Macrocycles, the edge of drug-likeness chemical space or Goldilocks zone?

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Some glass ceilings are waiting to be broken. If you are a follower of Chris Lipinski's rules(1) then you should probably stop reading: any commentary about macrocyclic drugs is likely to induce nausea, dizziness and disbelief in devotees. The rules were of course derived from a dataset of known orally bioavailable drugs and represents a snapshot in time: dataset selection is everything in this field and is the elephant in the room. Empirically derived rules are tautologies and we shouldn't be surprised when they are broken once we step outside of the dataset(2).

The most fragile part of this particular glass ceiling is the molecular weight limit of 500 Da; a limit easily smashed by modern blockbuster drugs and some older former blockbuster macrocycles such as cyclosporine **1** (Figure 1). As medicinal chemistry has developed and encompassed protein-protein interaction targets so the size of molecules has increased over time leading to the beyond Ro5 or bRo5 concept (3). This trend was first evident with the HIV protease inhibitors such as saquinavir **2**, but continues to the present day with the new BCl2 inhibitor ABT-199, ventoclax **3**, the HCV drug velpatasvir **4** and many other natural product examples (Figure 1).

Figure 1, Figure 2

Verteporfin **5** (Figure 2) is a photodynamic therapy drug delivered intravenously for the treatment of AMD in conjuction with red light and is therefore outside of normal considerations of orally bioavailable drug likeness space. Verteporfin and similar therapies still have to cross cell membranes however, have an acceptable toxicity profile, be formulated adequately, and achieve active concentrations at the target site. All these are in fact drug-likeness characteristics in the wider sense. This special issue describes the use of macrocycles in different aspects of drug use from photodynamic therapy to potential new antibiotics, formulation uses and imaging. Macrocycles can interact with a greater variety of protein targets and have many more applications than small molecules which makes them ideal for new therapies. Our tendency as medicinal chemists is to look at the molecules in Table 1 and see them as outliers whereas in reality they are the forerunners of many more drugs to follow. We are learning to understand such molecules however(4) but much more remains to be done.

This macrocyclefest is a celebration of the creativity and dedication of organic and medicinal chemists, often drawing on inspiration from nature but also open to the limitless inventiveness for the development of new structures and applications. These molecules stretch our preconceptions of drug-likeness chemical space – and this is no bad thing.

In the review by **Richard S. Brzozowski and William M. Wuest(5)** the authors argue that 12 membered ring lactones are "privileged scaffolds" whose potential as biologically active molecules and potential drugs is still unrealized. Chemically fascinating, these structures show diverse chemistry and biological activities. Of course macrocyclic lactones are well known and the macrolide antibiotic drugs such as erythromycin **6** are mainstays of therapy. The authors show biosynthesis, synthetic methods and describe biological activity. A notable example is carolacton **7** (Figure 3) a highly potent bacterial biofilm inhibitor(6) which was synthesized by the Wuest group in 14 steps(7). Though this is still a little long for a drug candidate it represents a useful synthetic route that could with adaptations be utilized for analogue preparation. Perhaps this is the most tantalizing aspect of the 12 membered ring class, they are, thanks to the heroic efforts of synthetic chemists and the many advances in chemical methods, amenable to chemical synthesis. This will allow their properties and activities to be optimized and adjusted for different targets and drug uses. The crystal structure shows a relatively compact structure for the core ring with the side chain providing facility to make more extended contacts(8).

Figure 3

In the review by the **Michael Hamblin(9)** and co-workers tetrapyrrole photosensitizer design features are described. The authors point out that the molecules are usually delivered by intravenous injection and highly lipophilic molecules are favoured over hydrophilic ones. In contrast to most drugs the molecules do not bind specific proteins but rather are localized to different organelles within the cell for example APSC 12, **8** initially localizes to liposomes but on photoactivation relocalizes to ribosomes where it kills the cell(10). In contrast the cationic species such as **9** tend to relocalise to mitochondria(11) (Figure 4).

Figure 4

The photosensitizer theme is continued in an original article by **Homem-de-Mello(12)** and co-workers where density functional theory is utilized to for analysis and a number of chemical descriptors (molecular volume, LUMO energy, oscillator strength, dipole moment and free energy of solvation) are proposed as useful in separating or classifying pthalocyanine photosensitizers. The study included the clinical agent verteporfin **5** (Visudyne) and a range of experimental molecules.

