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## Quantifying the chameleonic properties of macrocycles and other high-molecular-weight drugs

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Key to the pharmaceutical utility of certain macrocyclic drugs is a 'chameleonic' ability to change their conformation to expose polar groups in aqueous solution, but bury them when traversing lipid membranes. Based on analysis of the structures of 20 macrocyclic compounds that are approved oral drugs, we propose that good solubility requires a topological polar surface area (TPSA, in $\text{Å}^2$) of $\geq 0.2 \times$ molecular weight (MW). Meanwhile, good passive membrane permeability requires a molecular (i.e., 3D) PSA in nonpolar environments of $\leq 140 \text{ Å}^2$. We show that one or other of these limits is almost invariably violated for compounds with MW > 600 Da, suggesting that some degree of chameleonic behavior is required for most high MW oral drugs.

## Introduction

It is well established that certain compounds with MW in the range 500–1500 Da can be useful as drugs, including as oral drugs [1,2], despite appearing to egregiously violate conventional definitions of druglikeness. Many of these high MW oral drugs are macrocycles [3–5]. However, the detailed molecular features that allow these high MW compounds to achieve good pharmaceutical properties remain incompletely understood, and this lack of knowledge presents a major obstacle to the broader exploitation of such non-canonical drug chemotypes [2,4,5]. A factor that contributes to the pharmacological utility of certain large macrocycles is an ability to adopt conformations in which multiple polar groups are internally complemented through intramolecular hydrogen bonding, or are otherwise shielded from solvent [6–10]. This

property enables a compound to present a largely nonpolar surface when in nonpolar environments, such as when passing through a cell membrane, while changing conformation to present more polar functionality in aqueous conditions (Fig. 1). However, our ability to exploit this phenomenon by incorporating such 'chameleonic' behavior [11,12] into synthetic compounds remains rudimentary. Here, we provide a quantitative description of the role that chameleonic behavior plays in the pharmaceutical properties of high MW drug chemotypes. We additionally propose an approach to estimating the extent of the need for chameleonic properties for a particular compound, and the degree to which an actual or proposed compound structure satisfies this need, with a view to advancing our ability to rationally exploit chameleonic properties when developing high MW compounds as drugs.

## The theoretical basis for chameleonic behavior

A useful way to think about chameleonic properties is in terms of the Biopharmaceutical Classification System (BCS) [13]. The BCS categorizes compounds in terms of their experimentally determined aqueous solubility and cell permeability (Fig. 2a), two properties that are key for oral bioavailability and activity against intracellular targets. Both solubility and passive membrane permeability are primarily functions of the balance between polar and nonpolar structure within the compound. A high content of polar groups favors aqueous solubility, but, simultaneously, tends to confer a high desolvation energy barrier, retarding passage into and through the hydrophobic interior of cell membranes. Consequently, properties relating to compound polarity feature prominently in
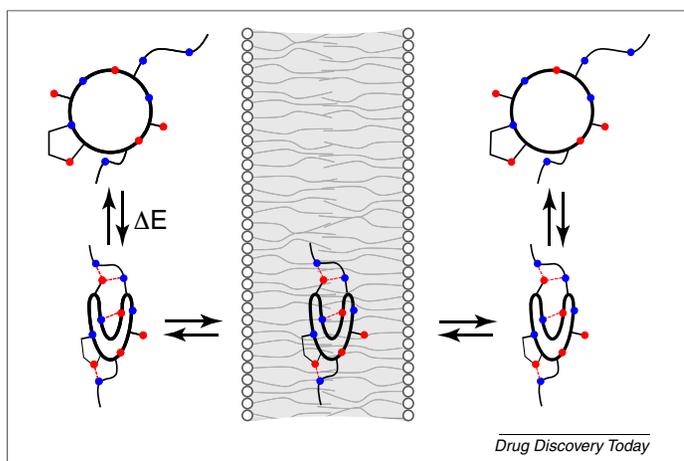
**FIGURE 1**

