Drug Design

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Opportunity Knocks: Organic Chemistry for Fragment-Based Drug Discovery (FBDD)

*Christopher W. Murray and David C. Rees**

biological chemistry · drug design · drug discovery · fragment-based drug discovery

Introduction

This Essay highlights the growing need for organic chemistry research to enable FBDD and we address two questions often asked: "What are the chemical characteristics of a good fragment?" and "Is organic synthesis a limiting factor in FBDD?"

FBDD is well-established within many Pharma, biotech and academic institutions as a technology for generating new chemical leads and drugs.[1] Over 20 compounds derived from FBDD are being evaluated in clinical trials[2] and the BRAF kinase inhibitor, vemurafenib (Zelboraf) is a launched drug for late-stage melanoma.[3]

Differentiating Features of FBDD

The fundamental difference between FBDD and other lead discovery approaches, such as high-throughput screening (HTS), is the small size of the individual molecules in the screening library, with typical MWs (molecular weights) of 140–230 g mol^{-1}. This represents the key advantage and key challenge of FBDD. The smaller size means superior sampling of chemical space, leading to higher hit rates and the opportunity to identify leads for targets previously regarded as difficult to drug with small molecules.[4] However, the smaller the fragment, the weaker the binding affinity. Millimolar (mM) or high micromolar (μM) affinity is common and this often requires sensitive biophysical screening methods (e.g., X-ray, NMR, ITC, SPR) instead of bioassays. X-ray crystallography is now widely used to elucidate the molecular binding interactions of fragments and to allow iterative design of elaborated compounds in the fragment-to-lead stage where affinity is increased to nM.

[*] Dr. C. W. Murray, Dr. D. C. Rees
Astex Pharmaceuticals
436 Cambridge Science Park, Cambridge, CB4 0QA (UK)
E-mail: david.rees@astx.com

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In our experience the chemistry required for FBDD is differentiated from that which underpins traditional drug discovery techniques in two respects, both of which require new synthetic methodology research:

- Design and synthesis of new fragments
- Elaboration of mM or weak μM fragments into nM leads, guided by X-ray crystal structures.

Chemistry Challenges for FBDD

1. Despite the small size, apparent simplicity and the commercial availability of many fragment-like molecules, there is a pressing need for the design and synthesis of

Table 1: Typical chemical properties of many Astex fragments.[a]

Property	Guideline
Molecular recognition	Diverse, usually polar groups for binding to a protein (a single pharmacophore) (see Figure 1 and 2). An aspiration is to express any given binding pharmacophore in a variety of diverse scaffolds (chemotypes).
Synthetic vectors	Multiple synthetically accessible vectors for fragment growth in 3 dimensions to access new binding interactions.
Physico-chemical properties	Molecular weight: 140–230 g mol^{-1}; Non-hydrogen atoms: 10–16; Lipophilicity (clogP): 0.0 to 2.0; Properties commensurate with biophysical screening at high concentrations, e.g., aqueous solubility (preferably $\geq$5 mM in 5% DMSO, or other screening co-solvents); stability (>24 h in solution); avoid compounds/functional groups known to be associated with high reactivity, aggregation in solution, or false positives.[5] NB: aromatic C–H bonds or ^{19}F may assist NMR screening.
Synthetic tractability	Typically, 50–100 mg and $\leq$4 steps from commercially available reagents.
Shape	Variety of 3-dimensional shapes for each scaffold and pharmacophore; Number of freely rotatable bonds: 0–3; Number of chiral centres: 0–1, sometimes 2

[a] These are the properties we currently aspire to and are based on over a decade of FBDD research. Note that there are many examples of fragments outside of these guidelines that have been progressed into useful leads.