The review by **Horne and Cronjé(13)** discusses mechanistic aspects of photosensitizer design and the wider photosensiter classes and also goes into detail on some of the shortcomings and difficulties of formulation of such lipophilic structures. Liposomes, cyclodextrins and lipoproteins are all discussed as formulation aids. Photosensitizers may not be delivered orally but the constraints imposed by crossing membranes are still evident. The summary of the different light sources utilized is also particularly illuminating for the non-expert.

The use of macrocycles as scaffolds is highlighted by **Naseer(14)** and co-workers with a review on therapeutic potential of calix[4]arenes. Calix[4]arenes are well known for their well defined central cavity and host-guest properties but the potential of these structures as molecular scaffolds for biologically active molecules is less well appreciated. Of the many examples given I was struck by the potent tuberculosis activity of the guanidine functionalized molecules exemplified by CX1 (Figure 5). These molecules were designed as analogues of the anti-microbial peptides(15). This ability of calixarenes to display supramolecular structures is perhaps their best asset.

Figure 5

Another well studied host macrocycle class are reviewed by **Ghasemi(16)** and colleagues but from the aspect of computer aided design. The ability to effectively model cyclodextrin complexes is important given that relatively few X-ray structures are known. When structures are available as for paroxetine **11** they reveal a (17) beautiful symmetrical and 1:2 arrangement effectively shielding the hydrophobic paroxetine from the aqueous medium (Figure 6). Unlike calixarenes and tetrapyrroles cyclodextrin macrocycles are notably water soluble making them suitable for use as formulation components as well as scaffolds. As Ghasemi and colleagues note they are biocompatible and biodegradable and could be expanded to many more applications.

Figure 6

The next review in this series contains some extraordinary molecules as described by **Siddappa, Shivaputra and Renukadevi Patil (18)**; (benz)imidazole and indole based macrocycles might seem terribly familiar but dicationic structures such as **12** are notably active against bacteria(19). Away from these exotic structures the use of macrocycles in mainstream drug discovery is demonstrated by the clinical candidate TMC647055 **13**, a potent inhibitor (77 nM) of the NS5B polymerase from hepatitis C virus(20) (Figure 7).

Figure 7

This series completes with two original articles, in the first **Jasleen Kaur(21)** and co-workers outline the synthesis of a DO3A based macrocycle **14** for MRI imaging and potential theranostic use (Figure 8). The compound demonstrated high relaxivity 7.1 mM^{-1}s^{-1} superior to some standard agents. In the second article **Zhang(22)** and colleagues prepare a ^{99m}Tc(CO)$_3$ –glucose conjugate **15** utilizing click chemistry and determined good tumour localization opening up the possibility of using this molecule as a tumour imaging agent.

Figure 8

Table 1. Comparison of Lipinski Ro5 with PPI inhibitors and macrocyclic drugs.

Parameter	Lipinki's rule of fives: Small molecule drugs	Ventoclax	Cyclosporine	Verteporfin (pdt therapy)
CLogP	<5	10.3 (XlogP 8.2)	2.7*	5.9
Hydrogen bond donors (NH + OH)	<5	3	5	2
Molecular weight	<500	868	1202	718
Hydrogen bond acceptors	<10	14	12	12
tPSA#	*<140*	*176*	*279*	*165*

See figures for structures. *Experimentally determined see ref(23), #Veber's PSA limit.

Figure Legends

Figure 1. Breaking the glass Lipinski ceiling, high molecular weight drugs.

Figure 2. The i.v. injectable photodynamic therapy drug verteporfin.

Figure 3. Structures of erythromycin, carolacton and the carolacton crystal structure. Structure CCDC 735883 was downloaded and visualized with MOE.

Figure 4. Tetrapyrrole photosynthesisers APSC, and the cationic photosynthesiser 9.

Figure 5. Guanidine functionalized calix[4]arene.

Figure 6. Structure of paroxetine and X-ray structure of the cyclodextrin complex as side and top view. Structure CCDC 184570 was downloaded and visualized with MOE.

**Figure 7**. Antibacterial indole based dication 12 and hepatitis C virus NS5B polymerase inhibitor TMC647055.

Figure 8. Macrocycle based chelating agents for MRI and SPECT/CT imaging applications.