Cartoon illustrating how chameleonic compounds bury polar groups to improve passive membrane permeability. The upper structures represent the molecular conformation favored in aqueous solution, with hydrogen bond donors (red dots) and acceptors (blue dots) fully exposed and, thus, extensively solvated by water. This open conformation is in equilibrium with a 'closed' conformation (lower structures), in which a subset of hydrogen bond acceptor and donor groups participates in intramolecular hydrogen bonds (red dashed lines), or are otherwise buried and sequestered from solvent. This conformational change reduces the number of water molecules engaged in strong solvating interactions with the compound, and lowers the energetic cost of desolvating the compound as it enters into, and passes through, the cell membrane.

conventional metrics for druglikeness. Indeed, three of the four criteria that comprise Lipinski's Rule of Five (Ro5) [14] involve limits on compound polarity. The Ro5 criterion that the calculated octanol–water partition coefficient ($c \log P$) should generally be $\leq 5$ helps ensure that compounds are sufficiently polar to be soluble. Conversely, the Ro5 limits on the number of hydrogen bond acceptors (HBA $\leq$ 10) and particularly hydrogen bond donors (HBD $\leq$ 5) ensure that the energetic cost of desolvating the compound is not too high for good passive membrane permeation. As we discuss below, the remaining Ro5 criterion (MW $\leq$ 500 Da) also in part reflects the need for an appropriate polar–nonpolar balance, albeit indirectly. Similarly, one of the two druglikeness criteria proposed by Veber et al. [15] is that the PSA of the compound should not exceed 140 Å$^2$, representing an alternative expression of the need to limit the number of polar groups. Importantly, the measure of PSA used by Veber was the TPSA [16], which depends only on atom content and does not take into account the degree to which given atoms are exposed to solvent in a given 3D conformation of the compound.

The aqueous solubility of a neutral compound depends, to a first approximation, on the balance of polar and nonpolar groups in the molecule. A molecule of almost any size can be water soluble, provided it contains a sufficient number of polar groups to counterbalance its nonpolar atom content. By contrast, the energetic penalty for desolvation and transfer into a nonpolar medium scales with the number (and type) of polar groups. Consequently, as MW increases, it becomes more difficult for a compound to have high solubility in both aqueous and nonpolar solvents. For example, a compound with MW < 500 that contains approximately 25% polar atoms, roughly average for oral small-molecule drugs [17], will typically have an acceptable value for $c \log P$ and, at the same time, will contain <10 HBA and <5 HBD and also have TPSA $\leq$ 140 Å$^2$. However, for a larger molecule, such as a large macrocycle with MW = 1000 Da, the same proportion of approximately 25% polar atoms will confer a similar $c \log P$, but the number of polar groups will have doubled, driving HBD, HBA, and PSA above conventionally acceptable levels. If the number of polar atoms is reduced to avoid this problem, the nonpolar:-polar atom ratio will increase, raising $c \log P$ and reducing the aqueous solubility of the compound. Thus, high MW compounds tend to belong to BCS Categories II, III, or even IV, presenting significant challenges for their development as drugs.

Chameleonic compounds are able to square this circle by modulating how many polar atoms are exposed to solvent depending on the polarity of their environment. Thus, a large macrocycle containing approximately 25% polar atoms will likely be reasonably soluble in aqueous solution if it can adopt a conformation in which all or most of the polar atoms are exposed and, therefore, well solvated. This combination of properties would normally place the molecule in BCS Category II. However, upon encountering a nonpolar environment, such as the interior of a cell membrane, a chameleonic compound changes conformation to shield several polar groups, as illustrated in Fig. 1, resulting in a low effective PSA that, in a rigid compound, would likely confer membership in BCS Category III. The result is that the compound can, as needed, have the high aqueous solubility and the high membrane permeability required to place it in the most favorable BCS Category I (Fig. 2a). Most high MW oral drugs, and large macrocycles in particular, tend to conform to a polar:nonpolar atom ratio of approximately 25:75 (Fig. 2b, inset), with $c \log P$ values in the same range as small oral drugs, but with higher TPSA values, typically in the range 180–320 Å$^2$ [4,5]. Therefore, based on consideration of polar versus nonpolar content alone, such drugs should be Category II compounds, with poor passive membrane permeability. The ability of such compounds to access intracellular targets, and in particular their oral bioavailability, likely depend in many cases on their possession of chameleonic properties.