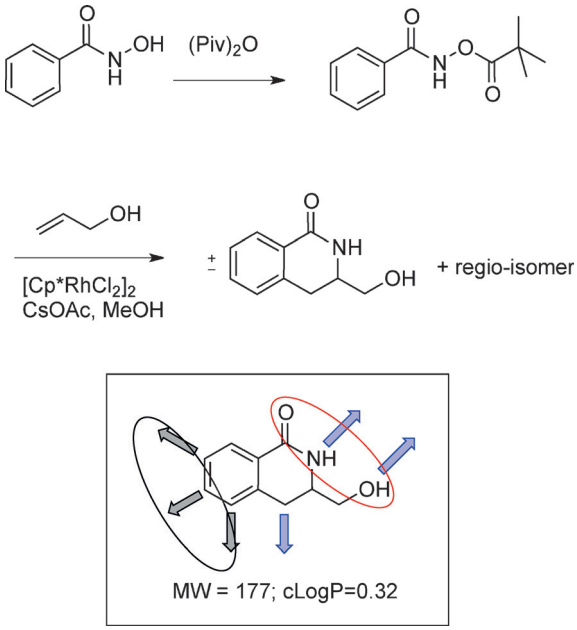
more fragments that are not commercially available and preferably in-line with the guidelines shown in Table 1.

2. Ideally it should be possible to synthetically elaborate fragments in 3 dimensions from many different growth points/vectors using methodology that is experimentally worked out prior to fragment screening. This will increase the chance of success during fragment-to-lead optimisation stage.

One of the first approaches to describe the chemical properties of a fragment was the "rule-of-three", introduced 12 years ago[6] and there are a number of other influential papers on fragment library design.[7] Properties that we find useful are listed in Table 1. Many of these are easily calculated or predicted prior to synthesis and we always calculate lipophilicity (clogP) and MW before deciding which fragments to add to our library.

As an illustration, Scheme 1 shows a published synthesis of a racemic dihydroisoquinolone[8] that meets many of the criteria for a valuable fragment hit, including MW = 177 g mol^{-1} and cLogP = 0.32. Rh^{III}-catalysed C–H bond functionalization provides access to racemic dihydroisoquinolones in 2 steps from commercially available reagents. The regioisomers are separated by chromatography.

An important consideration for FBDD is the availability of synthetically accessible growth vectors in 3 dimensions from the fragment. The methodology in Scheme 1 is attractive from this perspective because it is possible to incorporate substituents onto related structures,[8,9] indicated with grey arrows on Scheme 1. However, to make this even more appealing for FBDD we would like published methodology that incorporates synthetic handles for growing the fragment in the presence of the polar binding group. In practise, it is common to work out the experimental methodology during a live FBDD project but this causes delays. Of course, other growth vectors are also implicit and are marked with blue arrows, including the OH and NH groups. This potentially encompasses an enormous accessible chemical space and illustrates the advantage of screening such a fragment.



Scheme 1. Example of a fragment synthesis,[8] which meets the guidelines in Table 1. The structure at the bottom is annotated to show fragment-like MW and cLogP. Red circle: polar functionality for protein binding; grey circle: synthetically precedented vectors for fragment optimization without disrupting the likely binding pharmacophore; blue arrows: other implicit growth vectors.

Another consideration for fragment optimisation is the availability of closely related, readily available compounds to probe the fragment–protein binding interactions. We note that recent important publications related to Scheme 1 have devised methodology to incorporate one N atom into the aromatic ring (via an *N*-oxide),[9a] to achieve chiral induction at the asymmetric carbon utilising an engineered metalloenzyme[9c] or a chiral Rh^{III} catalyst,[9d] and to achieve regioselective synthesis by modulating the steric properties of the Rh^{III} catalyst.[9b] Research into C–H bond functionalization and late-stage halogenation in the presence of amines and other polar groups is particularly useful and offers potential for fragment elaboration.[10]

Compared to the synthesis of larger and more complex compounds, fragments may at first appear to be relatively less challenging. However, in our experience the design and synthesis of fragments has been more demanding than we had originally anticipated. With hindsight, reasons for this include:

- X-ray informed fragment-design often requires chemists to devise tailored synthetic transformations to the central core of the fragment;
- Lack of methodology that allows synthetically accessible vectors to incorporate substituents without disrupting the binding interactions;

David Rees received his PhD in 1982 (Cambridge, UK, A. J. Pearson) and worked as a post-doc with E. J. Corey (Harvard). Currently, he is Senior VP Chemistry at Astex, a drug discovery company in Cambridge, UK that has pioneered fragment-based drug discovery. Previously, with colleagues at Organon, he discovered Sugammadex an anaesthetic reversal agent used in over 40 countries. He served as President of the RSC Organic Division 2010–2013 and is a Visiting Professor in Cancer Medicinal Chemistry at Newcastle University.

