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Lessons from Natural Products Chemistry Can Offer Novel Approaches for Synthetic Chemistry in Drug Discovery

Miniperspective

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INTRODUCTION

Natural products (NPs) are a rich source of new drugs. Of the 877 small molecule new chemical entities (NCEs) introduced in drug discovery between 1981 and 2002, roughly half (49%) were NPs, semisynthetic NPs, analogues, or synthetic compounds based on NP pharmacophores.[1]

After several decades of decline in NPs research we have recently seen a real explosion of interest in natural-based compounds. However, although many NPs have been synthesized since the first total synthesis of urea (Wöhler, 1828), α-terpineol and camphor (Perkin, 1904), tropinone (Robinson 1917), haemin (Fisher, 1929), and equilenin (Bachmann, 1939)[2] the synthesis of every new NP remains a challenging task that is primarily interesting to academic researchers.

At the same time, for the past 30−50 years medicinal chemistry has been evolving in a different direction toward rapid delivery of synthetically more feasible, cost-effective compounds that obey the Lipinsky rules of druglikeness. During this period properties of synthetic compounds such as molecular weight, cLogP, TPSA, rotatable bonds, complexity, and fraction of sp^3-hybridized carbon atoms have changed dramatically.[3]

There are a number of structural differences between NPs and NP-like compounds and synthetic molecules used in medicinal chemistry.[4−7] Both medicinal chemistry and the chemistry of natural products have made tremendous progress in their fields and have developed a repertoire of transformations to achieve their respective target compounds. A recent review written by Roughley et al.[8] analyzes the output from three pharmaceutical companies, GlaxoSmithKline, Pfizer, and AstraZeneca, published during 2008 in the three journals *Journal of Medicinal Chemistry*, *Bioorganic and Medicinal Chemistry*, and *Bioorganic and Medicinal Chemistry Letters*. The authors proposed a set of the most common reactions performed by medicinal chemists working at these top tier pharmaceutical companies, referring to it as a "medicinal chemist's toolbox". Another review described the "toolbox" of a process chemist, working on the discovery and scale-up of the syntheses of potential drugs that originated from medicinal chemistry and were suitable for commercial manufacture.[9] The authors analyzed 128 drug candidate molecules originating from the same three pharmaceutical companies. We suggested that it would be interesting to compose the "toolbox of a NPs chemist" and compare to what degree these three toolboxes coincide. Such a comparison might be also useful because of the following reason.

In recent years drug targets in medicinal chemistry have been getting more complex, and moreover, discovery programs now encounter so-called "undruggable targets" that include protein−protein interactions and protein−DNA interactions. To disrupt such interactions, more complex compounds containing a number of rigidifying (macrocycles, polycycles, olefins, etc.) and protein-binding elements are needed.[10] Natural products can possibly meet these requirements. Simple derivatization of existing natural products scaffolds leads to libraries of structurally similar NP-like molecules, with diversity limited to variations in the periphery while retaining the same skeleton. At the same time it is well-recognized that the search for compounds capable of affecting "challenging targets" requires the generation of structurally diverse compounds. One of the ways to deal with this problem is diversity-oriented synthesis[10−13] that enables the creation of skeletally diverse NP-like libraries.[14,15]

For the design of NP-like libraries it would be helpful to consider the set of reactions that are used for the total synthesis of natural products because the same set may be used for synthesis of NP-like libraries. There are a number of reviews[16−24] describing the application of some types of reactions for the syntheses of certain classes of NPs. However, to the best of our knowledge there is no comprehensive review describing a collection of amassed knowledge and experience of robust transformations used in the chemistry of natural products, the so-called "toolbox of a NPs chemist".