**Quantifying chameleonic properties**

Predicting the aqueous solubility of organic compounds is difficult [18–21]. One reason is that even a relatively polar molecule can be poorly soluble if it has a particularly stable crystal form. However, it is possible to identify features that are necessary for good solubility while not being sufficient to guarantee it. For example, Fig. 2b shows that approved oral drugs that are large macrocycles tend to have a minimum TPSA of ~0.2 Å$^2$ per unit of MW, corresponding to the dashed line in Fig. 2b, which defines the lower bound of the data set. This apparent requirement for a minimum level of polar content can be expressed alternatively in terms of fraction of polar atoms, as illustrated in Fig. 2b (inset), which shows that macrocyclic oral drugs tend to contain $\geq$20% polar atoms (considering nonhydrogen atoms only). Exceeding the lower limits for polar content indicated in Fig. 2b by no means guarantees that a compound will be soluble. It appears, however, that, if TPSA is significantly less than 0.2 MW, then achieving the degree of aqueous solubility (and perhaps also other properties) required for oral activity is unlikely.

It is well established for conventional druglike compounds that PSA $\leq$ 140 Å$^2$ is typically required to have sufficient membrane permeability for good oral bioavailability [15]. When applying this threshold to chameleonic
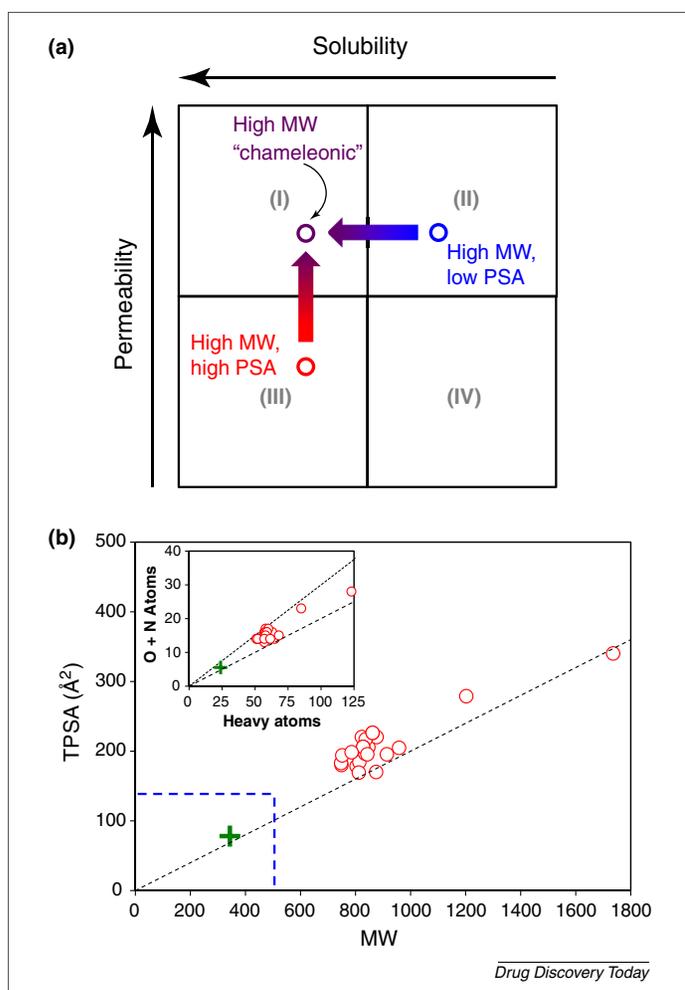
**FIGURE 2**