Christopher Murray received his BA (1986) in chemistry and PhD in theoretical chemistry (1989) from the University of Cambridge. Currently he is VP of Discovery Technology at Astex where he has contributed to the design and exploitation of fragment libraries. He has extensive experience of structure-based drug design and has helped discover a number of compounds that have demonstrated efficacy in human clinical trials.

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- Difficulty incorporating heteroatoms, 3D architecture, stereo-control and regio-control without having to devise new synthetic routes;
- Insufficient synthetic methodology compatible with multiple heteroatoms and polar H-bonding functionality required in attractive fragments;
- Fragments preferably have high aqueous solubility and polar functionality (H-bonding groups such as amines, alcohols, amides, etc.) for screening and binding, respectively (Table 1) and we have often found polar fragments of this type difficult to make and isolate;
- Requirement to retain physicochemical properties commensurate with drug-likeness.[11]

The most recent batch of 33 fragments selected for synthesis at Astex required a total of 13 different reaction types. This is in contrast to the alternative approach of synthesising several compounds based on one or two highly optimised chemical transformations and varying the starting materials (sometimes referred to as library synthesis) and it supports the view that medicinal chemists in the pharmaceutical industry utilise a wide variety of different organic transformations for drug discovery.[12]

Binding Pharmacophores

The term pharmacophore refers to the binding interaction between a ligand and its protein (or macromolecular) target. Simplistically, a fragment might be represented as having just one pharmacophore feature whilst a drug molecule might have nM binding affinity for a protein target resulting from 3 such pharmacophore features. Figure 1 shows some fragment pharmacophores experimentally determined by X-ray crystallography; many more are publically available in the protein data bank (PDB).[13] Knowledge of fragment-binding pharmacophores favoured by particular proteins has been used in the design of targeted fragments.[14] Binding pharmacophores tend to be driven by polar interactions and it has been found that the binding of most fragments is enthalpically driven although the precise balance of enthalpy and entropy is often complex and difficult to predict.[15] To maximise the advantages of screening small fragments we tend to avoid fragments with multiple, distally separated pharmacophores because such fragments can, and should, be represented by simpler examples.[4]

Elaboration of mM or Weak μM Fragments into nM Leads

The goal of the fragment elaboration stage is to increase binding affinity by several orders of magnitude leading to a selective chemical tool or drug candidate suitable for progressing into clinical trials. A critical aspect is the design and synthesis of compounds which add new points of interaction deduced by examining the X-ray crystal structure of the fragment and its protein target. Six examples taken from our own experience are shown in Figure 2. These are from projects that have all led to drug candidates progressed