To address this gap, papers devoted to the synthesis of NPs or their fragments, which were published in the *Journal of Organic Chemistry* during 2011, were analyzed. *The Journal of Organic Chemistry* was chosen as one of the most reliable sources of new advances in the field of organic synthesis. Our analysis was restricted to secondary metabolites, excluding such natural compounds as peptides, nucleic acids, and sugars. Reactions for analysis were retrieved manually, and of all processes described only successful reactions leading to target NPs or NP fragments were considered. Reaction sequences that failed at any step or model reactions performed in order to elaborate a method or to study the scope and limitation of some reaction were omitted. All manipulations with protective groups accounted for 26% of total reactions (179 protection reactions and 259 deprotection reactions), which is very close to the percentage of similar reactions in medicinal and process chemistries (24% and 21%, respectively). So although being of high practical relevance, these routine operations are common

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Table 1. Summary Data for Medicinal Chemistry, Drug Candidate Chemistry, and NPs Chemistry Analysis

	medicinal chemistry[8]	drug candidate chemistry[9]	NP chemistry
research institute and university/company input	0/3	0/3	141/8
total papers	139	no data	122
total substances	2973 (3566)[a]	128	144
total number of chemical transformations (excluding protection−deprotection steps)	11290[b]	819	1233
average number of synthetic steps per compound (including protection−deprotection)	4.8	8.1	13.6
percent of chiral compounds	30.65	54	91.7
number of chiral centers per compound	~1	1.04	3.94
percent of chiral centers generated (asymmetric synthesis, relative induction, and resolution) of total stereocenter	13.5 (6.3 for asymmetric synthesis and relative induction)	45 (17 for asymmetric synthesis and relative induction)	57.5 (all for asymmetric synthesis and relative induction)

[a]The total amount of compounds mentioned is 3566. For 2973 of them a synthetic route is outlined. [b]The total number of transformations including protection−deprotection reactions is 14 309. The value 11 290 reflects our extrapolation to get the number of reactions without protective group manipulation. To get this value, we used the data from Table 2 in ref 8 ((5771/7315) × 14309 = 11290, where 5771 is the number of reactions in Table 2, excluding PG manipulation, and 7315 is the total number of reactions in the same table).

for medicinal, process, and NP chemistries. Moreover, although these manipulations are often unavoidable, they are not constructive and do not participate in skeleton formation. This means that as soon as new methods of synthesis not requiring functional group protection are developed, these reactions would no longer be necessary. Thus, we decided to exclude all manipulations with protective groups from our consideration. As a consequence, 1233 reactions used for the synthesis of NPs were chosen for consideration.

REACTION ANALYSIS AND DISCUSSION

Table 1 confirms the fact that NPs synthesis is typically much more complex than the synthesis of small druglike molecules in terms of both the number of synthetic steps and number of chiral centers. On average, while a paper devoted to medicinal chemistry describes 25.7 new compounds, a paper devoted to NP synthesis describes only 1.2 compounds. This fact could reflect the use of combinatorial approaches to generate analogues for SAR in medicinal chemistry, when a set of related compounds are made from a common building block by similar transformations. Derivatization at the late stages in medicinal chemistry (e.g., hit-to-lead optimization) often involves extensive use of routine reactions such as acylation and alkylation. Compounds synthesized by process chemists originate from medicinal chemistry, but the syntheses are directed toward a single drug candidate compound, just as in the syntheses of NPs. That is why we decided to include for comparison not only the medicinal chemistry toolbox but also that of process chemistry.

As expected, the number of chiral centers per compound is considerably higher in NPs than in druglike molecules. While only one-third of all compounds derived from medicinal chemistry (medchem) libraries contain at least one chiral center, most NPs are chiral compounds, containing on average 3.94 chiral centers per molecule. Moreover, more than a half of these centers were generated during the synthesis.

Analysis of the reactions leading to NPs reveals 327 reactions (26.5% of the total number) generating new chiral centers. Almost half of these (143 reactions) yield a hydroxy group connected to an asymmetric carbon atom. Of these, 35 reactions belong to the class of stereoselective reduction of a carbonyl group, and an approximately equal number of reactions (38) execute a nucleophilic attack on a carbonyl group, leading to a hydroxy group, for instance a Grignard or aldol reaction. Eighteen examples of asymmetric hydroxy group formation utilize opening of cis-epoxides, 14 utilize cis-oxidation of double bonds, and 6 utilize oxidation at tertiary carbon atoms. Mitsunobu inversion was used 4 times, and some other reactions were used sporadically. Other asymmetric reactions included enantioselective enolate alkylation (22 examples), sigmatropic reactions (Diels−Alder, 8; aza-Claisen, 2), asymmetric epoxidation (18 examples), and cis-cyclo-addition to a double bond (6 examples).