Effect of chameleonic behavior on Biopharmaceutical Classification System (BCS) Class. **(a)** Diagram representing the BCS for evaluating drug candidates [13]. For the purpose of the current discussion, the gridlines represent the degree of aqueous solubility (vertical gridline) and membrane permeability (horizontal gridline) required for the compound to be developable as an oral drug. A high-molecular-weight (MW) compound that contains many polar atoms (red circle) can have acceptable aqueous solubility. However, a high polar surface area (PSA) will confer a high desolvation energy barrier to entering and passing through the low-polarity interior of cell membranes, making the compound poorly soluble. A similarly large molecule that contains few polar atoms (blue circle) might readily permeate cell membranes, but because of its low polarity will have poor aqueous solubility. A chameleonic compound (purple circle) contains enough polar atoms and groups for good aqueous solubility, but can undergo a conformational change that buries or internally complements multiple hydrogen bond donors and acceptors, thereby allowing good membrane permeability. This combination of aqueous solubility and membrane permeability places the compound in the most favorable BCS Class I. **(b)** TPSA values for all 20 approved oral drugs that are macrocycles (red circles) [4,5], plotted as a function of the molecular weight (MW) of each compound. The dotted line represents the minimum PSA per Da seen among this compound set, and has a slope of 0.20 $Å^2$/Da. The green + shows the mean TPSA and MW values for 1193 oral drugs (taken from [17]). The blue dashed lines show the upper limits to MW and topological PSA (TPSA) as defined by Lipinski's Rule of Five (Ro5) and Veber's Rules, respectively. Inset plot: Relation of compound polarity to compound size for the same set of macrocycle drugs, expressed in terms of polar atoms versus total heavy (i.e., nonhydrogen) atoms in the structure of each compound. The dashed and dotted lines correspond to the minimum and maximum polar atom content observed for this set of drugs, and have slopes corresponding to 20% and 30% polar atoms, respectively.

compounds, it is necessary to use a measure of PSA that takes into account 3D structure of the compound in a particular solvent environment and, thus, whether polar atoms are buried or exposed to solvent [6,7,10]. The extent of PSA that is exposed to solvent in a particular 3D conformation is called the 'molecular' PSA (MPSA) [16,22], or sometimes the 'solvent-accessible' or 'solvent-exposed' PSA. MPSA is significantly more complicated to calculate than TPSA, because it is first necessary to compute what molecular conformation(s) will predominate in a given solvent environment. Nonetheless, methods exist for calculating MPSA with various degrees of theoretical rigor [16,22], and MPSA values have been determined for several macrocyclic drugs and other high MW compounds [22,23].

Based on the above reasoning, we propose that, for good aqueous solubility, $PSA_{Aq} \geq 0.2$ MW, and for good membrane permeability, $PSA_{np} \leq 140$ $Å^2$, where $PSA_{Aq}$ and $PSA_{np}$ are the MPSA values for the molecular conformations that predominate in aqueous solution and in the nonpolar membrane environment, respectively. For a reasonably flexible molecule, the major conformer in aqueous solution will have all or most polar groups exposed to solvent, such that $MPSA_{Aq}$ can be approximated simply by using TPSA. However, a formally calculated MPSA can also be used in the aqueous term if additional rigor is desired. These PSA thresholds are illustrated graphically in Fig. 3a, which shows the range of MPSA values that correspond to a likelihood of good aqueous solubility (blue shading) and good membrane permeability (red shading) for compounds of a given MW. Fig. 3a shows that a compound with MW < 600–700 Da can have sufficient polar content to achieve $PSA_{Aq} \geq 0.2$ MW without exceeding PSA = 140 $Å^2$. Thus, for low MW compounds, modulating the exposure of polar groups through conformational change is generally not required to balance aqueous solubility with membrane permeability, consistent with the observation that small drugs are often relatively rigid and generally are not thought to display chameleonic behavior. Indeed, this analysis likely accounts, at least in part, for the Ro5 criterion that MW $\leq$ 500 [14].

