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PERSPECTIVE

Designing the molecular future

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Abstract Approximately 25 years ago the first computer applications were conceived for the purpose of automated 'de novo' drug design, prominent pioneering tools being ALADDIN, CAVEAT, GENOA, and DYLOMMS. Many of these early concepts were enabled by innovative techniques for ligand-receptor interaction modeling like GRID, MCSS, DOCK, and CoMFA, which still provide the theoretical framework for several more recently developed molecular design algorithms. After a first wave of software tools and groundbreaking applications in the 1990s—expressly GROW, GrowMol, LEGEND, and LUDI representing some of the key players—we are currently witnessing a renewed strong interest in this field. Innovative ideas for both receptor and ligand-based drug design have recently been published. We here provide a personal perspective on the evolution of de novo design, highlighting some of the historic achievements as well as possible future developments of this exciting field of research, which combines multiple scientific disciplines and is, like few other areas in chemistry, subject to continuous enthusiastic discussion and compassionate dispute.

Keywords Drug design · Computational chemistry · Fragment-based design · De novo design

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Introducton

Approximately 25 years ago the first computer applications were conceived for the purpose of automated "de novo" drug design [1–4], prominent pioneering tools being ALADDIN [5], CAVEAT [6, 7], GENOA [8], and DYLOMMS [9]. Many of these early concepts were enabled by innovative techniques for ligand-receptor interaction modeling like GRID [10], MCSS [11], DOCK [12], and CoMFA [13], which still provide the theoretical framework for several more recently developed molecular design algorithms. After a first wave of software tools and groundbreaking applications in the 1990s [14–18]—expressly GROW [19], GrowMol [20], LEGEND [21, 22], and LUDI [23, 24] representing some of the key players—we are currently witnessing a renewed strong interest in this field. Innovative ideas for both receptor- and ligand-based drug design have recently been published [25, 26]. We here provide a personal perspective on the evolution of de novo design, highlighting some of the historic achievements as well as possible future developments of this exciting field of research, which combines multiple scientific disciplines and is, like few other areas in chemistry, subject to continuous enthusiastic discussion and compassionate dispute.

Broadly speaking, the main scientific challenges for de novo drug design are compound scoring (activity prediction, ΔG° estimation), sampling (on-the-fly compound assembly and navigation in search space), and the synthetic accessibility of the designs [27]. In their pioneering study from 1991 [19], Moon and Howe argued that: "Given detailed structural knowledge of the target receptor, it should be possible to construct a model of a potential ligand, by algorithmic connection of small molecular fragments, that will exhibit the desired structural and

electrostatic complementarity with the receptor". At the time, searching the space of candidate compounds was considered the most critical issue of the design process, and molecular fragments as building blocks were primarily used to obtain a manageable search space. This was one reason for choosing peptides and peptide-mimetics as a preferred molecule class for exploration. Among the various algorithms that have been employed for de novo design ever since, the methods for navigation in chemical space probably have diversified the most, ranging from exhaustive product enumeration and deterministic combinatorial approaches to stochastic sampling by evolutionary algorithms and particle swarms, simulated annealing, and Markov chains, to name just some of the prominent examples [26]. By method transfer the field has massively benefited from parallel developments in computer science and engineering. Today, visualization of the multi-objective compound optimization progress and online structure–activity landscape modeling can be used to observe and potentially prevent premature convergence or misguided design runs [28–30]. It is fair to say that one might consider the task of chemical space navigation solved. With the first structure-based de novo design study published in 1976 [31, 32], this is mirrored in the continuously increasing number of successful compound designs that have been published ever since (Fig. 1).

With few exceptions, the early design methods relied on static X-ray structures providing the essential structural and pharmacophoric feature constraints for in situ ligand assembly. Evidently, rigid models of ligand-accommodating receptor cavities cannot account for induced or flexible fit phenomena that may be observed upon fragment binding, which certainly has contributed to a somewhat curbed enthusiasm and acceptance of de novo design by the medicinal chemistry community at the time. Some of the current molecular design tools explicitly allow for molecular flexibility, albeit sometimes at the price of strongly increased needs for computation time. Unrealistic CPU time requirement has been an argument repeatedly put forward by molecular designers when applications were unsuccessful or too demanding challenges were posed. While this argument might have been acceptable in the past, it may no longer be justified in light of continuously increasing capacity of modern computers. From a technical point of view, it seems realistic that GPU computing, cloud computing and other massively distributed hardware solutions will provide the necessary technological framework enabling sustained progress in de novo design. Still, we must not forget that our

