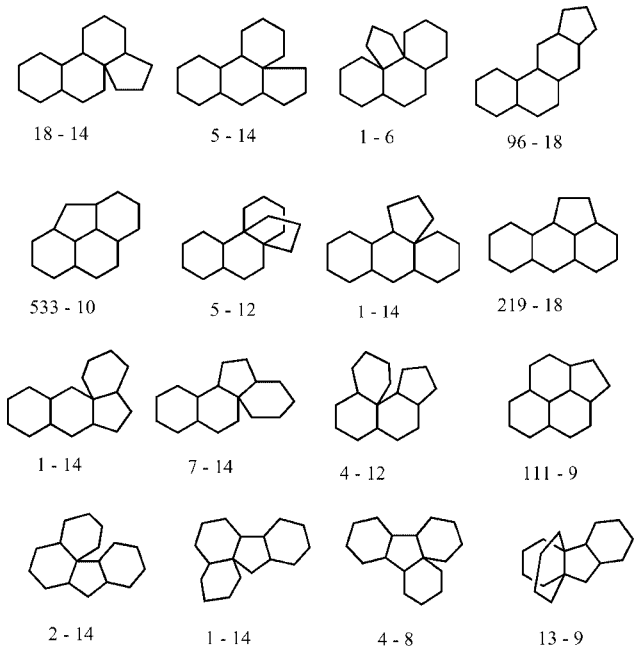



Figure 2. Known fused structures with the number of hits found in the Beilstein database and the number of possible Diels–Alder reactions to build the skeleton. No Diels–Alder syntheses have been described for these structures.

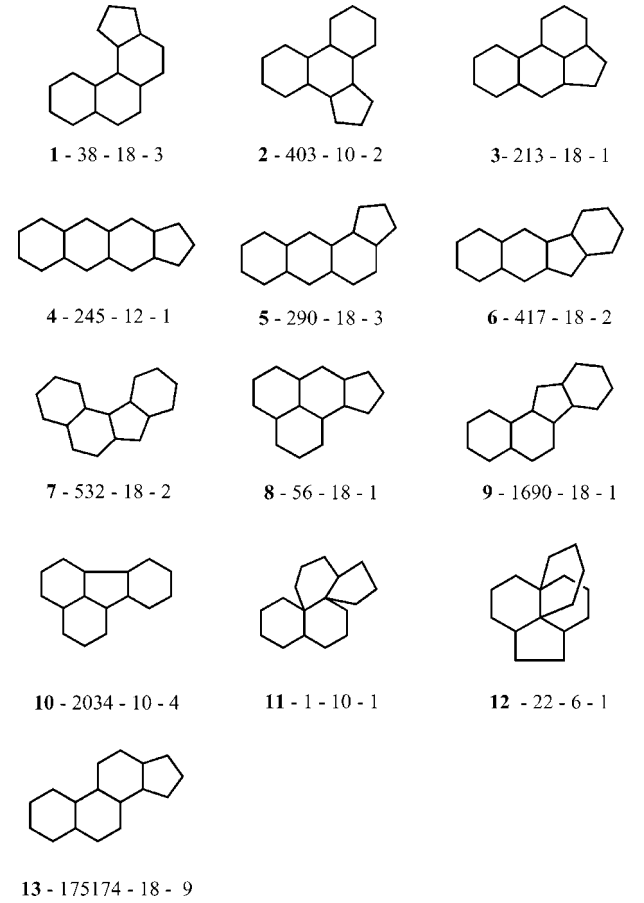



Figure 3. Known fused structures. The number under each structure indicates: (1) the number in the text, (2) the number of hits in the Beilstein database, (3) the number of possible Diels–Alder reactions and (4) the number of syntheses involving Diels–Alder reactions found in the database (see Figures 4, 5, 6).