However, for compounds with MW > 700 Da, there is a gap between the blue- and red-shaded areas in Fig. 3a, indicating that, for these high MW compounds, there is no single PSA value that can simultaneously satisfy the conditions 0.2 MW $\leq$ PSA $\leq$ 140 $Å^2$. The higher the MW, the larger the gap between the minimum PSA required for good aqueous solubility and the maximum that is compatible with good membrane permeability. For example, for a compound with MW = 800 Da, 0.2 MW = 160 $Å^2$, suggesting that, in the absence of a chameleonic conformational change, a compound of this size that has enough polar content for good aqueous solubility will have a PSA that is at least ~20 $Å^2$ higher than is compatible with good membrane permeation. Similarly, for a compound with MW = 1200, approximately the
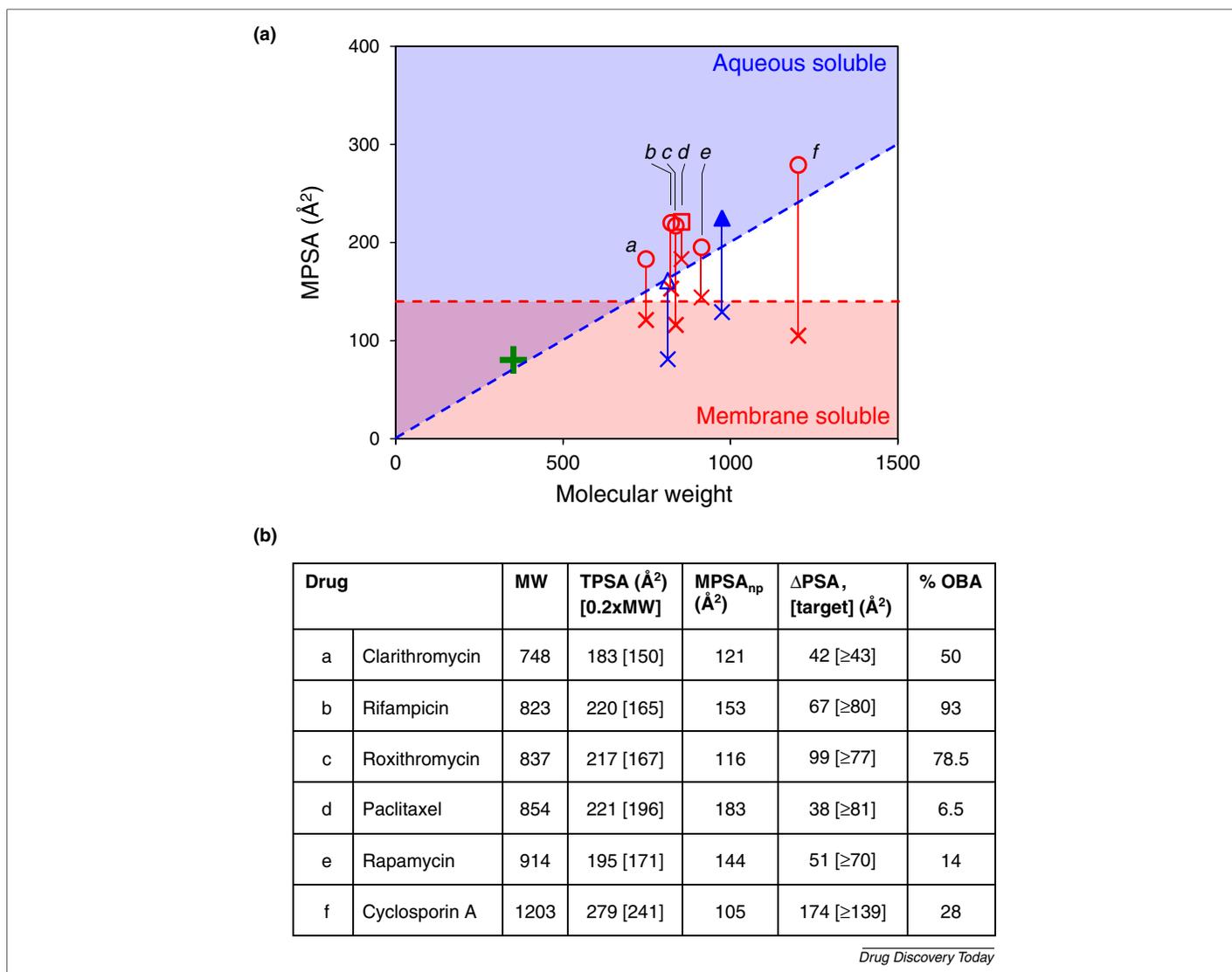
**FIGURE 3**