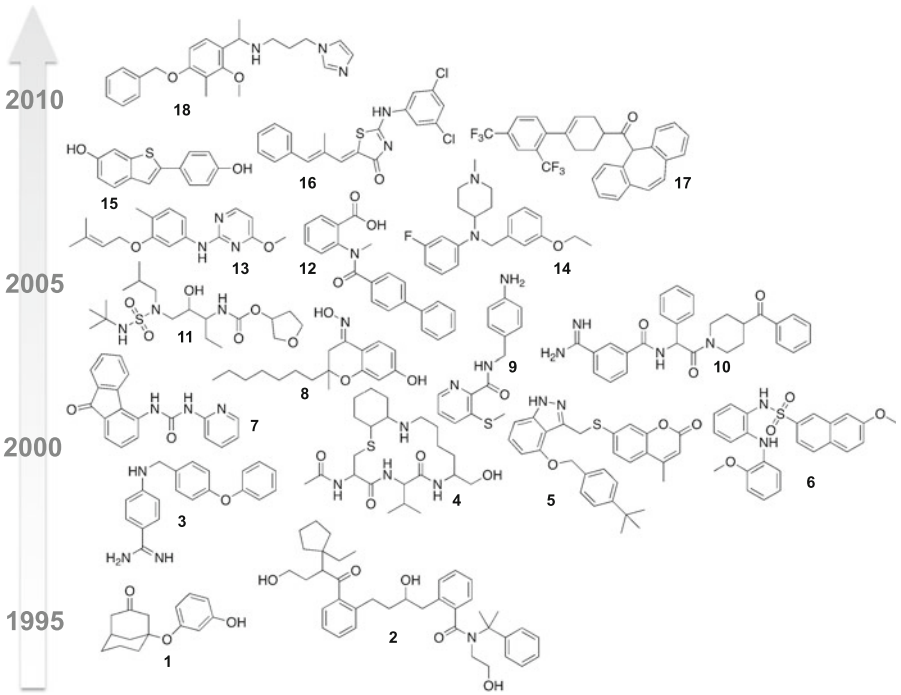

Fig. 1 Selected computationally de novo designed or motivated compounds that were synthesized and successfully tested for bioactivity. **1**: FKBP12 inhibitor [51]; **2**: HIV-1 protease inhibitor [52]; **3**: thrombin inhibitor [53]; **4**: pepsin inhibitor [54]; **5**: DNA gyrase inhibitor [55]; **6**: Kv1.5 potassium channel blocker [56]; **7**: CDK4 inhibitor [57, 58]; **8**: CYP51 inhibitor [59]; **9**: HIV-1 reverse transcriptase inhibitor [34]; **10**: factor Xa inhibitor [60]; **11**: HIV-1 protease inhibitor [61]; **12**: DHODH inhibitor [62]; **13**: HIV-1 reverse transcriptase inhibitor [63]; **14**: Tat-TAR interaction inhibitor [64]; **15**: Estrogen receptor ligand [65]; **16**: Cdc25B phosphatase inhibitor [66]; **17**: CB1 inverse agonist [40]; **18**: Plk1 type II inhibitor [67]

understanding of the physical forces governing ligand-receptor interaction is incomplete, and gaining a decimal point in computational precision is meaningless if insufficient models are used.

With the advent of reaction-driven compound fragmentation and assembly techniques (e.g. RECAP [33], virtual organic synthesis approaches like SYNOPSIS [34] or TOPAS [35]) and fast substructure-based prediction of "complexity" the issue of synthetic feasibility has been partially addressed. Despite several convincing applications, the accurate computer-based assessment of context-dependent building block reactivity still remains profoundly challenging—in particular when rapid estimations for high-throughput applications are mandatory like in de novo compound construction.

