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Scaffold Flatness: Reversing the Trend

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Abstract Fraction sp^3 (Fsp^3) values were used to compare the flatness of known scaffolds (used as privileged structures, drug scaffolds, and in scaffold-hopping approaches) and natural product (NP) scaffolds. The vast majority of the known synthetic scaffolds are planar with Fsp^3 values <0.45 while the NP scaffold set is composed of mainly non-flat scaffolds. The identification of new or novel scaffolds to provide libraries of small diverse bioactive compounds is of the utmost importance to chemical biology and medicinal chemistry research. Non-flat scaffolds embedded in NPs may explore neglected areas of chemical space. We performed a scaffold abstraction from the dictionary of natural products (DNP), which resulted in 15,822 scaffolds. From this scaffold set, the vast majority (70 %), are non-flat scaffolds with Fsp^3 value >0.45. These non-flat scaffolds may cover 83 % of ring systems that are absent from screening set.

Keywords Scaffold · Scaffold flatness · Fraction sp^3 · Natural product scaffolds

Introduction

"Chemical space" is vast, even the subset of the chemical universe that is of interest to drug development of molecular weight (MW) <500 Da is estimated to number $\sim 10^{60}$ [17]. This number is out of the practical range for synthetic accessibility and not surprisingly, chemists have covered only a tiny portion of this space. According to SciFinder $\sim 10^7$ chemical structures have been reported, to date. Bioactive molecules generally exert their effect through interaction with proteins so that biological space is significantly more limited. Proteins are limited in their combinations of 20 different of amino acids, and the human genome for instance, encodes only 20,000–25,000 protein-coding genes (Consortium IHGS [11]). Binding molecules are recognized by the protein in specific binding pockets, complementary in shape and physicochemical properties to the accommodated small molecule [57]. Biologically relevant chemical space (BRCS) is just a tiny fraction of the complete chemical space [13]. It is worthwhile mentioning that "drug space" is even smaller than BRCS, such that not every bioactive molecule presented in BRCS can be considered as a drug molecule. Drug space contains those bioactive molecules that have favorable potency, selectivity, and pharmacokinetic properties (absorption, distribution, metabolism, and excretion) for use as a drug [32].

To cover the expanse of BRCS, it is necessary to avoid strategies that generate structurally similar compounds with similar biological profiles. However, current approaches suffer from insufficient overlap of compounds (usually from synthetic libraries) and biological structure space [58]. Optimization of the processes of producing new chemical entities to help match chemical and biological space is of great significance to modern drug discovery. Several approaches, such as libraries of privileged scaffolds, scaffold-hopping, diversity-oriented synthesis (DOS), and biology-oriented synthesis (BIOS) have been introduced to address the issue.

Molecular scaffolds (core structures) play a fundamental role in the navigation of "biologically relevant chemical

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space" and drug development. Identification of new scaffolds that have potential to provide libraries of small diverse bioactive compounds is of utmost interest to chemical biology and medicinal chemistry research. Several studies have been directed toward the assessment of scaffold diversity of drug data sets [4, 20, 55], screening libraries [24, 29, 50], organic compounds databases [34, 59], and natural product (NP) databases [20, 24, 27]. These studies show that scaffold space is vast and diverse while bioactive and drug-like compounds only represent a small fraction of principally available scaffold space [30], suggesting that scaffold selection is important.

Natural products and their analogs have had high impact as drugs because of the embedded biosynthetic molecular recognition that transfers to therapeutic targets as described by protein fold topology (PFT) [26, 38]. Computational analysis revealed that NPs exhibit a remarkable structural diversity of molecular frameworks and scaffolds. They possess desirable drug-like properties rendering them ideal starting points for the design of focused libraries [20]. Approximately 40 % of the chemical scaffolds displayed in NPs are absent from synthetic compounds [31]. Furthermore, according to Hert et al. [24] 83 % of the ring scaffolds among the NPs are unrepresented among commercial molecules. More complex molecules have the capacity to access greater chemical space and results in greater potential for compounds to complement the spatial subtleties of target proteins [36].

We performed a statistical analysis on the known scaffolds presented in three different reviews, i.e., scaffold-hopping, privileged scaffolds, and drug-building blocks [54–56] to determine the proportion of the scaffolds that were planar. The "Carbon bond saturation" defined by fraction sp^3 value (Fsp^3) was used to classify flat and non-flat scaffolds [36]. We undertook a scaffold abstraction from the dictionary of natural products (DNP) to determine the proportion of flat scaffolds ($Fsp^3 \leq 0.45$) versus non-flat scaffolds ($Fsp^3 > 0.45$). Non-flat scaffolds have a potential to introduce new anchor points to explore additional areas of "biologically relevant chemical space". Increased out-of-plane substituents may translate to increased selectivity in interactions with proteins. The analysis shows that NP scaffolds have a higher proportion of non-flat members compared to set composed of scaffold-hopping, privileged scaffolds, and drug-building blocks.