Quantifying chameleonic behavior. **(a)** Molecular (3D) polar surface area (MPSA) values that we propose to be compatible with good aqueous solubility (blue area) and good membrane permeability (red area), as a function of compound molecular weight (MW). The green + shows mean values reported for 1193 oral drugs, from [17]. Red symbols show MPSA values for approved macrocyclic drugs, for the compound conformation that predominates in aqueous solution (O) and in nonpolar solvent (x). Blue symbols describe the properties of the Bcl-xL inhibitors ABT737 (open triangle) and ABT263 (filled triangle). **(b)** Properties of the six macrocyclic drugs plotted in (a). All PSA and oral bioavailability data are from [22,23]. ΔPSA = TPSA − $MPSA_{np}$. The target value for the extent of ΔPSA required for effective chameleonic behavior is the larger of 0.2 MW − 140 $Å^2$ or TPSA − 140 $Å^2$, according to Eqns (1) and (2).

size of the macrocyclic drug cyclosporin A, 0.2 MW = 240 $Å^2$, implying that an aqueous soluble compound of this size must find a way to bury approximately 40% of its polar groups to achieve good membrane permeability.

The above analysis suggests that the minimum PSA that a chameleonic compound must bury to have both good aqueous solubility and good membrane permeability can be estimated from Eqn (1):

$$\Delta PSA \geq 0.2 MW - 140 \, \mathring{A}^2 \qquad (1)$$

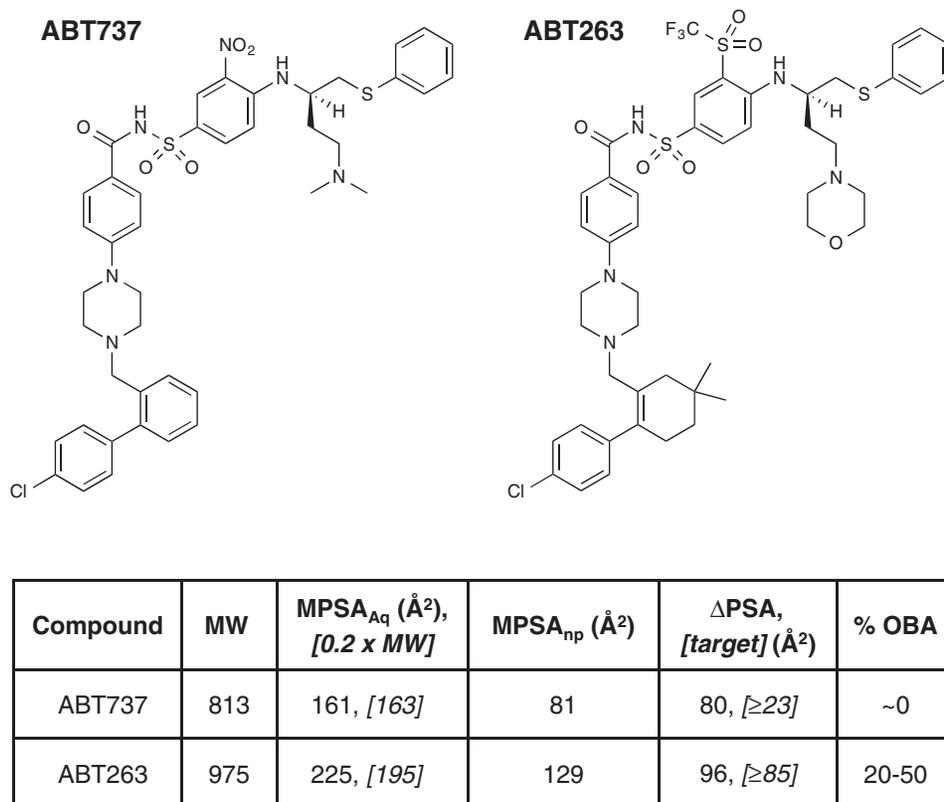For a compound with TPSA that exceeds 0.2 MW, as will often be the case, the minimum amount of PSA that must be buried is given by Eqn (2):