The great importance of using a suitable set of fragments for virtual compound generation is highlighted exemplarily by three selected case studies. The first describes the design of novel inhibitors of hepatitis C virus (HCV) helicase. Brancale and coworkers equipped the receptor-based de novo design software LigBuilder [36] with two different sets of molecular building blocks, which resulted in the initial designs A and B, respectively (Fig. 2) [37]. It is evident that the highly complex compound A is an attempt to fill the complete binding site, which most likely is a consequence of poor scoring as larger compounds often yield better scores. To some degree, such complex structural suggestions produced by de novo design software have hampered acceptance of computer-based de novo design by medicinal chemists in the past. Design B—despite its nondrug-like structure—might be considered as a prototype ligand of HCV helicase, which was actually successfully converted into the chemically feasible inhibitor **19** (IC_{50} = 260 nM). Derivative molecules with such changes still fit the in silico models but have improved synthetic accessibility and more desirable physicochemical properties.

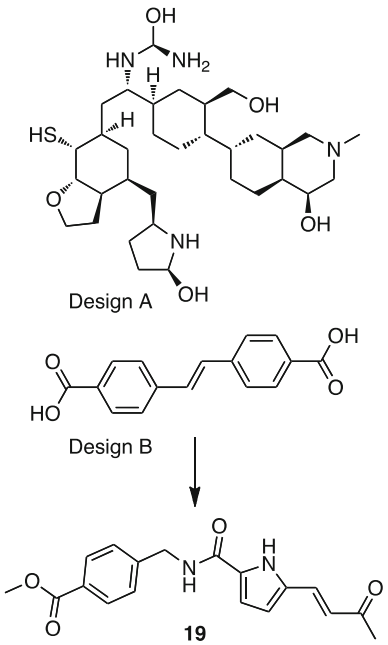

Fig. 2 De novo designed inhibitors of hepatitis C virus (HCV) helicase. Designs A and B were suggested by the software using different sets of fragments for compound generation. Bioactive compound **19** was developed from Design B as a starting point for optimization

A conceptually related ligand-based approach has been presented by Feher et al. who used the Evolutionary Algorithm Inventor (EAI) software together with a topological pharmacophore model for generating compound modifications of inhibitors of the gonadotropin releasing hormone (GnRH) receptor [38]. Basically, the software suggested scaffolds and their decoration by suitable side-chains that matched reference pharmacophore models. Several potent combinatorial variations were synthesized, one of which (compound **20**) exhibited strong antagonistic activity (K_i = 50 nM) on the GnRH receptor (Fig. 3) [39]. Tight interaction with medicinal chemists proved to be essential for post hoc candidate selection and building block prioritization.

A third example of compound optimization from a de novo designed prototype to a potent lead structure is presented in Fig. 4. The software TOPAS produced a small series of structural suggestions that were further optimized as potent inverse agonists of cannabinoid receptor 1 (CB1) [40]. A single known reference compound served as a template for fragment-based virtual ligand assembly, guided by a topological pharmacophore model (CATS) [41]. One of the initial designs (**21**) had poor activity (K_i = 1,500 nM) but was chosen for subsequent optimization

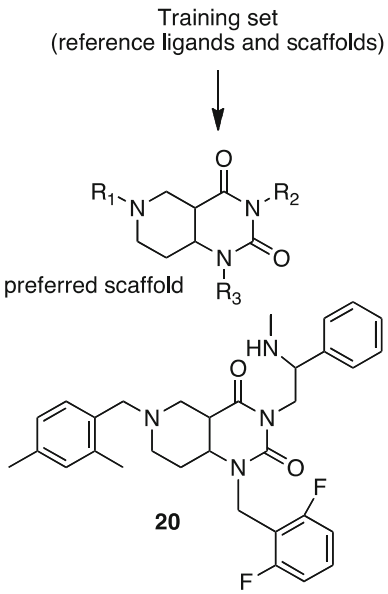

Fig. 3 Combinatorial design of GnRH receptor ligands. Several potent hits were obtained by in silico side-chain optimization