Two Sources of Chemical Space

Current chemical space includes compounds isolated from nature, and those synthesized by different strategies. Although NPs interrogate a different and larger area of chemical space than synthetic compounds [18, 48], drugs derived from both spaces show similar values for Lipinski parameters. Lipinski's "rule of five" (Ro5) has been proposed to evaluate the drug-likeness of a chemical compound, based on the physico-chemical properties [33]. About 80 % of NPs have less than two violations of the Ro5 [45]. Overall, NPs are more similar to drugs than compounds obtained from combinatorial synthesis [16]. Drug molecules are generally developed from less complex lead compounds, so that lead compounds usually have a smaller number of rings, fewer rotatable bonds, and smaller MW and are more hydrophilic than the final drug molecule [21].

NPs as a Source of Drug Leads

Historically, NPs have proven to be one of the richest sources of active ingredients of medicines. They are biosynthesized by enzymes within organism as primary or secondary metabolites. Unlike primary metabolites, the absence of secondary metabolites does not result in immediate death, but the molecules may play an important role in organism survival. Some NPs have been evolutionary preselected to modulate biochemical pathways as toxins, pheromones, attractants, and repellents. The medical outcomes far exceed the conversion of these natural systems into drugs and, for example, in the area of cancer, of the 175 small molecules therapeutics developed between 1940s and 2010, 48.6 % are NPs or directly derived thereof (Newman and Cragg [41]).

High-quality libraries for high throughput screening (HTS) are of the utmost importance to modern drug discovery. Some technical drawbacks associated with NPs render these molecules unfavorable for HTS [28]. The major problems include the problem of the inherent slowness of working with NP extracts using bioassay-guided isolation [23]. Therefore, traditional iterative NP extraction and isolation methodology cannot be easily integrated into modern drug development programs. Several methods and strategies have been developed to promote the speed and efficiency of the NP discovery process. The introduction of fractionation and advances in structure elucidation has been a great step forward in fulfilling this goal [7–9, 22, 51, 62].

Combinatorial Chemistry as a Solution

For more than a decade, a super rapid method of synthesis, combinatorial chemistry, promised to help solve the productivity issue for HTS that would lead to a wealth of new drugs. As a result, pharmaceutical companies started to invest in making large libraries based on this strategy, which resulted in a significant decline in attention toward NPs. The focus of combinatorial chemistry was on quantity, with insufficient attention given to quality. Although combinatorial chemistry techniques proved to be successful in the optimization of structures of many recently

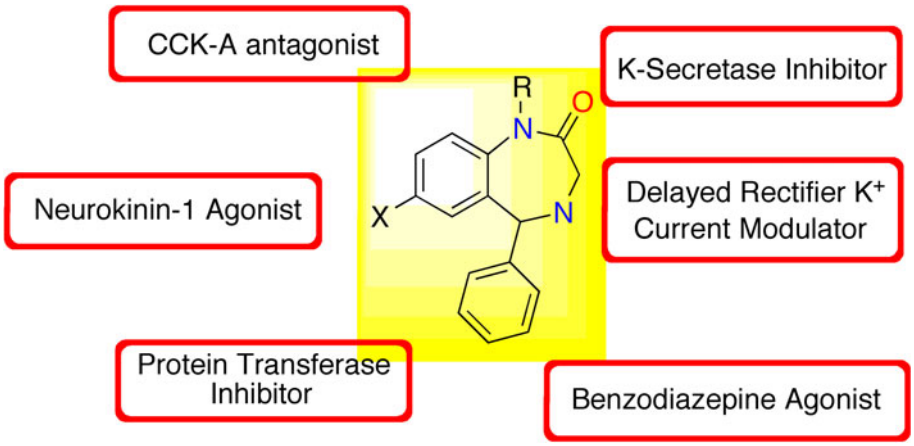


Fig. 1 Benzodiazepines and some of their numerous biological properties

approved drugs, the number of new drugs has not increased significantly [12, 14, 52].

Two Alternative Approaches

Two main approaches, diversity-oriented synthesis (DOS) and libraries of "privileged structures" have emerged to address the inherent combinatorial chemistry's shortfalls [40]. Lessons learned from NPs are beginning to impact on synthetic strategies.