$$\Delta PSA \geq TPSA - 140 \, \mathring{A}^2 \qquad (2)$$

We emphasize that TPSA ≥ 0.2 MW does not guarantee good aqueous solubility, and $MPSA_{np}$ ≤ 140 $Å^2$ does not guarantee good membrane permeability. Many compound structures might exist that violate these expectations. However, compounds (especially high MW compounds) with TPSA significantly below 0.2 MW are unlikely to have good solubility, and those with $MPSA_{np}$ much above 140 $Å^2$ are unlikely to have good permeability. Therefore, these proposed

thresholds represent reasonable approximations of the minimal requirements for possession of these key pharmaceutical properties, and provide a useful framework for evaluating the need for chameleonic properties in favorable cases.

We tested the validity of this hypothesis with respect to the properties of known chameleonic compounds from the literature. Fig. 3b shows reported TPSA and $MPSA_{np}$ values for six macrocyclic drugs. Five of these compounds (clarithromycin, rifampicin, roxithromycin, rapamycin, and cyclosporin A) have oral bioavailabilities in humans of ≥14%, and are all oral drugs [22,23]. Fig. 3a shows that all five of these compounds

| Compound | MW | MPSA$_{Aq}$ (Å$^2$), [0.2 x MW] | MPSA$_{np}$ (Å$^2$) | ΔPSA, [target] (Å$^2$) | % OBA |
|---|---|---|---|---|---|
| ABT737 | 813 | 161, [163] | 81 | 80, [≥23] | ~0 |
| ABT263 | 975 | 225, [195] | 129 | 96, [≥85] | 20-50 |

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**FIGURE 4**

Chemical structures of ABT737 and ABT263, with calculated molecular polar surface area (MPSA) values for the conformations that predominate in aqueous solution (MPSA$_{Aq}$) or in nonpolar environments (MPSA$_{np}$), and values for target and actual ΔPSA. Data are plotted in Fig. 3b. The target value for the extent of ΔPSA required for effective chameleonic behavior is the larger of 0.2 molecular weight (MW) − 140 Å$^2$ or TPSA − 140 Å$^2$, according to Eqns (1) and (2). See the supplementary information online for details of the MPSA calculations.

meet, or come very close to meeting, our proposed guidelines that TPSA ≥ 0.2 MW and MPSA$_{np}$ ≤ 140 Å$^2$, showing chameleonic changes in exposed PSA that conform approximately to our proposed threshold, from Eqn (2), of ΔPSA ≥ TPSA − 140 Å$^2$. Cyclosporin A, in particular, shows the large ΔPSA of 174 Å$^2$, burying approximately 62% of its PSA when in nonpolar environments [24], in close agreement with the expectation from Eqn (2). Another macrocyclic drug, paclitaxel, has some degree of chameleonic behavior (ΔPSA = 38 Å$^2$), but even in nonpolar environments has a high MPSA of 183 Å$^2$. Thus, paclitaxel violates one of our two guidelines (Fig. 3a), resulting in a low oral bioavailability of 6.5% and enabling only parenteral administration [22].