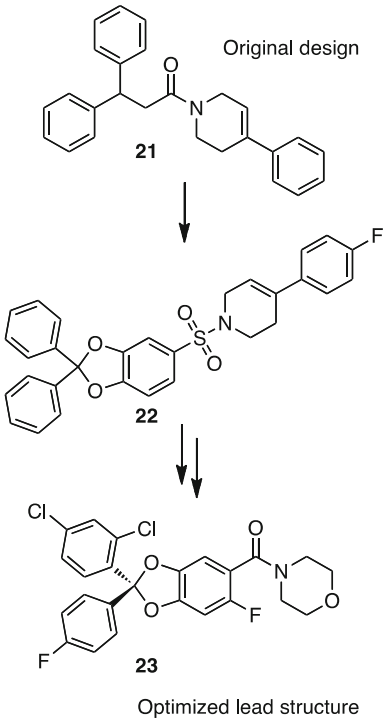

Fig. 4 De novo designed hCB1 inverse agonists. The original design (**21**) was step-wise optimized to become a potent lead structure with desired in vivo efficacy

through iterative modeling, synthesis, and testing, which via intermediate compound **22** ($K_i = 13$ nM) eventually led to the benzodioxole **23** ($K_i = 4$ nM) exhibiting desired in vivo efficacy [42].

These selected examples confirm that profound chemical understanding is essential for successful application of computer-based de novo design tools. One cannot expect that these software tools deliver potent leads from scratch. Future drug design tools should incorporate as much medicinal chemistry knowledge as possible to facilitate candidate selection and increase their acceptance and utilization for drug discovery.

The greatest remaining challenge is activity prediction—not just for individual targets but also whole target panels aiming at polypharmacology predictions guiding automated computer-based molecular design. Since the early days fragment growing and linking has become a recurring scheme pursued by the majority of de novo design approaches. When fragment contributions to the free energy of ligand-receptor binding are of an approximately additive enthalpic nature, even computationally demanding methods may be employed for energy estimation. Despite its appeal building block additivity cannot be assumed a priori. Irrespective of such considerations, we are still far from being able to reliably estimate entropic contributions to ligand-receptor complex formation. With few exceptions, scoring of de novo designed compounds usually ignores or explicitly avoids attempts of entropy calculation. Here, we see a massive demand for innovative concepts and approaches before significant progress will be possible for de novo design. Similar to structure sampling, the field might benefit from intensified crosstalk and interaction between drug designers, theoretical chemists and physicists.

"Top-down" machine learning models complement the "bottom-up" scoring concepts and have found productive application in de novo design software. For example, different types of artificial neural networks and kernel-based regression models have replaced the early QSAR models. A particular appeal lies in their speed of calculation and adaptability to new data, without the need for explicit energy computation. Possibly the machine-learning paradigm offers a temporary solution to the scoring problem, by providing "knowledge-based", target-specific models instead of "global" energy computation. A major limitation of these methods is their need for training data, which are available in great amounts for massively researched targets only. The most simplistic approach to compound scoring is offered by methods based on chemical similarity. Here, the objective is to maximize similarity between the de novo designs and reference compound(s) with known activity. This technique may be considered as similarity searching in virtual chemical space. Again, the concept does not apply to novel targets or pockets, but has been successfully employed for the purpose of scaffold-hopping and bioisosteric replacement.

We expect immediate progress for receptor-based de novo design from a combination of flexible pocket models with advanced methods for shape and pharmacophore matching. Such a scoring scheme would include extended pharmacophoric features allowing, e.g., for "strong", "medium" and "weak" hydrogen bridges, better consideration of arene–arene interactions and geometries, as well as explicit solvent molecules, and would allow for moderate pocket and ligand adaptation during the actual ligand construction, thereby possibly avoiding artifact ligand poses [43]. With continuously better scoring functions available, de novo designed compounds will have a greater chance of exhibiting the desired activity and property profile, and due to increased "chemical attractiveness" getting accepted for synthesis.

With high-throughput screening and fragment-based approaches fuelling today's drug discovery pipelines, computer-assisted de novo design plays an increasing role in this game [25, 44, 45]. It will be most interesting to see how this situation will develop during the next decade [46–48]. Structural novelty combined with synthetic feasibility might be more important for a de novo design than actual bioactivity, which can often be increased by means of medicinal chemistry [49]. In 1987, Sheridan et al. wrote [50]: "Only a few novel bond 'frameworks' in which important

pharmacophore atoms are held in the proper arrangement need to be found to suggest new areas for drug design and synthesis." This statement is true today as it was in the early days of computer-based drug design. The primary aim of de novo design tools is to fuel the creativity of chemists by making surprising and innovative suggestions.

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