It was found that a substantial part (13%) of the NPs synthesis reactions led to tertiary and quaternary sp^3-hybridized carbon atoms. Besides the reactions mentioned in the previous paragraph, they include reduction of double bonds in a branched skeleton, nucleophilic substitution for C-nucleophiles, and oxidative dearomatization of phenols.

The analysis of reactions leading to new linear or cyclic bond formation revealed some important features of NPs chemistry. While C−N bond formation is the most common conversion in medicinal and process chemistry, this bond is formed in only 11% of cases during NPs synthesis. In contrast, the formation of new C−C bonds accounts for almost half of all new bonds in NPs synthesis. Of the rest, approximately 30% involves C−O bond formation (Figure 1).

It is noteworthy that almost half of all reactions used in medicinal chemistry fall into the N-acylation and N-alkylation categories (Table 2). These values are 2-fold lower for process

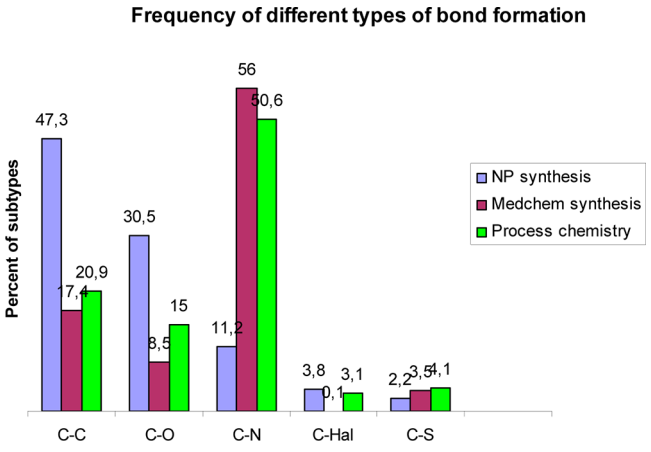

Figure 1. Comparison of the frequency of the main categories of bonds formed in NPs chemistry, classical medicinal chemistry, and process chemistry (as a percent of total newly formed bonds).

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chemistry, which probably reflects the influence of combinatorial approaches in the creation of medicinal chemistry libraries.

Table 2. Frequency of C−N Bond Producing Reactions

	% of syntheses		
	medicinal chemistry	process chemistry	NPs
N-acylation and related process (including lactam)	23.7[a] (5.3)	12.7[b]	2.0 (0.4)
N-alkylation and arylation	23.0	14.7	2.3
N-heterocycle formation	9.3	6.3	0.5

[a]The number of reactions was taken from Table 2[8] (category "acylation and related processes" excluding N-sulfonylation) and divided by the total number of reactions, excluding protective group manipulations (23.7 = [(1165 + 155 + 42 + 4)/5771] × 100). Similar procedures were performed for N-alkylation and arylation and for N-heterocycle formation. [b]The number of reactions was taken from Table 8[9] and divided by the total number of reactions, excluding protective group manipulations (12.7 = [(84 + 8 + 7 + 5)/819] × 100). Similar procedures were performed for N-alkylation and arylation (Table 11[9]) and for N-heterocycle formation (Table 4[9]).

The methods used for new C−C bond formation are summarized in Table 3. Notably, Pd-catalyzed coupling reactions are more widely used in medicinal chemistry than in NPs chemistry. Availability of commercial starting materials and the amenability of such processes to parallel synthesis boosted the popularity of these reactions in the creation of medicinal chemistry libraries. NPs chemistry relies on more "classical" reactions known for many years before the boom of palladium-catalyzed cross-coupling chemistry. The typical process may involve aldol condensation, the Wittig reaction, and the Grignard reaction. Another reaction frequently used in NPs chemistry is enolate alkylation, which can be explained in part by the need to couple sp^3 hybridized carbon atoms, while Pd-assisted chemistry is best suited for coupling of sp^2 and sp hybridized carbon atoms.

The formation of new chiral centers during C−C bond formation is another important distinctive feature of NPs chemistry. While asymmetric C−C bond forming reactions hardly appeared in medicinal and process chemistry, 26% of C−C bond forming reactions in NPs chemistry lead to the formation of new stereogenic centers.