Diversity-Oriented Synthesis

DOS aims to maximize the number of structures and scaffolds produced from a given synthetic scheme to find the most efficient ways to populate the largest amount of chemical space. In order to achieve the highest levels of structural diversity: (i) the building blocks, (ii) the stereochemistry, (iii) the functional groups and, most importantly, and (iv) the molecular framework must be varied [5]. A wide variety of libraries has been made based on this approach [39, 44, 53]. Recently, a new concept of DOS, so-called biology-oriented synthesis (BIOS) has developed [27]. In BIOS, NP scaffolds are employed as a core and diversity is created around it. Several libraries have been generated using this strategy resulting in discovery of protein phosphatase inhibitor [42], protein tyrosine phosphatase inhibitor [43], estrogen receptor α/β (ERα/β) inhibitor, and 5-LOX inhibitors [60]. A "parent–child scaffolds" concept was derived from a "structural classification of natural products (SCONP)" tree [6]. In fact, combining the results of SCONP with the structural classification of proteins "PSSC" was a great step toward the developing concept of BIOS.

Libraries of Privileged Scaffolds

Another important strategy to guide synthetic design and to help enrich compound collections in biological activities is that of privileged structures. The concept of privileged structures was first proposed in relation to benzodiazepines that bind to multiple, unrelated classes of proteins as high affinity ligands (Fig. 1) [15].

Research over the next three decades has revealed more privileged structures [46]. Recently, a comprehensive list of privileged structures has been assembled [56]. According to the IUPAC definition, a privileged structure is a substructure "that often consists of a semi-rigid scaffold, which is able to present multiple, hydrophobic residues without undergoing hydrophobic collapse." In this way, the core preserves most of the binding potential when the compound is exposed to an aqueous medium [3]. The evolving role of NPs in drug discovery to provide effective drugs supports the idea that NPs can be viewed as a population of privileged structures selected by evolutionary pressures to interact with a wide variety of proteins [26, 28]. NP-like libraries based on privileged scaffolds attempt to rapidly generate large collections of compounds that possess greater diversity and incorporate optimized physical and pharmacological properties into their structures. Interestingly, these libraries also provide a useful tool in the identification of new targets [1, 49].

How Diverse are the Known Scaffolds?

Molecular scaffolds play an important role in providing the tools to interrogate BRCS and in drug development. The identification of new scaffolds is of utmost importance to chemical biology and medicinal chemistry research.

The term scaffold is context- and chemist-dependant. In chemoinformatics, "the term scaffold is mostly applied in a rather subjective manner without adhering to clear, formal and consistent definition" [25]. In most cases, the term scaffold has been used interchangeably either as core structure, building block, substructure, template, ring system (RS), and/or framework. One of the most interesting types of study of scaffolds is in the assessment of scaffold diversity. Diversity analysis of scaffolds has been done on

various databases including drug data sets [4, 20, 55], screening libraries [24, 29, 50], organic compounds databases [34, 59], and NP databases [20, 24, 27]. These studies show that scaffold space is vast and diverse while bioactive and drug-like compounds represent a small fraction of principally available scaffold space [30], suggesting that there are many scaffolds that can be systematically exploited. NPs, as a source of therapeutically useful compounds, are biosynthesized through interaction with proteins, and carry-forward the "embedded" molecular recognition through interactions with drug targets [26, 38].

The majority (80 %) of NPs possess desirable drug-like properties [45]. In a similar fashion, computer-based analysis revealed that NPs exhibit a remarkable structural diversity of molecular frameworks and scaffolds with desirable drug-like properties rendering them ideal starting points for the design of focused libraries [20]. Approximately 40 % of the chemical scaffolds displayed in NPs are absent from synthetic compound [31]. Making NP-like libraries to create more complex, drug-like compounds has the capacity to access greater chemical space [36].

Escape from Flat Scaffolds

Aromatic and heteroaromatic rings comprise a significant proportion of compounds in "drug space," however, the developability of compounds (efficacy, pharmacokinetics, pharmacodynamics, toxicology, and drug–drug interactions) decreases with increasing number of aromatic rings [47]. Insertion of aromatic rings into drug-like compounds is used to increase the potency of compounds because an aromatic ring possesses fewer degrees of freedom than acyclic chains, and this favorable entropy generally increases the ligand–receptor-binding energy leading to improved potency [47]. The prevalence of aromatic and heteroaromatic rings in drug molecules has been attributed to the synthetic ease [47]. Making compounds with aryl–aryl systems are more time and cost effective. This is due to the fact that most of the available synthetic methodologies and chemical substances (both substrate and building blocks) are based on flat aromatic systems. Limiting the number of aromatic rings in a drug candidate will make it more "drug-like" [47].

Compounds with a greater fraction of saturated carbons (defined by Fsp^3), which is an intuitive measure of complexity, have a higher access rate in the drug discovery process [36]. The Fsp^3 as a simple and interpretable measure of complexity of molecules is defined as:

$$\mathrm{F}sp^3 = \left(\text{Number of } sp^3 \text{ hybridized carbons}/\text{Total carbon count}\right).$$

More highly complex molecules, as measured by saturation and number of chiral centers, have the capacity to access greater chemical space [36].

