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*Perspective*

# Physicochemical Properties of Antibacterial Compounds: Implications for Drug Discovery

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## Introduction

Antibacterial drug discovery peaked shortly after the middle of the past century with the discovery of most compound classes that are still in clinical use. After the introduction of streptogramins and quinolones in 1962, no novel class of antibiotics was identified and approved for clinical use until linezolid was launched in 2000. This fact is rather surprising because not only was research heavily supported during this time but also novel technologies such as genomics and high-throughput screening were introduced and applied to improve productivity.[1] With antibacterial resistance on the rise, we will have to replenish the arsenal of antibacterial drugs to provide physicians with the tools to successfully treat infections in the future.[2] Part of the difficulty associated with the discovery of novel antibacterial compound classes has been defined by stringent requirements for a safe, broad spectrum antibiotic: The target must be essential, highly conserved among various bacterial species, and absent, different, or nonessential in humans. The inhibitor must be potent and should ideally display target-related whole cell activity with a low propensity for the emergence of resistance. Furthermore, the initial "hit" scaffold should be amenable to structural changes to allow for optimization of the potency, efficacy, and safety of later-stage "lead" compounds. A number of authors have discussed not only the necessity of novel antibacterial drugs to ensure future treatment options but also difficulties previously encountered during the hit identification and lead optimization steps.[3–8] While the declining pipeline of antibacterial compounds arguably reflects the technical complexities of these requirements, relatively little has been published providing detailed information about the difficulties encountered at various companies over the past years. A recent review from the group at GlaxoSmithKline added valuable information on multiple issues related to this topic and provided insight into the successes and failures of a target-based, genomic approach.[9] Relatively little though has been published on the nature of the compounds themselves as a possible source for the paucity of new agents. The analysis of Payne and co-workers illustrates the challenge of antibacterial drug discovery and suggests that multiple parameters contribute to the high attrition rate. With the rise of multi-drug-resistant pathogens and the need for novel antibiotics, it is critical to understand as much as possible from prior efforts and to apply learned lessons to the discovery of future antibiotics. One important parameter in particular has previously been mentioned but, in our view, not sufficiently analyzed: the physicochemical property space of antibacterial drugs.[10]

Lipinski's landmark study[11] represented the first systematic attempt to correlate the physicochemical properties of drugs with the predicted successful matriculation of initial hits and subsequent late-stage leads. It was this work that connected for the first time physicochemical properties of drugs with both their oral bioavailability and their subsequent difficulties and attrition rates during preclinical and clinical development. Major findings from this analysis were the recognition of an ideal property space for orally available drug candidates (MW,[a] lipophilicity, hydrogen bond donors and acceptors), as well as the fact that corporate compound archives had been slowly moving away from an optimal area of this physicochemical space, most likely driven by synthetic convenience rather than by design. This awareness had a major impact on drug discovery, and today it is common to analyze these properties (the "rule of five" or "Lipinski's rules") prior to synthesizing novel candidates.

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[a] Abbreviations: CMC, Comprehensive Medicinal Chemistry; PSA, polar surface area; MW, molecular weight; RND, resistance-nodulation-cell division; ACD, Advanced Chemistry Development, Inc.; MIC, minimal inhibitory concentration; $MIC_{50}$, concentration at which 50% of organisms are inhibited in growth.

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Antibacterial compounds, though, have always been considered an exception to these rules primarily because of their higher MW and polarity, and various authors including Lipinski have pointed this out previously.

The physicochemical profiles of orally active drugs were investigated more recently in an article by Leeson and Davis.[12] They listed properties according to therapeutic categories and, in keeping with previous work, demonstrated a deviation for anti-infective drugs toward higher MW and increased polarity, suggesting a requirement of different properties for the penetration into nonhuman cells. However, no distinction was made in this analysis between antiviral, antifungal, antibacterial, antimalarial, and antiparasitic drugs.

