PRODUCT FOCUS

World largest collection of tangible building blocks and fragments for drug discovery

Synthesis of small organic molecules lies at the hard of modern drug discovery (1). High throughput biological screening (2) requires large diverse libraries of organic compounds whose structures and physical properties (molecular weight, clogP, logS, number of hydrogen bond donors and acceptors) obey certain rules such as rule of 5 (3) that increase the probability of biological activity. In silico designed focused libraries of small molecules are synthesized through attaching various functional groups to molecular cores (scaffolds) in a fashion predicted to maximize ligand – target interactions (4). The finding of small molecules (fragments) capable of interacting with binding sites of target biomolecules plays a key role in fragment based (5) structural design of potential drug candidates. Thus all these approaches rely upon availability or synthetic feasibility of small molecules that can be functionalized or linked to give compounds with predicted physical properties, chemical structure and biological activity. The functionalization of building blocks or linking fragments should result in drug like molecules obeying the rules of drug likeness, which puts a strict restraint on physical properties of building blocks and fragments that may be useful for drug discovery. The rule of 3 sets up the most common thresholds for molecular weight, cLogP, LogS, number of hydrogen bond donors and acceptors of building blocks and fragments suitable for the synthesis of biologically active compounds (6). A simpler approach is based on the fact that physical properties of a compound depend on the number of non-hydrogen (heavy) atoms making up its molecule. In case of molecular weight this dependence is obvious and mathematically simple whereas for cLogP and LogS it is much more complicated. Simple statistical analysis revealed that building blocks suitable for the synthesis of drug like compounds should consist up to 21 heavy atoms (7).

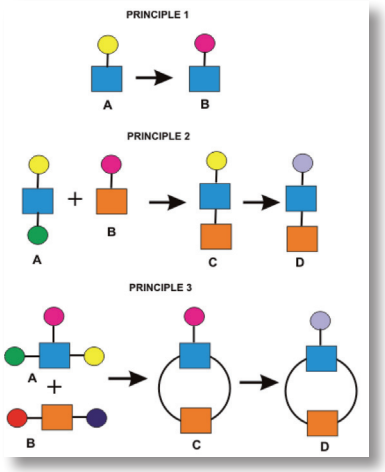

Figure 1. Design principles for building blocks and fragments. Rectangles-fragments, circles – active groups.

In 2007 UORSY Ltd (www.uorsy.com) and Enamine Ltd (www.enamine.net) have launched a joint project in order to establish a systematic chemically validated approach to tangible building blocks that consist of up to 21 heavy atoms and therefore can be used in medicinal chemistry and drug discovery. The approach is based on three types of well known and optimized organic reactions (reaction sequences) that result in molecules containing one reactive functional group such as NH_2, NHR, SH, SR, COOH, C=O, CN, CONHR, SO_2Cl, CSNHR etc. The main design principles of monofunctional building blocks and fragments for drug discovery are presented in Figure 1.

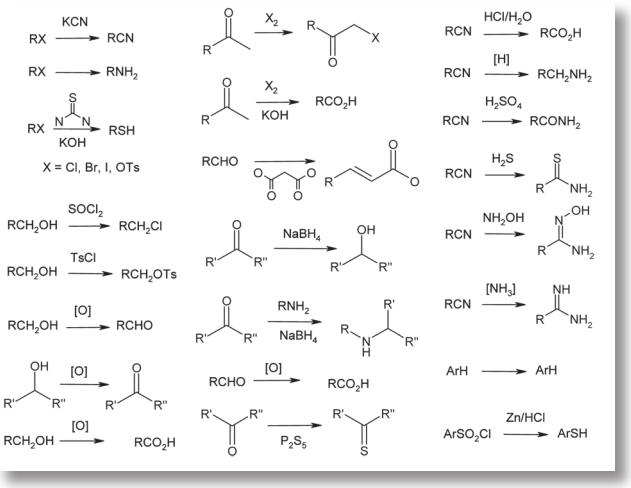

Figure 2. Examples of reactions used in the synthesis of building blocks according to principle 1.

Principle 1 is based on the transformations of monofunctional building blocks **A** to monofunctional building blocks **B**. This approach allows synthesizing n compounds **B** from n compounds **A**. Examples of reactions used in this approach are shown in Figure 2.

Principle 2 (Figures 1 and 3) is based on the selective reactions of bifunctional compounds **A** with monofunctional compounds **B** resulting in monofunctional building blocks **C**. Compounds **C** can be used as starting materials for the synthesis of compounds **D**. Apparently n compounds **A** and m compounds **B** can be transformed to nxm compounds **C** and **D**.

Principle 3 (see Figures 1 and 4) is based on cyclization reactions of trifunctional compounds **A** and bifunctional compounds B resulting in monofunctional cyclic building blocks C that can be further converted into compounds **D**. This principle allows synthesizing mxn building blocks **C** and **D** from m and n starting materials **A** and **B**.

1050 Reaction sequences of Principles 1-3 were used for virtual synthesis of building blocks from ca 4000 commercially available and 4500 Enamine/UORSY proprietary starting materials containing less than 13 heavy atoms to generate primary set of tangible building blocks. Tangible structures consisting of more than 21 heavy atoms were removed from the original set to give 2,100,000 structures of tangible building blocks suitable for drug discovery. To the best of our knowledge (8) this is the world largest commercial collection of tangible building blocks and fragments specially designed for drug discovery. The main chemical classes of tangible building blocks are listed in Table 1. The average values for number of heavy atoms, Mw and cLog P of the tangible building blocks are 18.3, 2.3 and 272, respectively. The distributions of calculated physical properties of tangible building blocks are shown in Figure 5.