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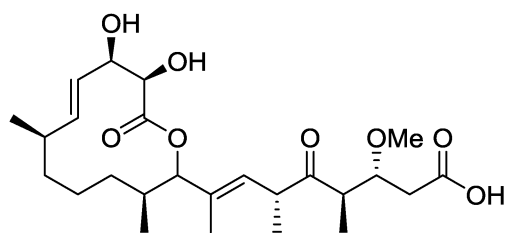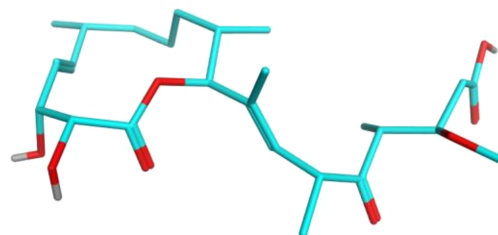
Figure 1

1 cyclosporine

3 ABT-199, ventoclax

2 saquinavir

4 velpatasvir
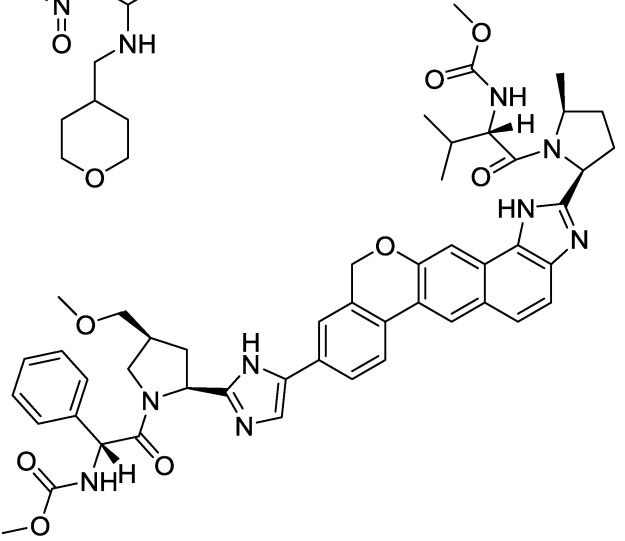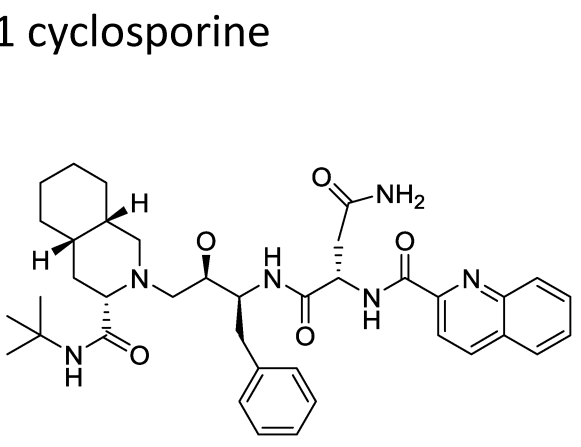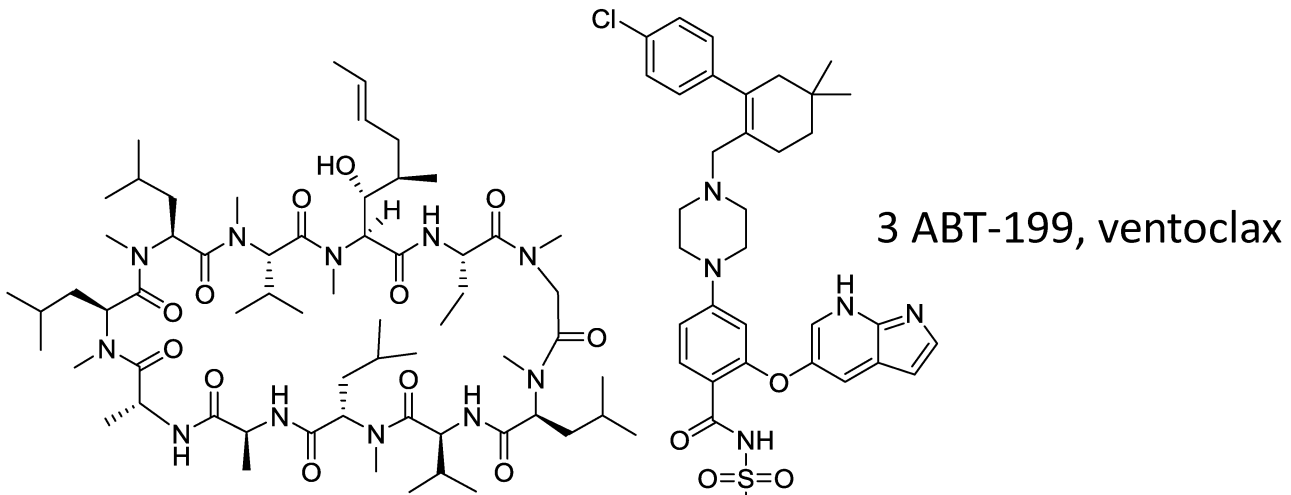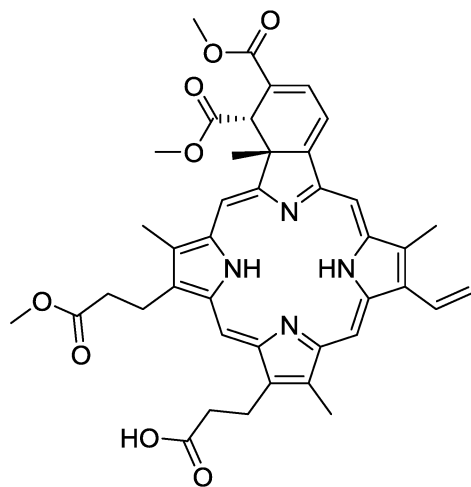
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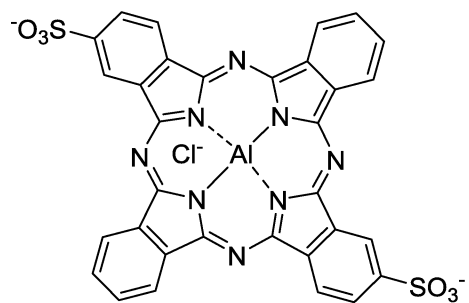