A number of other authors used selected sets of compounds, with and without antibacterial activity, to predict compound activity by applying various computational tools including linear discriminant analysis, artificial neural networks of a multilayer perceptron type, and logistic regression analysis.[13–19] All of these approaches allow the prediction of activity on bacterial cells to various degrees of accuracy, usually with a confidence level between 80% and 95%. Of particular interest is the work of Cronin and co-authors who compared discriminate with logistic regression analysis and showed the latter to be slightly more accurate, identifying six descriptors accounting for hydrophobicity and inter- and intramolecular hydrogen bonding that provided excellent parameters for antibacterial prediction.[16]

However, common to all these analyses is the fact that antibacterial activity was defined in general terms. The diversity of bacterial organisms is large, and one key factor for whole cell activity of drug candidates is their ability to penetrate the cell wall. Gram-negative organisms contain in addition to the inner membrane and the peptidoglycan layer an outer membrane that serves as an impermeable barrier for many small molecules. It has been demonstrated that porins serve as major entry gates for antibacterial compounds in these organisms.[20] These membrane proteins were originally thought to be exclusively responsible for the inherently higher resistance of Gram-negative bacteria to antibacterials. Characterization of different families of efflux pumps, especially some members of the RND superfamily (resistance-nodulation-cell division) that form tripartite transporter complexes such as AcrAB-TolC (*E. coli*) or MexAB-OprM (*P. aeruginosa*), revealed the contribution of efflux to the intrinsic drug resistance.[21,22] These efflux pumps were demonstrated to have a wide substrate specificity and often contribute to multi-drug resistance in clinical isolates. Both permeabilization of the outer membrane or elimination of key efflux pumps often sensitize Gram-negative bacteria to comparable extents, and a distinction for a given agent can only be made with the appropriate control experiments.[21,22] Taking the different cell-wall architecture of Gram-positive and Gram-negative bacteria into consideration, we reasoned that it would be useful to distribute antibacterial compounds in separate bins to allow the extraction of distinct property requirements that are driven by differences in cell wall composition.

We selected 147 antibacterially active compounds that encompass both currently used drugs and compounds that that are still under clinical investigation (see Methods for details). Where available, other property values were extracted from the literature, including protein binding and oral bioavailability in humans (incomplete data set). A shortened list from the commercially available CMC database served as drug reference set to compare and analyze various parameters (for a detailed description and data table, see Methods and Supporting Information). Two commercial software packages, ACD/Laboratories and Pipeline Pilot (SciTegic), were used to calculate the parameters discussed in this article. It is important to note that $pK_a$ values are difficult to calculate accurately and occasionally yield deviations in $clogD_{7.4}$ numbers from the corresponding experimental values. Nevertheless, the resulting trends seen in this analysis are consistent and can be reproduced using different software packages (data not shown).

**Table 1.** Comparison of Average (Mean) Compound Property Values of Three Drug Data Sets Representing General (CMC, Excluding Antibiotics) and Antibacterial Drugs

| parameter | CMC data set | antibacterials (only Gram-positive activity) | antibacterials (Gram-negative activity) |
|---|---|---|---|
| MW | 338 | 813 | 414 |
| clogp | 2.7 | 2.1 | −0.1 |
| $clogD_{7.4}$ | 1.6 | −0.2 | −2.8 |
| PSA (Å$^2$) | 70 | 243 | 165 |
| rel PSA (%) | 22 | 30 | 42 |
| H-donor | 1.6 | 7.1 | 5.1 |
| H-acceptor | 4.9 | 16.3 | 9.4 |