Flatness Investigation of the Known Scaffolds

A flatness investigation has performed in order to classify scaffolds that have been used in approaches involving scaffold-hopping, privileged sub-structures, and drug RSs. Based on some calculated mean Fsp^3 value reported for drug data sets [10, 35, 36], we defined flat and non-flat scaffold as follows:

Flat scaffold: scaffolds with F$sp^3 \leq 0.45$.

Non-flat scaffold: scaffolds with F$sp^3 > 0.45$.

Classification of Scaffold-Hopping Approaches

Sun et al. [54] recently reviewed approaches to scaffold-hopping. By making certain changes to the original scaffolds such as heterocyclic replacements, ring opening or closure, pseudopeptides, and topology-base hopping [54], there is possibility to produce novel scaffolds. In practice, since many of the original scaffolds came from flat molecules, the final scaffolds rarely have novel 3-D orientation of substitutions. The review classified the number of structurally diverse scaffolds into four categories based on the degree of novelty compared to the starting scaffold. For example, rimonabant, a failed antiobesity drug, was transformed by scaffold-hopping approaches to a novel CB1 antagonist with improved pharmacological properties. The change in the original scaffold to create the new scaffold is classified as first degree of novelty, with a small change of heteroatom or ring size. In this case, the methylpyrazole core in rimonabant was replaced with a range of five- and six-member heteroatom rings to overcome undesirable physicochemical properties [54]. Furthermore, the scaffolds that have been used more recently (March–October 2012) in a scaffold-hopping approach have also been examined based on their flatness feature [2, 19, 37, 61, 63–65].

Based on our defined criteria, we sorted the scaffolds as flat and non-flat scaffolds (Fig. 2). The vast majority of scaffolds (89 %) utilized in scaffold-hopping have incorporated planar frameworks (Fig. 3).

Privileged Scaffolds for Library Design and Drug Discovery

One of the most comprehensive listings of privileged scaffolds (PS) has published by Welsch et al. [56]. The authors provided a list of privileged scaffolds in drug and NPs, those found primarily in drugs, and other examples of privileged scaffolds. The authors stated that "there is a remarkable overlap between structures of drugs and NPs classes as the greater number of scaffolds have members from both groups". We have classified the privileged scaffolds in the review by Stockwell et al. as flat and

