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Opportunities and guidelines for discovery of orally absorbed drugs in beyond rule of 5 space

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Recent years have seen a dramatic increase in the number of drugs approved in chemical space outside of Lipinski's rule of 5, that is in what has been termed beyond rule of 5 (bRo5) space. The development of three major classes of oral drugs that treat HIV and HCV infections and the growing evidence that novel, difficult targets can be accessed has prompted research into understanding design of drugs displaying cell permeability, solubility and ultimately oral bioavailability in bRo5 space. Studies have found a consistent outer property limit for a reasonable chance of *de novo* designing oral bioavailability. In addition, several property-based guidelines, along with incorporation of chameleonic features, have emerged as strategies to aid design in bRo5 space. A more detailed understanding of the complex and environment dependent conformational landscape will likely be the focus of the next generation of guidelines allowing property predictions of ever more complex compounds. By pushing the boundaries of current orally designable chemical space we hope that discoveries will be made for fundamental science and also for discovery of novel therapeutics.

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Introduction

Half of all targets assumed to be involved in human disease have been classified as 'difficult to drug' [1,2] with traditional small molecules that reside in the chemical space defined by Lipinski's rule of 5 (Ro5) [3–5]. Biologics may be ideal for difficult targets, but in contrast to small molecules they lack the cell permeability required to reach intracellular targets and can not be administered orally. Interestingly, recent investigations have highlighted that compounds residing in beyond rule of 5 (bRo5) space [6,7] allow modulation of difficult classes of targets [7–9]. In particular, macrocycles [7,9], but also other compounds in bRo5 chemical space [7,8], are suited for modulation of targets that have large, flat or groove-shaped binding sites, for instance protein–protein interactions [8,10]. Compounds in bRo5 space may therefore provide breakthrough opportunities for drug targets that can not be modulated with Ro5 compliant small molecule drugs and are inaccessible to biologics.

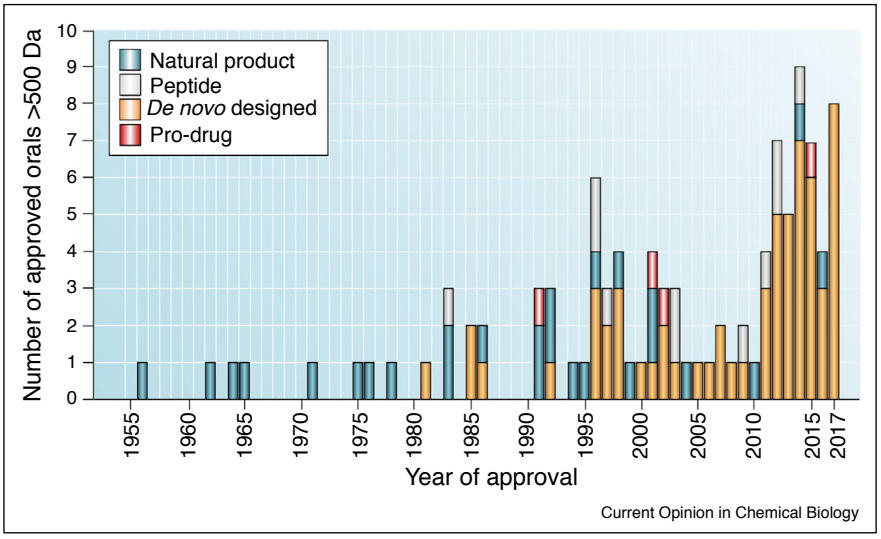
Herein we summarize approvals of orally absorbed drugs with molecular weight (MW) >500 Da, with particular emphasis on recent drug approvals in bRo5 space. We discuss how our understanding of the outer limits of chemical space in which orally absorbed and cell permeable drugs may be discovered has improved significantly in recent years. Finally, we give an overview of current guidelines for their design and optimization in this space. Our focus is entirely on compounds that enter cells by passive, transcellular permeability, whereas compounds that use endocytosis, such as stapled peptides and cell penetrating peptides, have been considered out of scope.