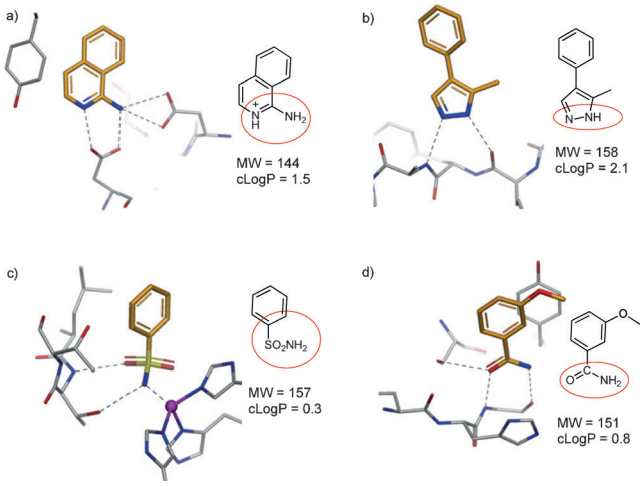

Figure 1. Examples of different fragment binding pharmacophores determined by X-ray crystallography. 2D structrues are also provided with the binding pharmacophore marked in red. a) Amidine-like pharmacophore in beta-secretase (PDB code: 2OHK). Growth vectors orthogonal to the ring are useful to increase binding affinity. This requires the incorporation of the amidine in semi-saturated rings,[16] b) A pharmacophore with H-bond donor–acceptor motif separated by one bond binding to protein kinase A (PDB code: 2UW3). c) Aryl primary sulfonamide pharmacophore binding to a metal in carbonic anhydrase (PDB code: 2WEJ). d) The fragment forms two H-bonds involving a single O atom and the N–H donor forms one H-bond in polyADP-ribose polymerase (PARP) (PDB code: 3PAX).

into preclinical development or clinical trials. Each of these fragments was identified by X-ray crystallographic screening and has at least one hydrogen bond with the protein. By examining the fragment–protein binding it was possible to identify potential new interactions and hence increase the affinity from weak μM into the nM leads shown.

This "precision synthesis" approach is guided by the experimental binding mode of the fragment and by modern computational design methodologies.[17] Many of the vectors for the historical examples in Figure 2 are straightforward from a synthesis perspective but this is not always the case. Some examples require bespoke synthetic elaboration along vectors that are selected only after examination of the binding interactions with each protein target. This requires extensive experimentation which delays FBDD. Frequently we are restricted by a lack of synthetic methodology (e.g., Figure 2b and c) and this is likely to be increasingly the case as more difficult drug targets are screened in the future.

We observe that some well precedented (often commercially available) fragments do already have many synthetic vectors worked out but there is a risk that without more research, FBDD scientists will default to these fragments. To discover chemical leads and drugs for challenging targets such as protein–protein interaction targets, we would like to see more original fragments published with synthetic methodology allowing many vectors to be developed. Furthermore, we would like the synthetic methodology allowing elaboration of fragments in all possible growth vectors to be experimentally precedented before biophysical fragment screening. This scenario requires significant investment from the scientific community to develop the chemistry. In our

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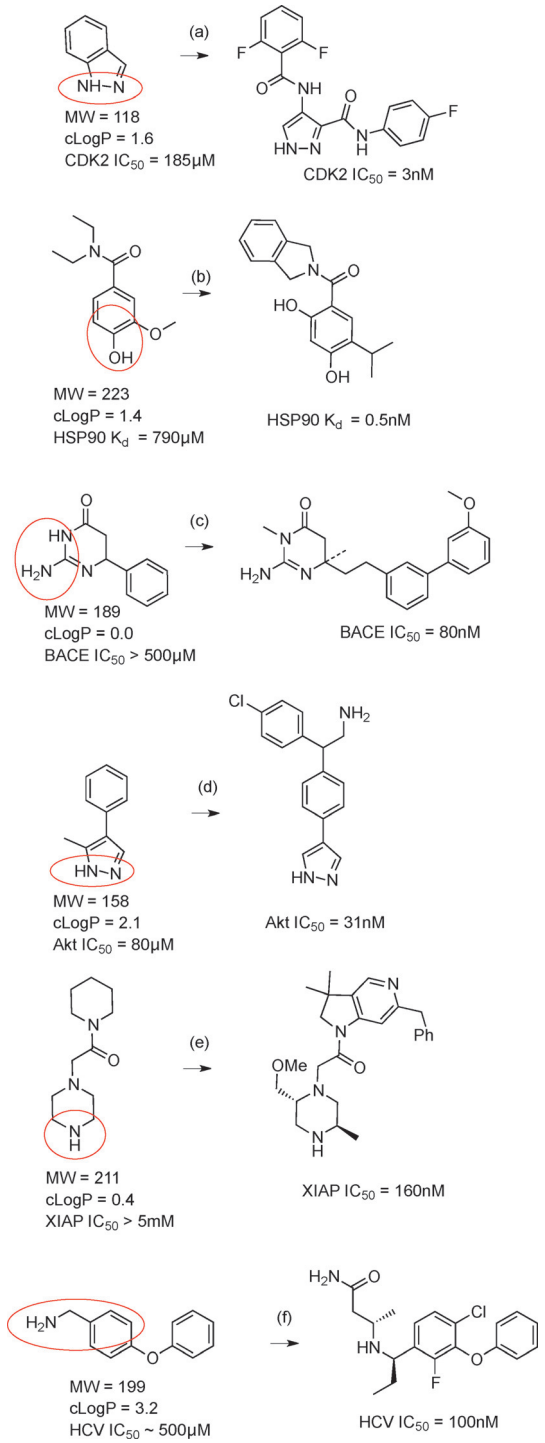