Newly formed C−C bonds could be part of a linear chain or a cycle. In NPs chemistry one-fourth of new C−C bonds lead to the formation of new cycles. In addition to the above-mentioned C−C bond forming reactions, ring closure metathesis, Pictet−Spengler and Diels−Alder reactions are also extensively exploited.

To achieve C−O bond formation, O-acylation, O-alkylation, and oxidation are the most common for both medicinal and NPs chemistry. Additionally, NPs chemistry widely employs epoxidation reactions and hydroboration/oxidation sequences.

The hydroxyl group has been identified as the most common pharmacophoric feature in NPs.[5] Reactions leading to the formation of hydroxy-substituted compounds account for 22% of total reactions in NPs syntheses, while the occurrences of such reactions in medicinal and process chemistries are only 3% and 2.5%, respectively.[25] Among these reactions nucleophilic addition to carbonyl and reduction of carbonyl and ester groups are the most frequently used (Figure 2).

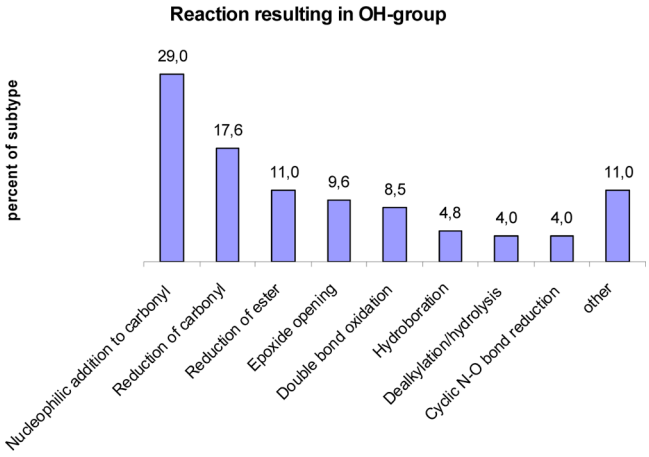

Figure 2. Frequency of reaction types resulting in OH-group formation used in NP synthesis.

Reactions resulting in C−O−C fragment formation (both ether and ester) are 2-fold less frequent (11.5%) than those resulting in C−OH.

Among the reaction types employed by chemists working on NPs, oxidation and reduction reactions stand out as the most prevalent. The occurrence of such processes in NPs synthesis is remarkably higher than for medicinal chemistry and process syntheses (14.6% versus 1.9% and 4.9% for oxidation and 13.1% versus 7.0% and 11.4% for reduction[8,9]). Moreover, oxidation and reduction reactions found in NPs vs medicinal and process chemistry are vastly different. For example, oxidation at nitrogen and sulfur and reduction of nitro groups

Table 3. Frequency of C−C Bond Producing Reactions

	% of syntheses		
reaction type	medicinal chemistry	process chemistry	NPs
addition of C-nucleophile to a carbonyl yielding alkene or *sec*-alcohol	2.2		12
Grignard reaction and metalorganic carbanion addition	0.8	0.2	4.3
Wittig and Julia−Kocienski reactions	0.6		3.5
aldol reactions	0.8 (ester condensation)	2.0 (ester condensation)	3.2
Pd-catalyzed coupling	9	3.2	3.8
Sonogashira reaction	2.7		1.2
Suzuki reaction	5.9	1.6	0.1
enolate alkylation	0.5 or less		2.9
metathesis			1.9
Diels−Alder reaction			1.1