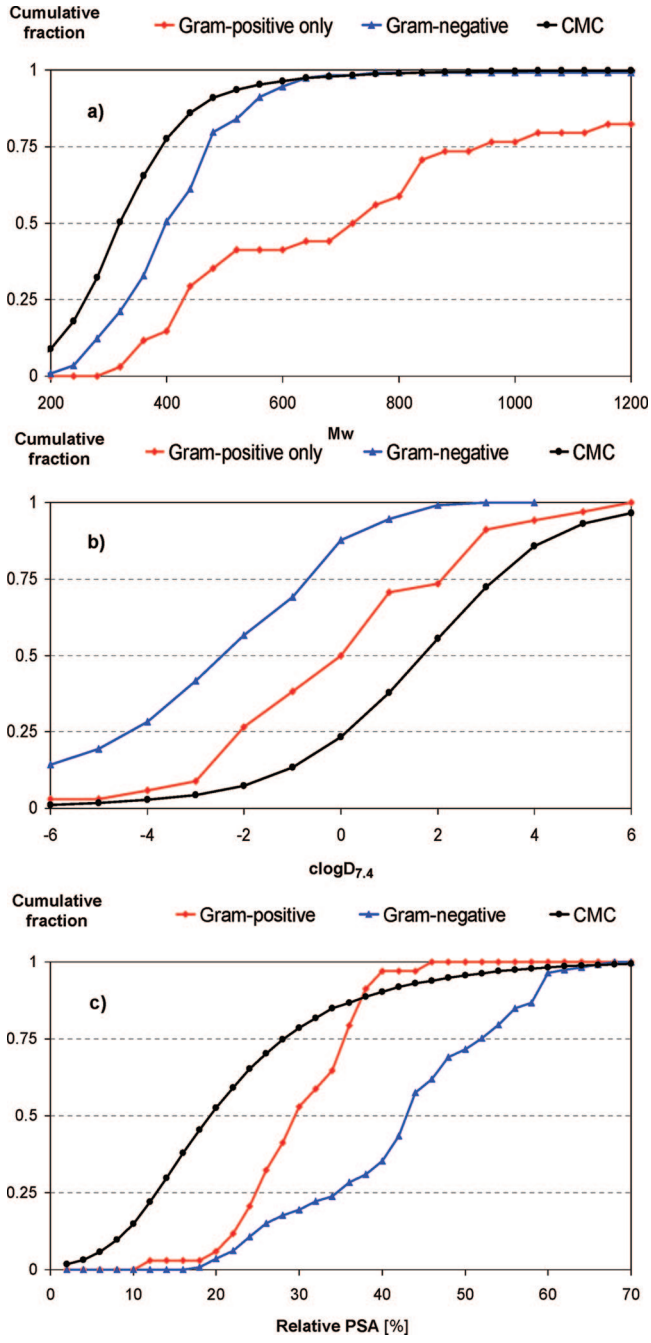
## Results

A simple comparison of important physicochemical parameters reveals substantial differences between compounds with Gram-positive only activity, compounds with Gram-negative activity, or drugs outside the antibacterial grouping, with the last defined by the subset of CMC compounds. Physicochemical values of the CMC benchmarking data set are quite similar to previously published data of drugs from other therapeutic areas (data not shown[12]) and therefore provide a good point of reference (Table 1) for the analyses performed in the present work. Average MWs are usually higher for antibacterials, especially the group with Gram-positive only activity. Major contributors for this dramatic increase are the cell-wall active glycopeptides, macrolides, streptogramins, and the lipopeptide daptomycin. Even though the average MW of Gram-negative antibacterials is slightly higher when compared to the CMC subset of compounds, there is a defined cutoff at 600 Da (Chart 1a), and roughly 95% of compounds are below this threshold value. Exceptions with substantially higher MWs are azithromycin (749 Da) and polymyxin B1 (1203 Da), both of which belong to classes of compounds with special permeability properties thought to enhance their ability to penetrate Gram-negative bacterial cells (vide infra).

As calculated in clogp values, the lipophilicity of the reference CMC compounds and the group showing Gram-positive activity is similar, but a substantial increase in polarity can be noted for the Gram-negative group (Table 1). This difference is even more striking when comparing $clogD_{7.4}$ values that account for the charged state of molecules at neutral pH (Chart 1b, Table 1). *The average value for Gram-negative antibacterials is more than 4 log units lower (more hydrophilic) compared to the CMC data set.* The increase in polarity is also reflected in the relative polar surface area (PSA), hydrogen bond donor, and hydrogen bond acceptor numbers, all of which increase substantially for Gram-negative antibacterials compared to the CMC data set (Chart 1c, Table 1).