Orally absorbed drugs outside the Ro5

In order to investigate recent trends in discovery of orally absorbed drugs outside the Ro5 we updated our recent dataset [6]. This was done by addition of all drugs having a MW of 500–3000 Da that had been approved in the three major markets, the US, EU and Japan, during 2012 and up to and including the second quarter of 2017. The number of orally absorbed drugs in this MW range was low and infrequent up to 1995, and dominated by natural products (Figure 1). Then approvals increased significantly with peaks in 1996 and 2001, before taking off more dramatically during the years after 2010. Interestingly, the increase in approvals starting in 1995 was dominated by the class of *de novo* designed drugs. It is also noteworthy that an increasing number of orally absorbed drugs of mainly peptidic nature have been approved recently, while the number of natural products has decreased since 2005.

Drugs having MW >500 Da may still adhere to the Ro5 as it allows compounds to reside a short distance outside of

Figure 1



Approval of orally absorbed drugs with MW >500 Da. The number and chemical class of drugs approved in the US, EU or Japan plotted versus the year of their approval. Drugs were categorized in one of four chemical classes; natural products, peptides, *de novo* designed and pro-drugs.

the guideline [5]. We therefore carried out a closer examination of drugs in chemical space far outside the Ro5, that is in bRo5 space [6,7], that have been approved since the 2011 upsurge (Figure 2, c.f. caption for definition of bRo5 space). During this period a total of 17 bRo5 drugs were approved, 10 of which are used for treatment of hepatitis C virus (HCV) infections and act by inhibiting either the HCV NS3/4A protease or NS5A (Figure 2a). The remaining seven drugs are used in diverse indications, ranging from hypercholesterolemia, HIV infections, cancer, constipation and liver disease to fungal infections. The majority of the 17 drugs were classified in bRo5 space because of having a MW >700 Da, but some also had high calculated lipophilicity (cLogP), polarity (HBA, hydrogen bond acceptor; TPSA, topological polar surface area) or number of rotatable bonds (NRotB).

These bRo5 drugs show a fascinating structural variation (Figure 2b), reflecting the nature of the different targets they modulate and the origin of the lead compounds. Interestingly, these 17 drugs reveal that diverse approaches for lead generation can be successfully employed in bRo5 space. The class of HCV NS3/4A protease inhibitors originates from optimization of a peptide lead [11], while the lead for the HCV NS5A inhibitor class was discovered in a high-throughput phenotypic screen [12]. Natural products, the traditional source of drugs in bRo5 space, have given rise to carfilzomib [13] and naloxegol [14]. Cobicistat was discovered by structural modifications of the human immunodeficiency virus (HIV) protease inhibitor ritonavir [15], and venetoclax was developed by linking and subsequent structure-based optimization of two fragment hits [16].

Limits of oral druggable bRo5 space

An understanding of the outer limits of bRo5 space in which oral absorption, and thus most likely also cell permeability, can be obtained has recently been provided by three independent studies [6,9,17]. Two of them came to similar results with upper guidelines for MW at 1000–1100 Da, cLogP at 10–13, HBD at 6, HBA at 14-15, TPSA at 230–250 $Å^2$ and up to 20 NRotB (Kihlberg and DeGoey, Figure 3a). The first study was based on analysis of a set of >200 orally absorbed drugs and clinical candidates having MW >500 Da (Kihlberg) [6], whereas the second relied on rat oral bioavailability data for >1100 preclinical compounds outside of the Ro5 synthesized at AbbVie (DeGoey) [17]. The third analysis utilized 18 macrocyclic drugs and yielded somewhat different results, in particular for cLogP, HBD and TPSA (Whitty) [9]. The discrepancy between this study and the two first ones most likely originates from the difference in size of the datasets, but also from that drugs such as desmopressin and fidaxomicin that have very low oral bioavailabilities (1 and <3%, respectively) in humans were included in the third, but not in the first and second studies. However, the analysis by Whitty highlights that very low bioavailabilities, which are usually not regarded to be satisfactory for oral administration of drugs, may be sufficient for certain indications if the drug is highly potent. As suggested by the ranges of properties displayed by oral drugs having MW >500 Da (Figure 3b), it may not be possible to design drugs in bRo5 space that 'have it all', that is drugs for which all properties are at their outer limits. Accordingly, the study of AbbVie's preclinical compounds [17] and one of carefully designed cyclic peptides [18], highlighted that