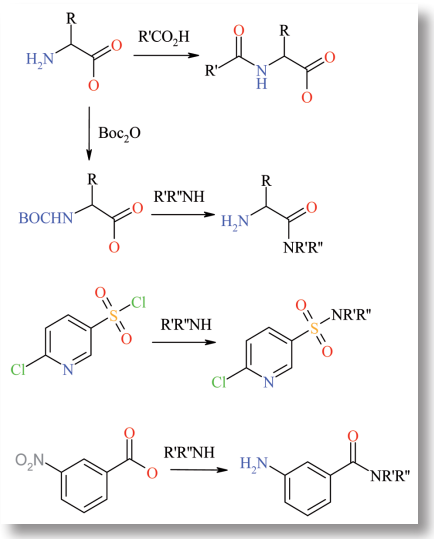

Figure 3. Examples of molecular design according to Principle 2.

Type of Building Blocks	Number Structures
Primary and Secondary Amines	1 250 000
Carboxylic Acids	380 000
Amino Acids	65 000
Alkylating and Arylating Agents	170 000
Sulfonyl Chlorides	5 000
Aldehydes and Ketones	87 000
Alkyl- and Arylhydrazines	5 100
Alcohols	189 000
Phenols	66 800
Thiols	10 400
Amidoximes and Amidines	24 000
Aryl bromides and Aryl iodides	235 000
Boronic acids	3500
Alkyl- and Arylazides	3100
Terminal acetylenes	9200

Table 1.

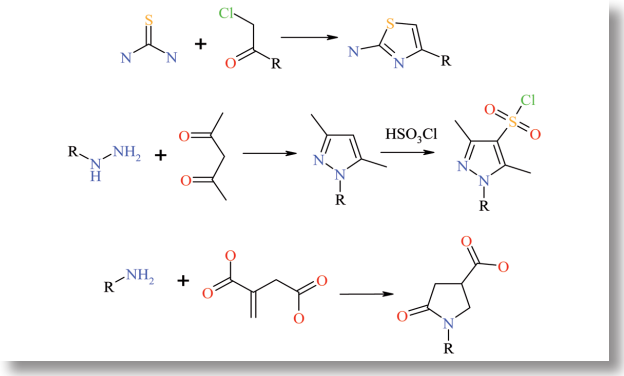

Figure 4. Examples of molecular design according to Principle 3.

Rigorously validated chemical procedures ensure high feasibility and cost effectiveness of tangible building blocks and fragments. About 8500 tangible building blocks were synthesized in 2009 with an average lead time of 5 weeks and feasibility of 80 percent. 4121 of these compounds were selected from the database of tangible building blocks and ordered by pharma and biotech companies worldwide at fixed prices ranging from 200 to 800 EUR per gram. Weekly progress reports on the synthesis of the ordered tangible building blocks and fragments are provided to the customers. Database files with structures, ID's and fixed prices can be found at http://www.enamine.net/files/uorsy. Online search of the database is also available at www.uorsy.com. The golden set of tangible building blocks 3 (300,000 structures, consisting up to 16 heavy atoms) have also been posted at Symyx® Available Chemical Directory (www.discoverygate.com). These databases are updated four times a year.

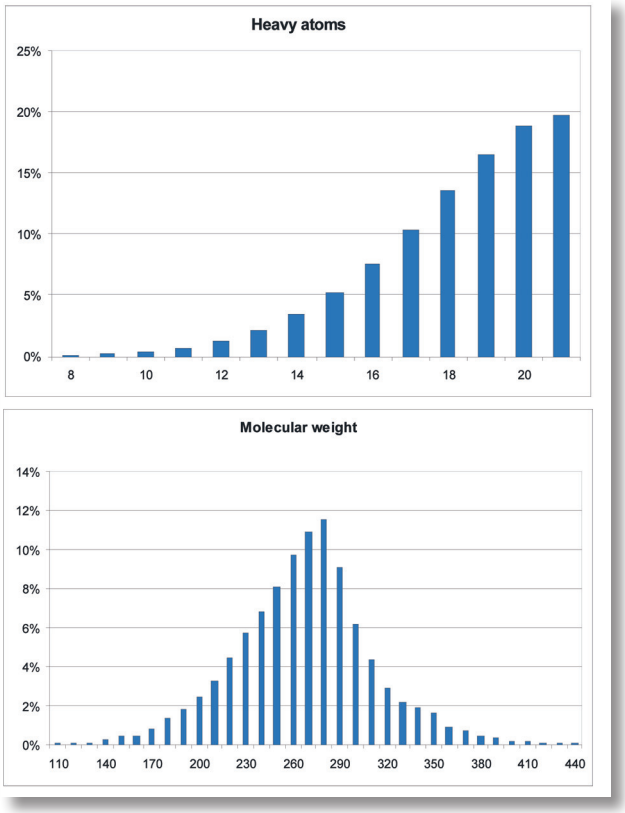

Figure 5. Distributions of physical properties of tangible building blocks and fragments.

REFERENCES AND NOTES

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DMITRY KROTKO[1], ALEXANDER CHUPRINA[2], ALEXANDER SHIVANYUK[2]*, ANDREY TOLMACHEV[2]

*Corresponding author

1. UORSY Ltd, Schchorsa Street 29, Kyiv, 01133, Ukraine
2. Enamine Ltd., Alexandra Matrosova Street 23, Kyiv, 01103, Ukraine