In this context it is worth considering the role of natural products in the field of antibacterial drugs. Microorganisms have made use of antibacterial xenobiotics as a defense mechanism to survive in a competing environment and refined their "chemical warfare agents" over time. In particular streptomycetes and actinomycetes produce a variety of secondary metabolites with antibacterial properties, and either crude or

**Chart 1.** MW, clogD$_{7.4}$, and Relative PSA Represented as Cumulative Fractions of Compounds within Data Sets of General (CMC, Excluding Antibiotics) and Antibacterial Drugs




fractioned extracts along with purified compounds of these organisms have been used as a source to discover novel antibiotics.[23,24] The historical success of this approach has been referenced by Newman and Cragg[25] and is best exemplified with the composition of the antibacterial drug set discussed in this article; roughly 70% of compounds are either natural products or semisynthetic derivatives thereof, and only 3 of the 20 represented classes are synthetic in origin (sulfa drugs, fluoroquinolones, and oxazolidinones). We suggest the reasons for this superior role of natural products to be evolutionary selection pressure for antibiotic-producing organisms, a higher degree of diversity, and an average increase of heteroatoms (mainly oxygen) compared to synthetic libraries that result in a higher average polarity of compounds.[26]

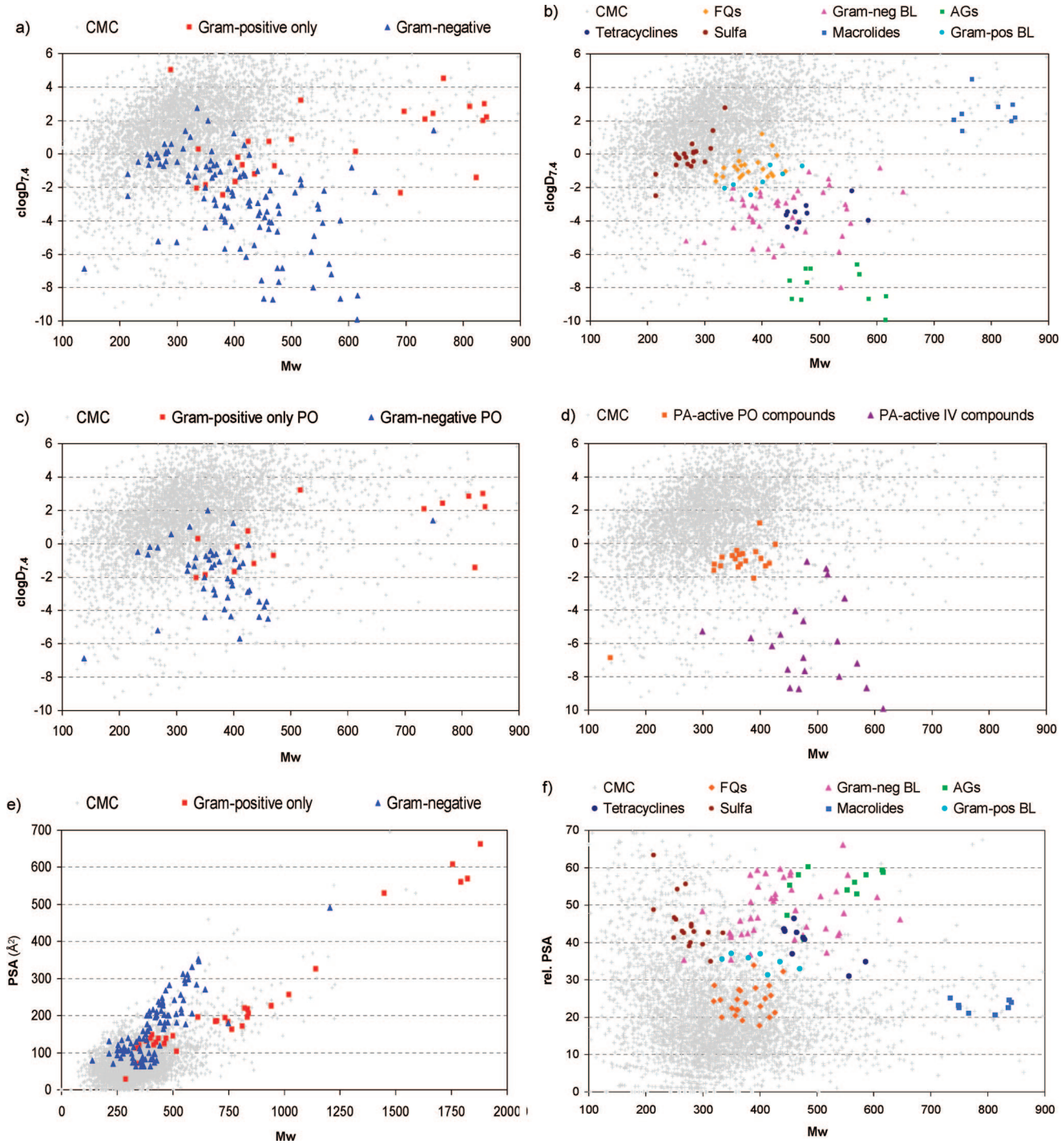
Plotting the lipophilicity descriptor clogD$_{7.4}$ versus MW delivers a more refined picture of the antibacterial property space. As previously reported, the reference set of drugs populates the upper left quadrant (Chart 2a) with a tendency toward higher lipophilicity as the MW increases. Most of antibacterial drugs are displaced toward higher MW and increased polarity, with a marked difference between Gram-positive (red) and Gram-negative (blue) antibacterials. The former antibacterials seem to have a lower limit for polarity (clogD$_{7.4}$ $>$ $-2.5$) but can possess MWs up to 2000 Da (for increased resolution, the graph has been cut off at 900 D; see Supporting Information for more detailed information). Exceptions with higher polarity are the membrane active molecules daptomycin and gramicidin, and the cell wall biosynthesis inhibitor vancomycin and its analogues. These agents can exercise their antibacterial activity either without requiring the penetration of a lipid membrane (e.g., vancomycin) or based on their ability to affect cellular permeability (e.g., gramicidin). The group of Gram-negative antibacterials is limited by size (MW $<$ 600) but can achieve a remarkable level of polarity best exemplified by aminoglycosides. Outliers in this group are the macrolide azithromycin with relatively weak Gram-negative activity and the membrane active agent polymyxin.