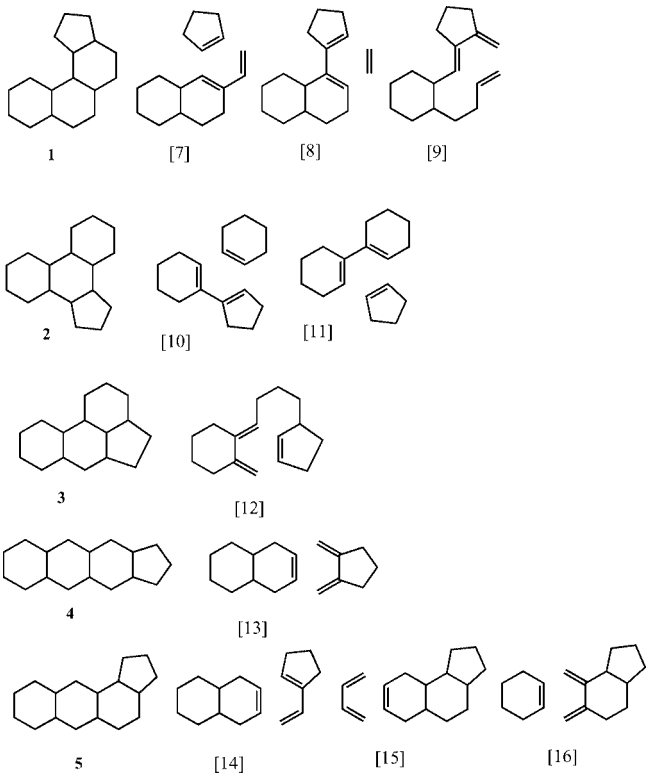



Figure 4. Known Diels–Alder schemes for structures **1**–**5**. Numbers in square brackets are reference numbers

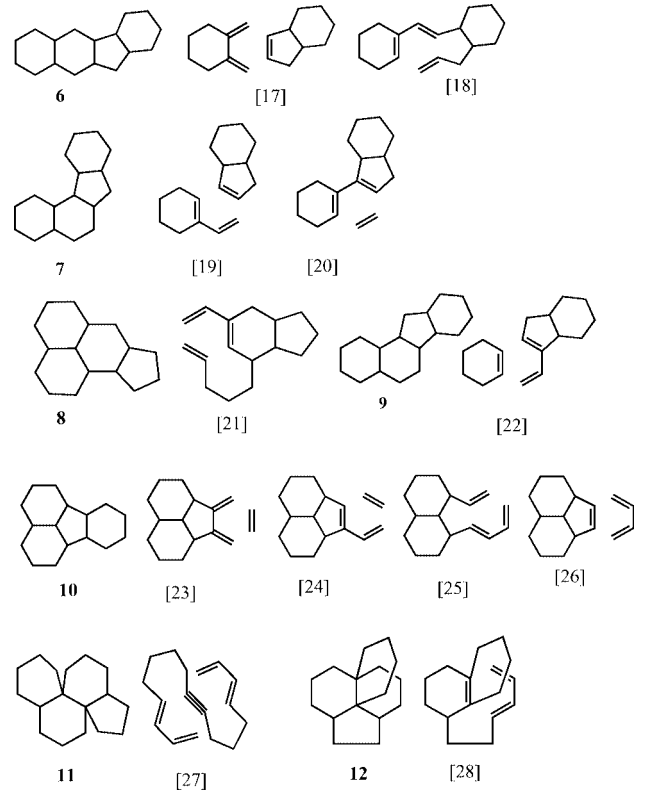



Figure 5. Known Diels–Alder schemes for structures **6**–**12**. Numbers in square brackets are reference numbers.

As it was done for GASP, a bibliographic search was conducted in the Beilstein database.[6] In the query, the bond order was set to "any", which allowed for the search of not only skeletons but also structures having multiple bonds, and all atoms sites were set to "free" (i.e. they can bear any substituent).

Figure 1 shows the structures which are unknown. Figure 2 displays structures which have been described but for which no Diels–Alder syntheses are known. The structures for which Diels–Alder syntheses have been found are displayed in Figure 3. It should be noted that the number of hits does not correspond to the number of references. For example for structure **12** there are 22 hits which correspond to only 4 references. The number of hits corresponds to the number of synthetic paths in the various articles.

The different kinds of Diels–Alder schemes that are found in the literature are displayed in Figures 4 and 5. The number of Diels–Alder routes for the different structures is low compared to the number of theoretical possibilities. It is obviously due to the structures themselves and their synthetic interest.

Figures 6 and 7 present the 18 possible Diels–Alder routes for the synthesis of the steroid skeleton. Known solutions are displayed in Figure 6, and Figure 7 displays those which have not been described. Because of the importance of steroids, the majority of the 18 possible schemes have been explored by this reaction. Nevertheless, some interesting ones such as **23** to **27** have not yet been developed, which shows the possibility of WTDWTR to suggest new synthetic strategies even for well-known structures.

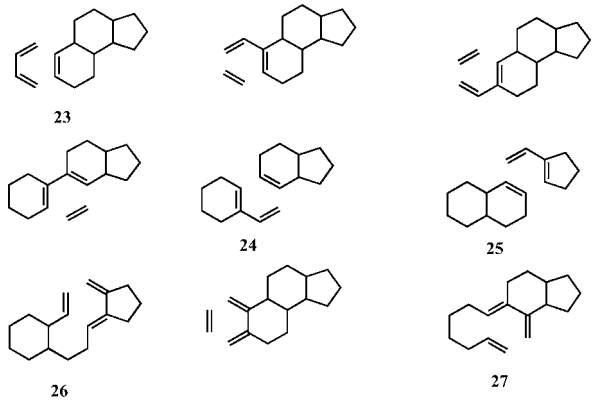



Figure 7. Diels–Alder approaches for the preparation of the steroid skeleton that are not found in the Beilstein database.