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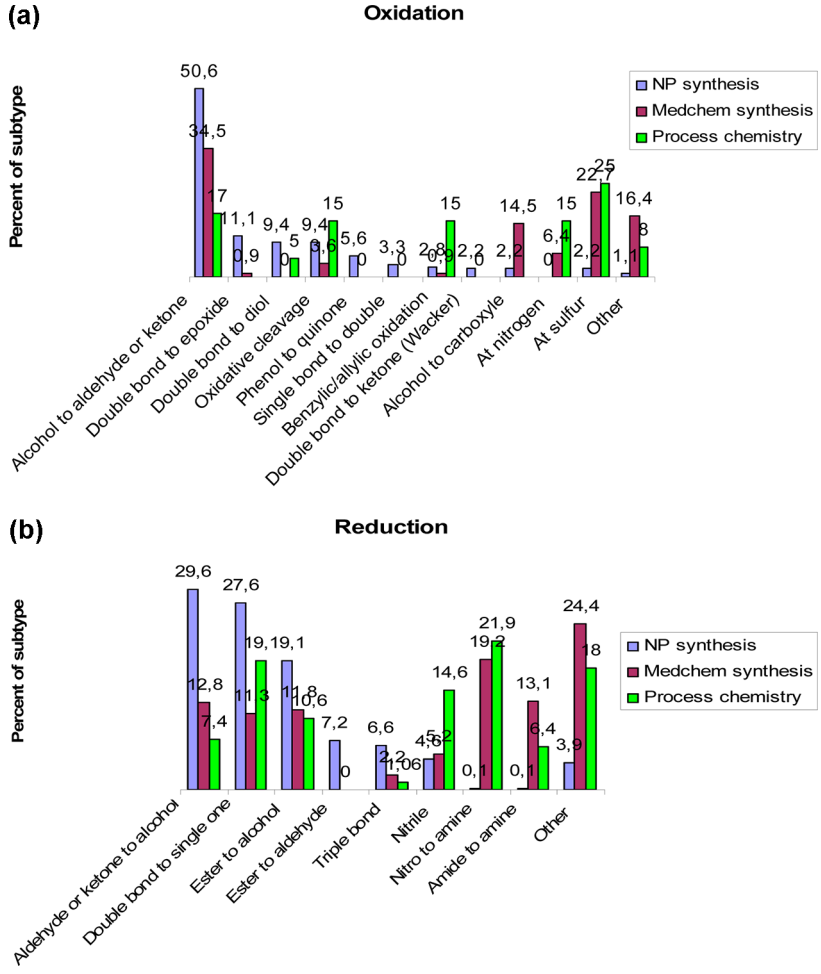

Figure 3. Subtypes of reactions of oxidation (a) and reduction (b).

and amides to amines are typical for medicinal and process chemistry. On the other hand, oxidation of double bonds and the reduction of carbonyl compounds and double bonds are more frequently used during the synthesis of NPs (see Figure 3). Interestingly, sequential alcohol oxidation to ketone followed by stereoselective reduction back to alcohol is frequently used in NPs chemistry to introduce new asymmetric centers.

Ring closure reactions are the most prominent process in the formation of molecular skeletons. Therefore, this type of reaction was analyzed as a separate group along with other distinct scaffold modifications: coupling, elimination, functional group interconversion, ring-opening, and rearrangements (Table 4).

Among the 236 rings formed, only 10 (4.2%) were aromatic; all the rest were partly or completely saturated. All the ring closure reactions were divided into four groups depending on the type of bond formed during the cyclization: C−C, C−O, C−N bond formation and epoxide ring formation. Since epoxides are usually used as intermediates for further transformations, this group was considered as a stand-alone case.

The category "ring transformations" encompasses all reactions conserving the number and order of all atoms in cyclic systems, allowing changes in covalent bond multiplicity.

All reactions resulting in any new linear bond formation fall into the "coupling" group, and according to the type of new bond, a further classification was performed.

The category "elimination" includes all reactions resulting in the removal of an existing group.

"Skeletal modifications" imply any changes in skeletal structure without the addition or removal of any atom except hydrogen. Most of the skeletal modifications fall into reduction and oxidation reactions. The remaining 1% consists of isomerization reactions.

The survey presented in this work may not be comprehensive, since only one source of papers was utilized and a relatively short time span was taken into account. However, we believe that the trends observed in this survey are representative of reaction types employed in the synthesis of natural products.

■ CONCLUSIONS

On the basis of this analysis, a number of key features were identified that distinguish NPs synthesis from medchem and process synthesis.