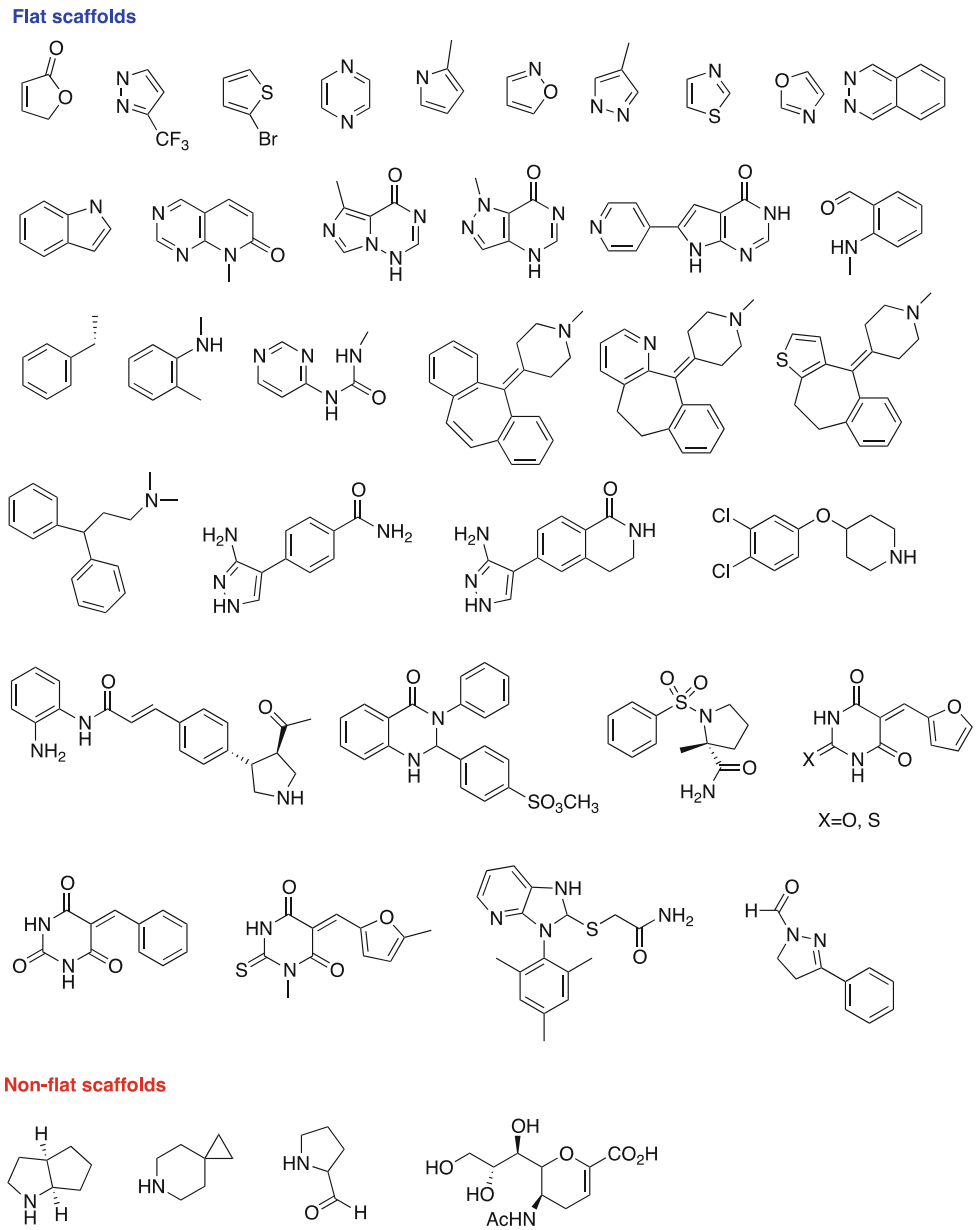


Fig. 2 Flatness classification of the scaffolds that have been used in scaffold-hopping approach

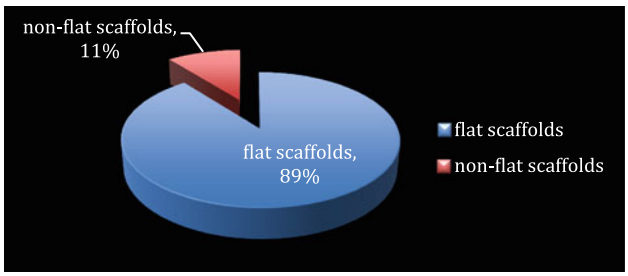


Fig. 3 The distribution of flat and non-flat scaffolds in scaffold-hopping approach

non-flat according to our previously defined Fsp^3 definition of flatness (Fig. 4). The privileged scaffolds in drug and NPs are colored red, the PS found primarily in drugs colored in violet and other examples of privileged scaffolds colored in black. As demonstrated in Fig. 5, only a small fraction (23 %) of the privileged substructures are saturated non-flat scaffolds with at least one chiral centre. This observation again implies that there has been a significant bias toward using flat aromatic or heteroaromatic rings by chemists according to earlier discussed reasons (ease of synthesis and conformational restriction to increase the potency of compounds).

Drug and Drug Candidate-Building Block Analysis

Wang and Hou [55] undertook a drug-likeness analysis in 2010. In this work, two drug data sets and one screening data set were subjected to building block analysis. The data