Finally, a new option has been written to introduce heteroatoms or multiple bonds into the solutions. It is possible to do this on a file of structures or on only one structure. To illustrate this option we selected the generation of iso-

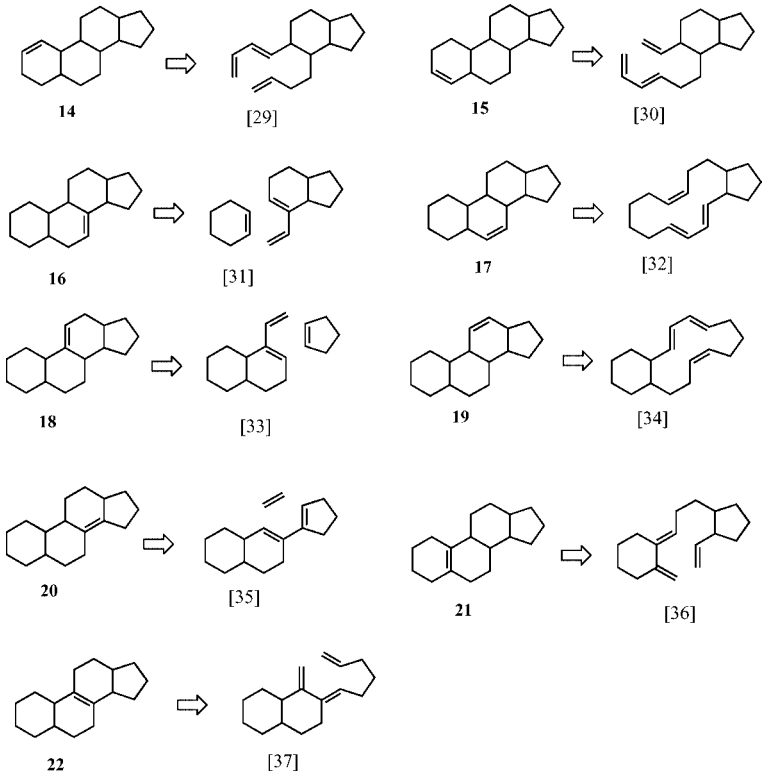



Figure 6. Known Diels–Alder strategies for the preparation of the steroid skeleton. Numbers in square brackets are reference numbers.

mers of the steroid skeleton with one and two nitrogen atoms. A bibliographic search has been done in the Beilstein database. All structures with one nitrogen atom are known. Figure 8 shows the number of hits found in the database for each position.

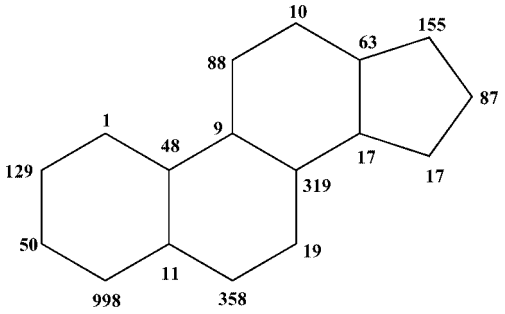



Figure 8. Number of hits for each position of nitrogen in mono azasteroids.

With two nitrogen atoms, WTDWTR generated 136 structures. Among them, 51 have been described and 85 are new. Figure 9 and Figure 10 show the known structures with the number of hits for each compound. All other combinations have not been found in the database.

## Conclusions

WTDWTR is a new approach in the field of computer-aided organic synthesis. In place of searching for a plan of synthesis for a given target, it tries to answer to the question: "What kind of cyclic structures can be obtained from a given reaction?". This approach may point out an original key step in the synthesis of such a compound.

Although for the sake of simplicity we selected the Diels–Alder reaction, there should be no technical difficulty to select a given biosynthetic reaction and apply it to starting compounds that are biologically simple and widespread, and to possibly generate new leads in a synthetic pathway.[38]

Furthermore, since WTDWTR is a structures generator it can be considered as a new combinatorial chemistry program, and it can suggest new analogues in a family of pharmacologically active structures.[39]

The program is available upon request from the authors.