The plot of clogD$_{7.4}$ vs MW for major antibiotic classes reveals an interesting pattern and allows a deeper insight into property requirements for antibacterial compounds (Chart 2b). The only compounds that fall well within the general drug property space, as defined for example by Lipinski's rules, are the sulfa drugs. The most promising space is occupied by fluoroquinolones (orange). These broad spectrum agents are tightly grouped at the periphery of the general drug property space with values toward higher polarity and MW. This class probably best represents ideal physicochemical properties for both Gram-positive and Gram-negative antibacterial activity, including the notoriously refractory Gram-negative pathogen *P. aeruginosa* (see also Chart 2d). In addition, all the fluoroquinolones have a high level of oral bioavailability, good pharmacokinetic properties, and a relative low level of serum protein binding.

The $\beta$-lactams were grouped according to their Gram-positive only or Gram-negative activity. The former set (cyan) is positioned between the fluoroquinolones and the latter group (purple), defining a relatively narrow space for Gram-positive $\beta$-lactams and suggesting that an increase in polarity leads to a gain in Gram-negative activity. The space containing the $\beta$-lactams also surrounds the tightly clustered group of tetracyclines (dark-blue), which includes the two higher MW compounds tigecycline and **1** (Figure 1).[43] Aminoglycosides (green) form the most polar class of antibacterials, although their mechanisms of cellular entry are somewhat cryptic and may include not only penetration through porins but also other poorly understood transport mechanisms.[27] Finally, macrolides (blue) take up a unique property space, with lipophilicity values resembling those of general drugs but with a substantially higher MW. Subsets of the macrolide class possess a surprisingly high level of oral bioavailability that is proposed to be a consequence of both passive membrane diffusion and active transport.[28–30]

The subset of antibacterial compounds with human oral bioavailability ($F$ $>$ 0.20; compounds with oral bioavailability but no quantifiable and publicly accessible data were omitted) reveals additional restrictions (comparison of parts a and c of Charts 2). Gram-negative antibacterials seem to have an upper size limit for oral bioavailibility at 450 Da, with azithromycin being the exception. For polarity parameters such as clogD$_{7.4}$