The "toolbox of a NPs chemist" outlined in Table 5 is very different from both the "toolbox of a medicinal chemist" and the "toolbox of a process chemist". The main reactions are oxidation, reduction, and C−C coupling as a result of the attack of a C-nucleophile on a carbonyl group. During NPs synthesis C−C bond formation occurs essentially more frequently than

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Table 4. Main Categories of Chemical Reactions Used for NPs Synthesis

category no.			no. of reactions	% of total	% of subtype
1		ring closure	236	19.1	
	1.1	C−C bond formation	83	6.7	35.2
	1.1.1	attack of C-nucleophile on a carbonyl group yielding alkene or alcohol	20 (including aldol condensation, 10)		24.1
	1.1.2	electrophilic attack on an aromatic ring	17 (including Pictet−Spengler, 8)		20.5
	1.1.3	ring closure metathesis	15		18.1
	1.1.4	Diels−Alder reaction	10		12.1
	1.1.5	Pd-catalyzed reaction	5		6.0
	1.1.6	other	16		19.3
	1.2	C−O bond formation	76	6.2	32.2
	1.2.1	esterification	23		26.7
	1.2.2	acetals, ketals, or hemiaminals formation	20		26.3
	1.2.3	oxa-Michael reaction	10		13.2
	1.2.4	alkylation	6		7.9
	1.2.5	other	17		22.3
	1.3	epoxide formation	24	2.0	10.2
	1.4	C−N bond formation	44	3.6	18.6
	1.4.1	alkylation	13		29.5
	1.4.2	lactam formation	5		11.4
	1.4.3	enamine or hemiaminal with cyclyc N formation	11		25.0
	1.4.4	thiazole/oxazole formation	3		6.8
	1.4.5	other	12		27.3
2		ring transformations	76	6.2	
	2.1	reduction of double bond to single	31		40.1
	2.2	oxidation of phenol to quinone	10		13.2
	2.3	enolization	9		11.8
	2.4	oxidation single bond to double	6		7.9
	2.5	isomerization	7		9.2
	2.6	other	13		17.1
3		coupling	483	39.2	
	3.1	C−C bond formation	262	21.2	54.2
	3.1.1	attack of C-nucleophiles on carbonyl yielding alkene or *sec*-alcohol	128 (including Wittig and Julia−Kocienski reactions, 43; aldol reaction, 30; Grignard reaction, 20; other metalorganic carbanions, 31)		48.9
	3.1.2	Pd-catalyzed reactions	42 (including Sonogashira reaction, 15; Suzuki reaction, 9; Heck reaction, 6)		16.0
	3.1.3	enolate alkylation	36		13.7
	3.1.4	coupling using Weinreb amide	8		3.1
	3.1.5	epoxide opening using C-nucleophiles	9		3.4
	3.1.6	metathesis	8		3.1
	3.1.7	other	31		11.8
	3.2	C−O bond formation	119	9.7	24.6
	3.2.1	oxidation	41		34.5
	3.2.2	alkylation	34		28.6
	3.2.3	acylation	32		26.9
	3.2.4	hydroboration	12		10.1
	3.3	C−N bond formation	41	3.3	8.5
	3.3.1	alkylation	15		36.6
	3.3.2	acylation	19		46.3
	3.3.3	other	7		17.1
	3.4	C−S bond formation	16	1.3	3.3
	3.4.1	alkylation	8		50.0
	3.4.2	nucleophilic substitution	4		25.0
	3.4.3	other	4		25.0
	3.5	C−Hal bond formation	27	2.2	5.6
4		elimination	88	7.1	
	4.1	elimination of water, tosylate, hydrohalogens, etc.	33	2.6	37.6
	4.2	reduction of carbonyl or halogen to methylene group	21	1.7	23.9
	4.3	dealkylation	13	1.1	14.8
	4.4	hydrolysis	7	0.6	8.0

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Table 4. continued

	category no.		no. of reactions	% of total	% of subtype
	4.5	other	14	1.1	15.9
5		skeletal modification	203	19.1	
	5.1	oxidation	89	8.4	44.8
	5.2	reduction	110	10.3	54.2
	5.3	isomerization	6	0.5	3
	5.4	other	1		0.5
6		functional group interconversion	41	3.3	
	6.1	nucleophilic substitution	36	2.9	87.8
	6.2	other	5	0.4	12.2
7		ring-opening	56	4.5	
	7.1	epoxide opening	23	1.9	41.1
	7.2	isoxazoline and isoxazolidine opening	7	0.6	12.5
	7.3	cyclic ether opening	7	0.6	12.5
	7.4	lactone opening	5	0.4	8.9
	7.5	hemiacetal opening	5	0.4	8.9
	7.6	other	9	0.7	16.1
8		rearrangements	17	1.4	