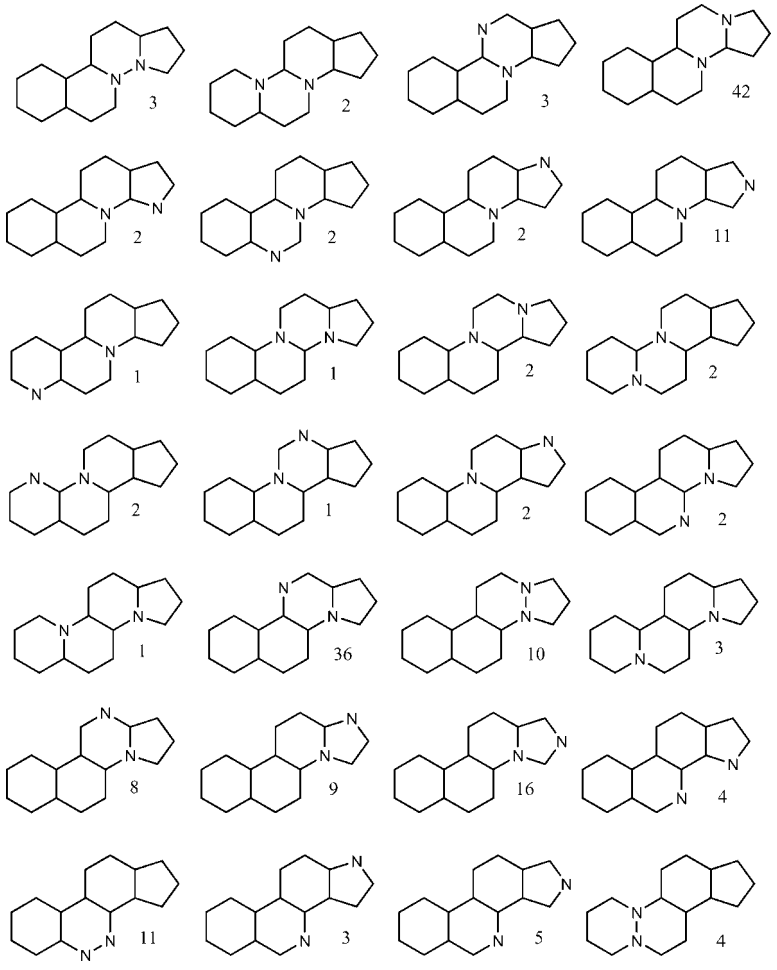



Figure 9. Diazasteroids found in the Beilstein database with the number of hits.

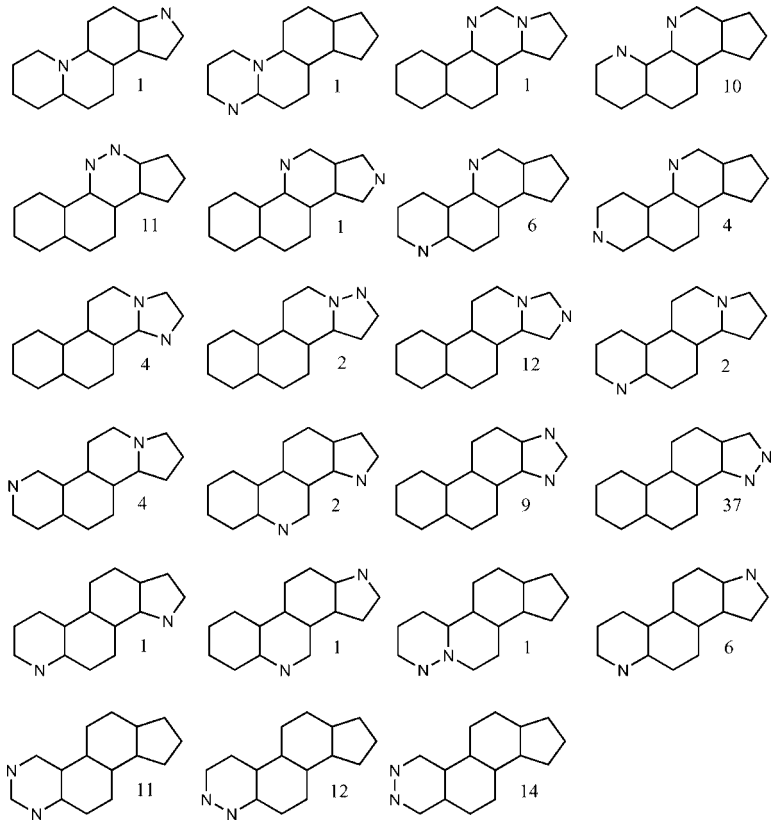



Figure 10. Diazasteroids (continued).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