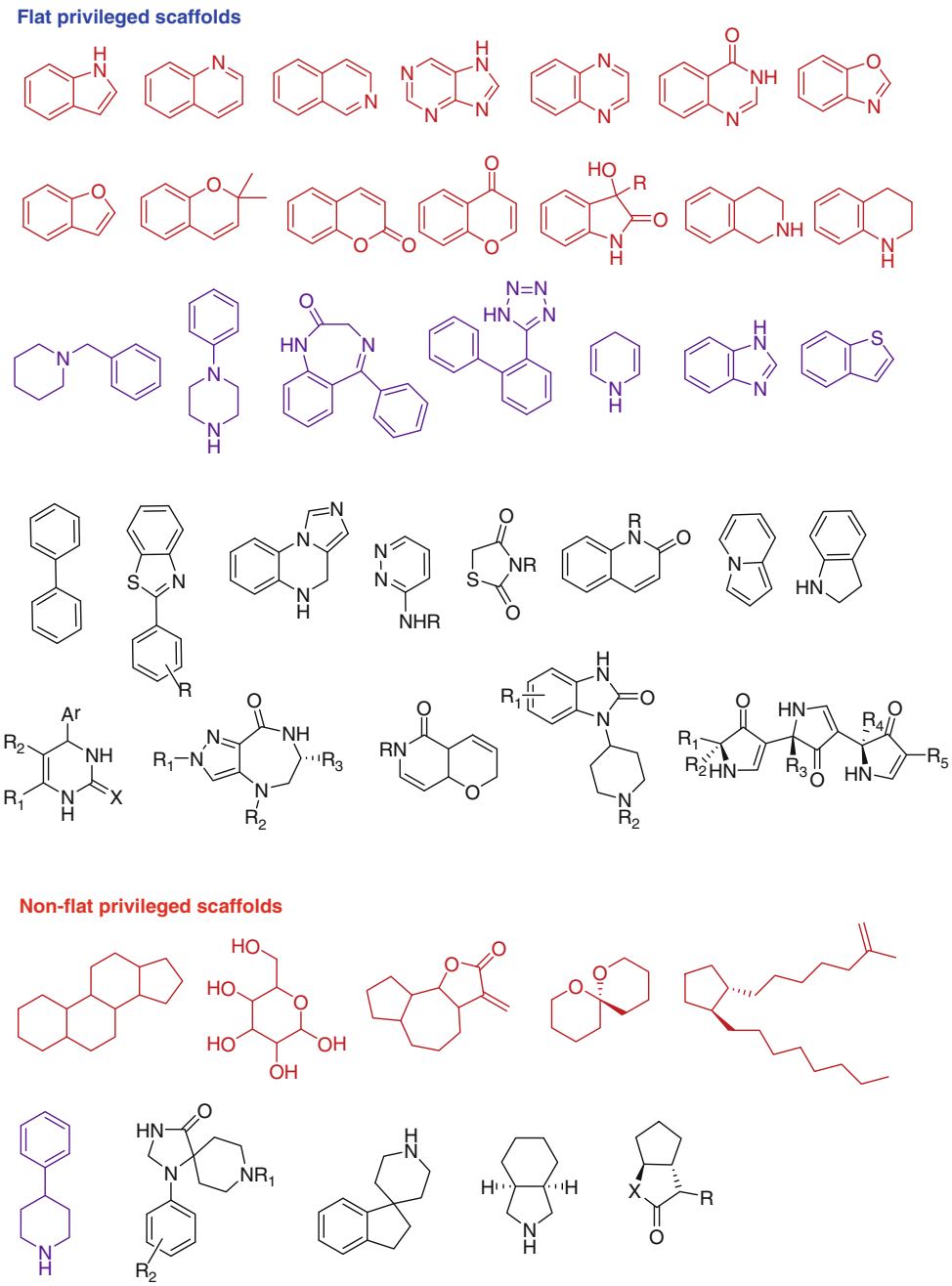


Fig. 4 Flatness classification of the scaffolds that have been used in a library of privileged structures. (The privileged scaffolds in drug and NPs colored *red*; the PS found primarily in drugs colored *violet* and other examples of privileged scaffolds colored *black*)

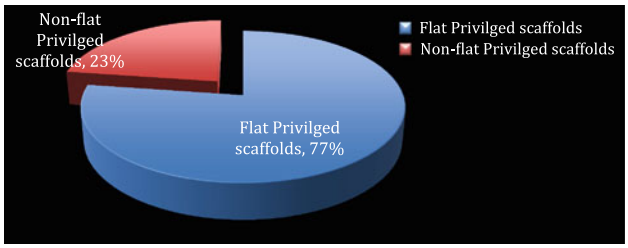


Fig. 5 The distribution of flat and non-flat scaffolds in privileged sub-structure libraries

sets were approved drug data set (ADDS; FDA-approved drugs; 1,240 entries), extended drug data set (EDDS composed of FDA-approved drugs and experimental drugs at different phases of clinical trials; 6,932 entries) and screening dataset (SDS; a subset of the "clean-drug-like" molecules in the ZINC database). At the first step, some clean up of the data sets was undertaken to remove small (MW <50 Da) and large (MW >1,000 Da) molecules, duplicated entries, and to eliminate those entries containing elements other than C, H, O, N, S, P, and halogens. In the