Table 5. "Toolbox of NPs Chemist" (Main Reactions in the Chemistry of NPs)

reaction type	% of total in NPs synthesis reviewed	medicinal chemistry, %	process chemistry, %
oxidation	14.6	1.9	4.9
reduction	13.1	7	11.4
addition of C-nucleophile to carbonyl yielding alkene or *sec*-alcohol	12.0	2.2	2.2
acylation of N, O, S	6.8	28.33	15.6
alkylation of N, O, S	6.1	29.23	23.9
Pd-catalyzed coupling	3.8	9	3.8
nucleophilic substitution	3.2	1.2	2.8
enolate alkylation	2.9	0.5 or less	
elimination to double bond	2.6	0.3	1.2
metathesis	1.9		
epoxide opening	1.9		
electrophilic substitution	1.9		
acetal, ketal, and hemiacetal formation	1.9		
Diels–Alder reaction	1.05		
hydroboration	1		

C–N and C–O bond formation and more frequently than during medicinal chemistry synthesis. About a quarter of new C–C bond formation yields new asymmetric centers. Generally, the number of asymmetric centers per compound is considerably higher for NPs than for compounds from medicinal chemistry. Importantly, more than a half of them are generated during synthesis. Every fifth reaction in NPs chemistry leads to ring closure, which is about 2-fold more frequent than in medicinal chemistry. Moreover, 96% of all cyclic systems formed during the synthesis of NPs are completely or partly saturated as distinguished from medicinal chemistry. Reactions resulting in C–OH and C–O–C groups account for more than a third of all reactions, which is considerably higher than similar transformations in medicinal and process chemistry. A significant proportion of reactions used in NPs chemistry yield tertiary and quaternary sp^3-hybridized carbon centers.

We believe that enrichment of "the toolbox of medicinal chemistry" with reactions used during the synthesis of natural product may enable us to hit such difficult drug targets as PPI or protein–DNA interaction that have emerged in recent years.

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Notes

The authors declare no competing financial interest.

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Roman V. Kombarov studied organic and medicinal chemistry at Moscow State University and received his Ph.D. in Bioorganic Chemistry in the group of Prof. Yurovskaya. In 2000 he joined Asinex, a company focusing on small-molecule compound libraries, as a medicinal chemist. Dr. Kombarov has extensive project leadership experience in international drug discovery programs, having participated in the completion of hit-to-lead projects in the areas of oncology and antibacterial drug discovery.

Dmitry V. Genis graduated from Moscow State University in 1993. His research interests have been focused on small molecule peptide mimetics and natural products synthesis. In 1994 Dmitry Genis established Asinex and held the position of Research Director until 2001 when he became the CEO. Dmitry Genis is a well-known scientist and entrepreneur in the field of compound library design. His work has been published in several peer-reviewed journals, and he has presented at numerous scientific meetings and conferences.

Michael A. Kirpichenok obtained his M.A. in 1979 and his Ph.D. (with Prof. Nicolai Zefirov) in 1981 from the Lomonosov Moscow State University, Russia. During 1981−1982 he worked on theoretical aspects of organic chemistry in the N. D. Zelinsky Institute of Organic Chemistry, Moscow, Russia. In 1983 he joined the Department of Chemistry of Timiryazev Russian State Agrarian University as a Senior Chemist where he was involved in research on aminocoumarin's laser dyes. In 1992 as Principal Scientist he gained his Doctor of Science degree and has since become Professor. In 1995 he joined Asinex as Research Director, and he continues in this role.

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(25) Estimated values are given. For the medicinal chemistry presented in Table 2[8] OH groups could be a result of Grignard reactions (46), other organometallic reactions (30), reduction of esters to alcohols (48), reduction of ketones to alcohols (52), and oxidation of alkenes (without cleavage) (1). In total 177 reactions yielded hydroxyl groups, which gives (177/5771) × 100 = 3%. For process chemistry hydroxyl groups were formed by alkene oxidation (2, Table 12[9]), reduction of esters to alcohols (10, Table 13[9]), ketones to alcohols (7, Table 13[9]), and Grignard reactions (2, Table 14[9]). In total 21 reactions yielded hydroxyl groups, which gives (21/819) × 100 = 2.5%.