5 verteporfin
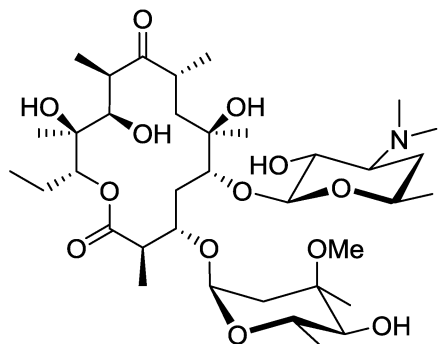
Figure 3

6 erythromycin

7 carolacton

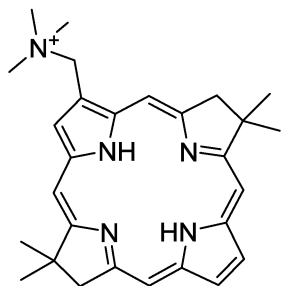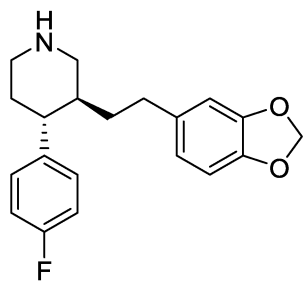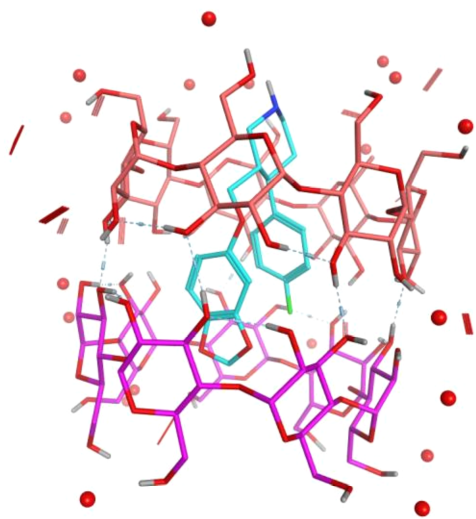carolacton X-ray
structure