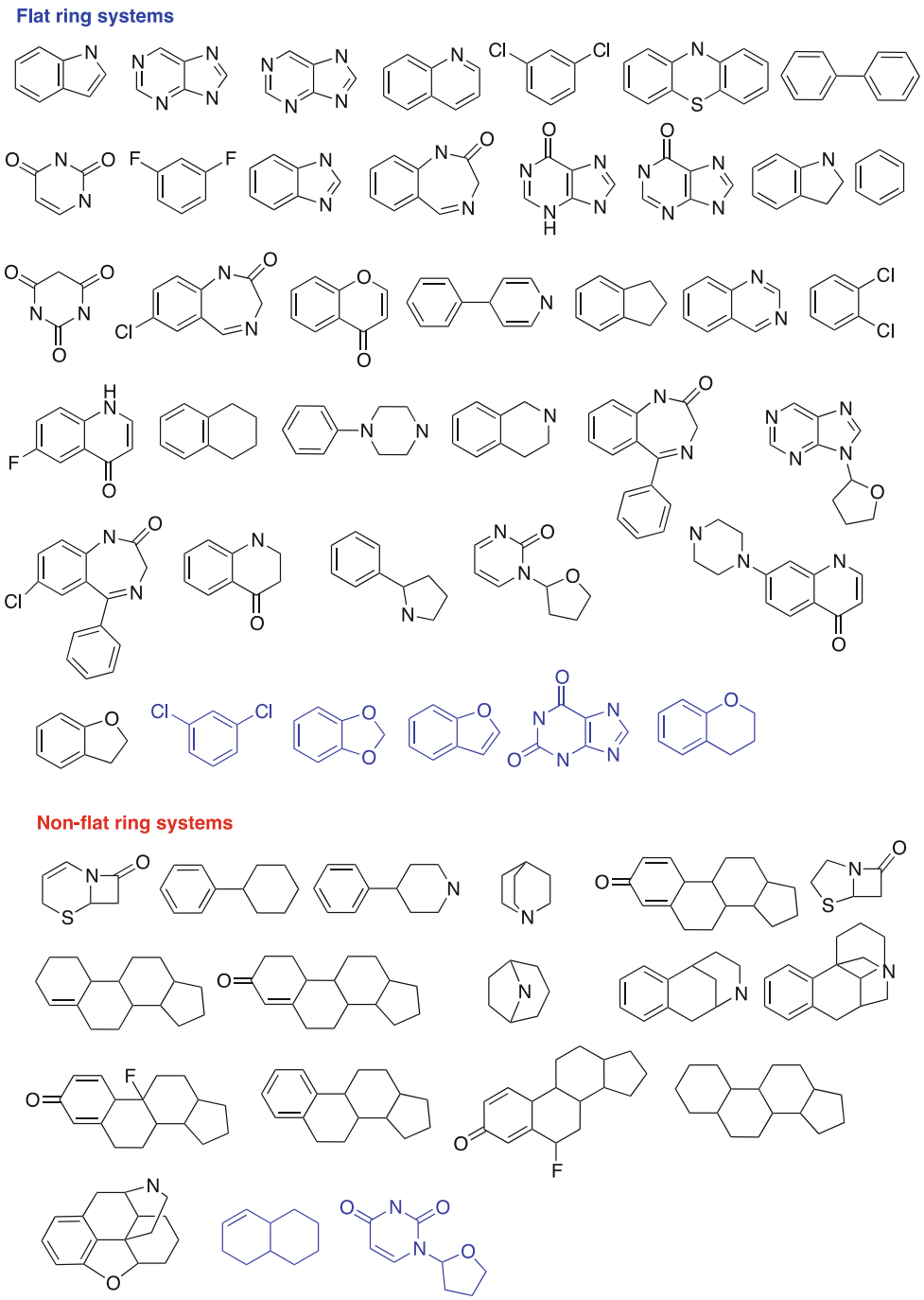


Fig. 6 Flatness classification of the RSs in Drug and drug candidates' data sets. The top 50 RSs identified in ADDSs colored *black* and those RSs in extended drug data set which were absent in the ADDS colored *blue*

next stage, a brute force algorithm was utilized for a fragmentation of all molecules in the drug data sets. This process cut every cleavable bond in silico to give fragments, where a cleavable bond was defined as a single, non-ring, non-terminal bond. A classification strategy was then used to group the molecular fragments into three types of building blocks, which were defined as drug scaffold (DS), RSs, and small fragment (SF). They loosely defined "drug scaffold" as a "molecular fragments having at least nine heavy atoms". The authors collected and individually sorted the top 100 DSs identified from FDA-ADDS and EDDS. We used the top 50 RSs obtained from these two drug data sets to investigate how the RSs of drugs are similar to each other in terms of planarity and controlling the geometry of the molecules. We observed that 42 rings systems were common to both data sets. In Fig. 6, we colored the top 50 RSs identified in the ADDS in black and those RSs in the extended drug data set but absent in the first data set (ADDS) in blue. Figure 7 shows the distribution of flat and non-flat scaffolds in the drug data sets.

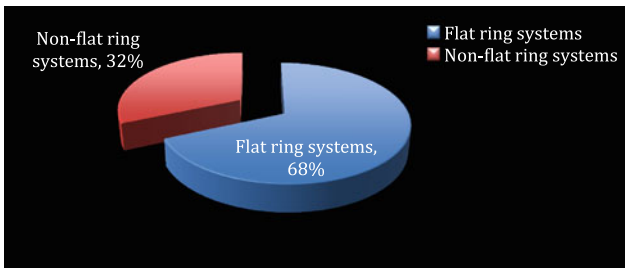


Fig. 7 The distribution of flat and non-flat RSs in drug and drug candidates' data sets