Figure 2. Six examples showing a fragment with weak μM binding affinity and the corresponding lead with nM affinity for different drug discovery targets. The key groups involved in the fragment–protein binding interactions are shown in red. These examples include two kinases (a)[18] and (d),[19] a chaperone protein (b),[20] an aspartic protease (c),[21] a protein–protein interaction (e),[22] and a novel allosteric site (f).[23]

experience synthetic organic chemistry is often rate-limiting in the fragment elaboration stage because the synthetic methodology has not been established.

When faced with a number of fragment hits from a screening campaign, factors to consider in order to select the best fragments for optimization include: binding interactions, ligand efficiency metrics,[11] potential for affinity increase, drug-likeness, and critically, the availability of synthetically accessible vectors for growth into new binding pockets. We note that the chemistry challenges referred to above require a different mind-set to those associated with total syntheses of complex natural products. For fragments we require synthetic methodology that works in the presence of polar groups and also permits future functionalization via multiple growth positions.

3-Dimensionality

Chemical methods to synthesise fragments with 3D shape are of current interest, especially for tough biological targets such as protein–protein interactions. Sp^3 carbons can increase the number and scope of vectors for fragment growth. The prototype publication in this area utilised diversity oriented synthesis (DOS) methodology for 3D fragment synthesis, incorporating structural and stereochemical diversity with geometrically varied growth vectors whilst keeping MW $< 300\,g\,mol^{-1}$.[24] The approach is notable because it shows that DOS and FBDD need not be seen as competing technologies.[25] There have also been other initiatives to synthesise 3D fragments[26] including those based on natural products.[27] We welcome any initiatives that allow the synthesis of novel fragment-like molecules that retain the sampling advantages of fragments and offer a range of synthetically accessible vectors for future elaboration. In our laboratories it is common to increase 3D character during the fragment optimisation stage and even fragments lacking chiral centres may adopt 3D or chiral conformations when binding to protein targets.[28] We caution against only prioritizing 3D properties when designing new fragments. This represents another challenge for organic synthesis: to incorporate shape whilst retaining small fragment size.

Conclusions

Organic synthesis is a key enabling science for FBDD and has been critical for the successful discovery of several drug candidates currently under evaluation in clinical trials. However, as the field of FBDD has evolved it has unearthed a need for more specialised organic chemistry. This Essay is a call to increase chemistry research and investment into the design and synthesis of diverse fragment molecules.

Guidelines, based on our experience, for the chemical properties of fragments are shown in Table 1. We emphasise the need for the synthesis of more fragments with diverse, hydrogen-bonding pharmacophores expressed in multiple scaffolds whilst keeping the size small (MW range 140–230 $g\,mol^{-1}$). We also stress the requirement for chemistry methodology that allows multiple synthetically accessible vectors for fragment elaboration in the fragment-to-lead stage (Figure 2). We are encouraged by many recent breakthroughs

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in chemical synthesis, for example selective C–H bond activation is highly relevant for fragment elaboration as it offers the potential to grow fragments without disrupting the polar functionality associated with fragment–protein binding.

We encourage academic chemists to develop synthetic methodology compatible with the polar functional groups present in attractive fragments and to engage with practitioners of FBDD to develop ideas about the chemical characteristics of useful fragments.

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