Additional validation involving a non-macrocyclic chemotype was obtained by considering the Bcl-xL inhibitors ABT737 (MW = 813) and ABT263 (MW = 975) (Fig. 4), well-known examples of high MW drug candidates from the recent literature. ABT737 provided initial proof of concept for the pharmacological utility of the chemotype [25], but showed extremely poor aqueous solubility and was not orally bioavailable [26]. ABT263 was developed to address this limitation and, despite its even higher MW, has good oral availability [26] and is currently in clinical development [27,28]. We calculated that ABT737, although having some degree of chameleonic behavior, has MPSA$_{Aq}$ that is below the level of 0.2 MW required for any prospect of good aqueous solubility and, thus, does not meet our proposed criteria. By contrast, the orally available ABT263 matches our guidelines very well, having a substantially higher MPSA$_{Aq}$ that now exceeds 0.2 MW, but simultaneously a large degree of chameleonic behavior that brings MPSA$_{np}$ down to <140 Å$^2$ in nonpolar environments (Figs. 3a and 4). ABT263 is itself poorly soluble [26], but the improvements in its properties compared with ABT737 are evidently sufficient to confer oral bioavailability and to enable its further development as an oral drug. The higher polarity of ABT263 is largely the result of replacement of a nitro group with the more polar trifluoromethylsulfone. Its increased ΔPSA is due to the fact that, in nonpolar environments, this sulfone group can be essentially entirely shielded from solvent by the neighboring thiophenyl moiety (see the supplementary information online for additional details). Taken together, the above results provide strong support that the rule of thumb we propose provides a reasonable approximation for the degree of chameleonic change in PSA required for high MW compounds to achieve both good aqueous solubility and good membrane permeability.

### Value of the analysis for compound design and optimization

The ability to quantify chameleonic properties does not directly address the difficult problem of how to design chameleonic properties into specific molecules, something that has rarely been attempted outside the arena of cyclic peptides [6–10]. However, we believe our analysis can help inform such efforts. First, in considering what compounds to make, for large macrocycles and other high MW chemotypes, it is important to realize that Veber's limit of TPSA ≤ 140 Å$^2$ does not apply in the conventional sense, and that exceeding this limit is not only permitted but is in fact required for good

aqueous solubility. Indeed, of the 22 approved oral macrocycle drugs [4,5], none has TPSA $\leq$ 140 Å$^2$, and approved macrocyclic drugs that are administered parenterally have even higher TPSA values [2,4,5]. The analysis presented here suggests that, for any prospect of good aqueous solubility, compound designs should aim for TPSA $\geq$ 0.2 MW, roughly corresponding to a minimum of approximately 20% of heavy atoms being N or O. A second insight is that some degree of chameleonic behavior will likely be required for almost any oral drug with MW greater than ~700 Da, as well as for some high MW compounds intended for parenteral administration if any degree of membrane permeability is required, for example to access an intracellular target. The analysis also provides a rough guide as to what proportion of the polar content of a compound must be shielded for it to pass readily through a cell membrane. For example, one might consider a hypothetical large macrocycle containing a total of 60 nonhydrogen atoms, with 16 N or O atoms leading to a TPSA of approximately 220 Å$^2$. The above analysis indicates that, for effective chameleonic behavior, such a compound must be able to adopt a conformation that buries approximately $220 - 140 = 80$ Å$^2$ of PSA, corresponding to approximately one-third of its polar groups, for example through formation of intramolecular hydrogen bonds. Although designing a compound that has this property is clearly nontrivial, having even an approximate target for what must be achieved should aid decisions about which compounds to make or test, and what to look for as outcomes from computational studies that model the effect of solvent polarity on compound conformation.

## Acknowledgements

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2016.02.005.

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