Figure 4

8 APSC

9

Figure 5
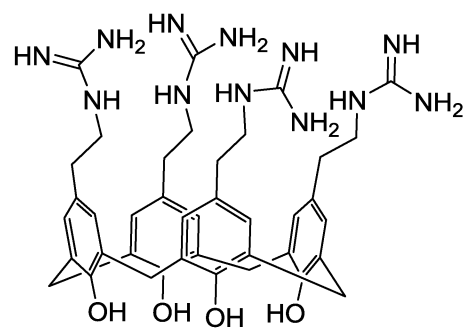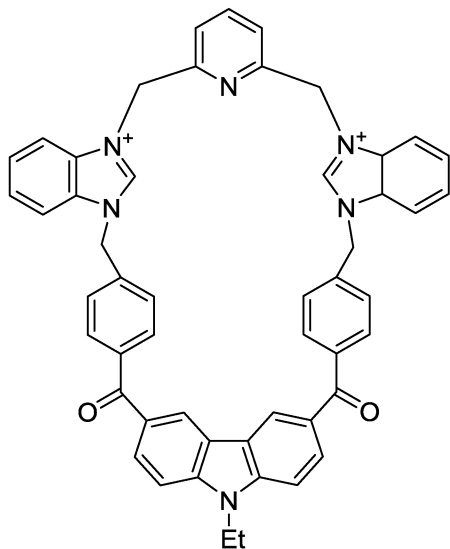

10 CX1

Figure 6

11 paroxetine
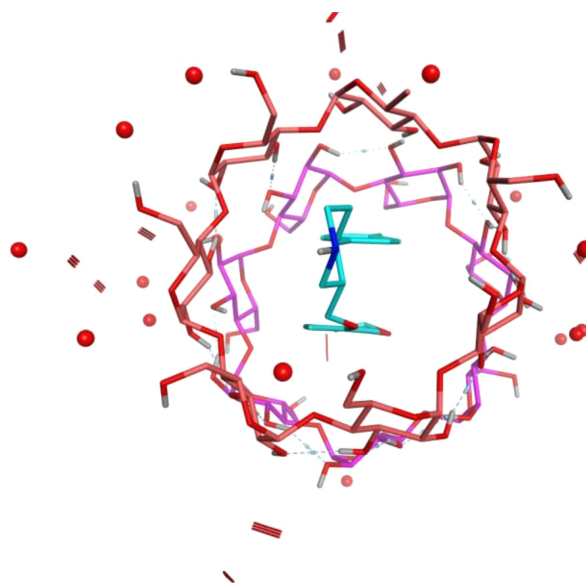
Figure 7

12

13 TMC647055

Figure 7
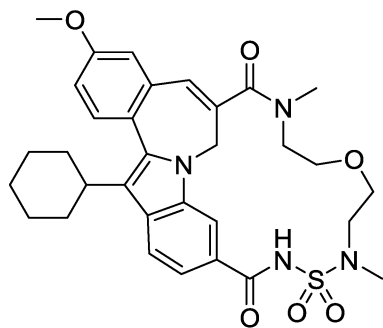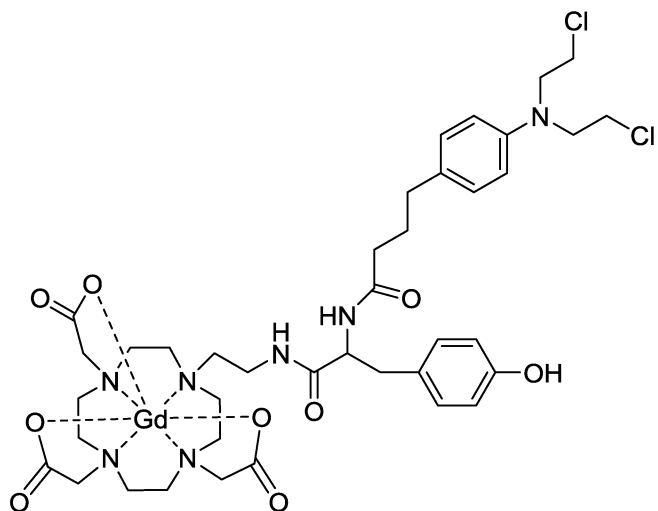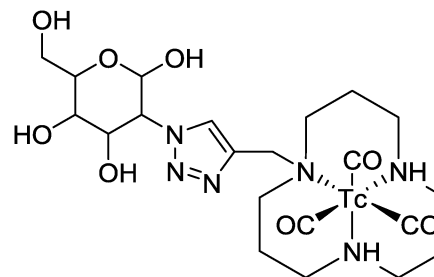

14 Gd(III)-DO3A-tyrosine-
Chlorambucil conjugate

15 ^{99m}Tc(CO)$_3$ complex