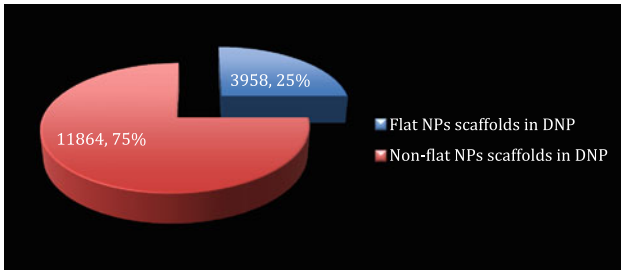
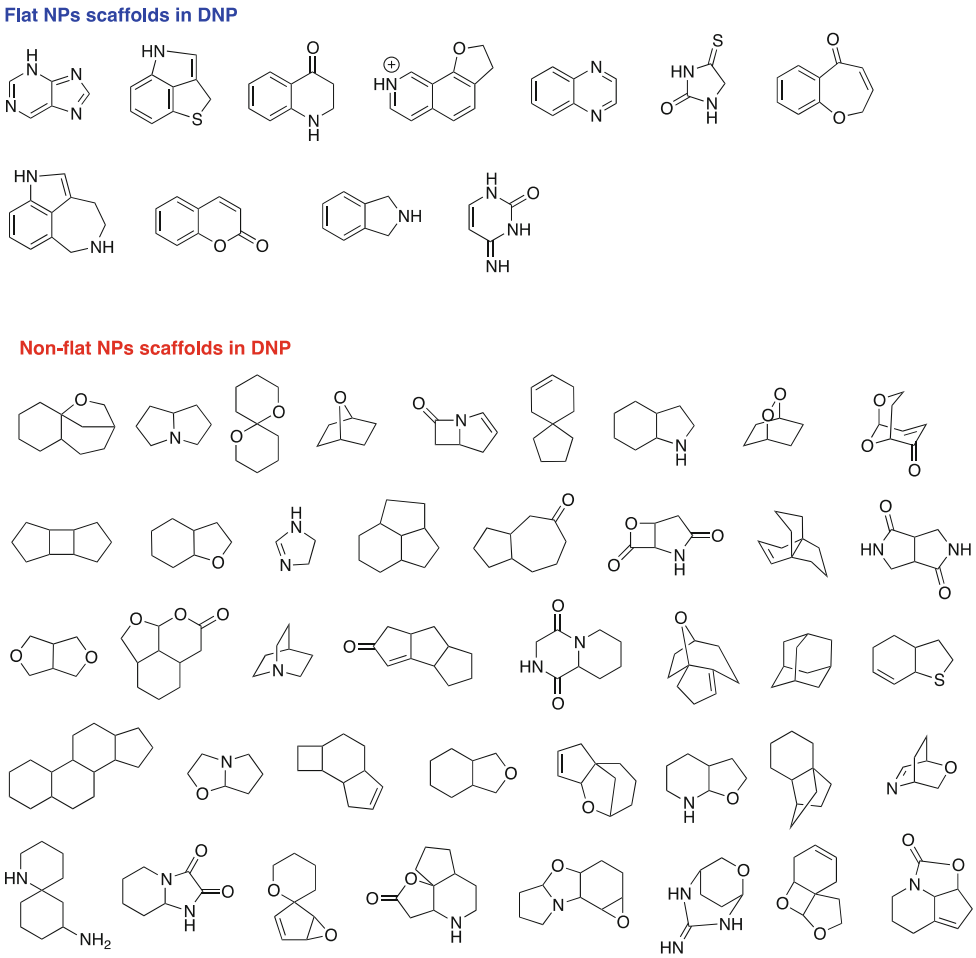


Fig. 9 The distribution of flat and non-flat NP scaffolds extracted from DNP

Fig. 8 Flatness classification of the scaffolds that have been abstracted from DNP



The proportion of non-flat RSs compared to planar RSs was 32 versus 68 %, respectively.

NP Scaffolds

Ring scaffolds embedded within all known NPs from The DNPs (sdf version 211.9) were abstracted. All contiguous RSs were extracted with retention of exocyclic double bonds to terminal atoms in order to preserve important chemical functionality. For example, to maintain the carbonyl oxygen present in a lactone or lactam ring.

Metal-containing RSs were excluded from consideration, resulting in the identification of 18,128 RSs. An additional MW filter (MW <350 Da) was applied to exclude large, non drug-like RSs (e.g., polycyclic RSs and macrocycles) resulting in 15,822 NP-derived scaffolds.

A number of selected flat and non-flat scaffolds embedded in NPs (abstracted from DNP) are shown in Figs. 8 and 9 and are indicative of the fact that the majority of NP-derived scaffolds are classified as non-flat by considering their corresponding Fsp^3 values.

Conclusion

Examination of Fsp^3 values calculated for each scaffold provides further insights into the characteristics that make naturally derived scaffolds appealing when compared to other sources of chemical diversity. Specifically, the predominance of non-flat scaffolds embedded within NPs (i.e., high Fsp^3) highlights a significant fundamental difference between synthetic and naturally derived compound screening libraries. We propose that the past and continued future success of NPs as a source of therapeutically useful chemical compounds may be attributed to their positioning wholly within regions of BRCS. One characteristic of NPs guiding this complementarity to protein-binding surfaces is the incorporation of non-flat molecular frameworks capable of orienting peripheral functional groups in all three dimensions.

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