**Chart 2.** Two-Dimensional Representation of Physicochemical Properties for General (Gray) and Antibacterial (Color) Drugs[a]




[a] Illustration of clogD$_{7.4}$ values plotted against MW: (a) Gram-positive only and Gram-negative antibacterials; (b) major classes of antibacterial compounds; (c) orally bioavailable compounds ($F > 0.20$; compounds that are likely orally bioavailable but for which no human data were found have been omitted, e.g., such as a number of sulfa drugs); (d) compounds with activity against *P. aeruginosa*, separated according to oral bioavailability; (e) illustration of PSA against MW for Gram-positive only and Gram-negative antibacterials; (f) plot of relative PSA against MW for major antibacterial classes.

there are threshold values beyond which highly polar compounds, such as aminoglycosides, are orally not bioavailable. Most compounds with a high level of oral bioavailability ($F >$ 0.85) are within a relatively narrow range of lipophilicity (clogD$_{7.4}$ between −1.4 and 1.2); $\beta$-lactams were excluded from this analysis as they distort the picture due to the involvement of active uptake by peptide transporters.[31] Macrolides and rifamycins take a special position for orally bioavailable Gram-positive only active antibacterials because they have MWs close to 1000 Da.

The set of Gram-negative antibacterials can be further refined by selecting compounds that display activity against *P. aeruginosa* (PA). This nonfermenting Gram-negative pathogen has historically been one of the most difficult to treat because of reduced permeability, highly efficient and diverse efflux pumps, and an increasing level of resistance against multiple antibiotic classes. With a paucity of novel agents under clinical investigation to treat this pathogen, there is a large unmet medical need that has been rapidly growing during the past few years. Understanding the required property space for an agent active

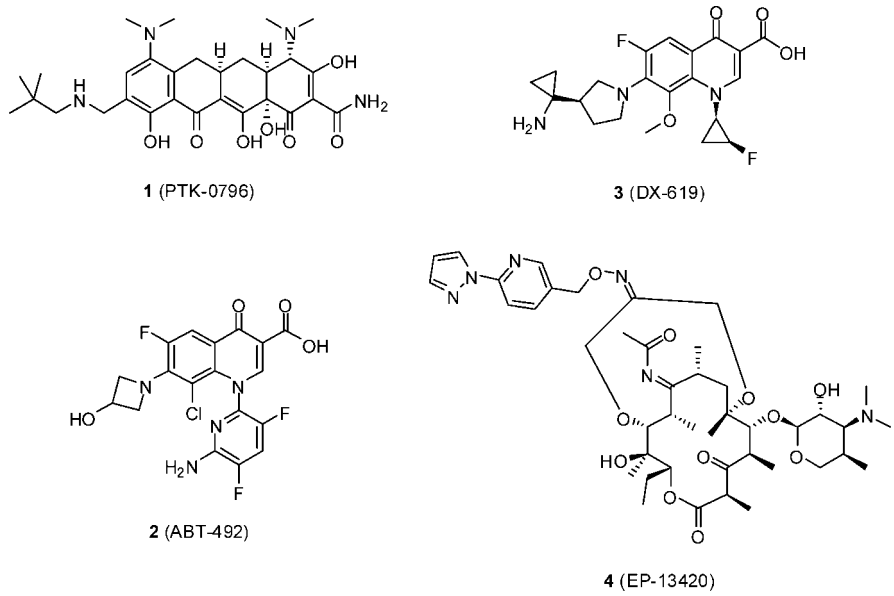



**Figure 1.** Structures of antibacterial compounds with code names.

**Table 2.** Average (Mean) Physicochemical Parameters for Antibacterial Classes

| class | *n* | MW (Da) | clogp | $clogD_{7.4}$ | PSA (Å$^2$) | rel PSA (%) | H-donor | H-acceptor |
|---|---|---|---|---|---|---|---|---|
| glycopeptides | 5 | 1740 | 1.3 | −1.8 | 586 | 37 | 22.8 | 37.2 |
| macrolides | 8 | 790 | 3.5 | 2.6 | 189 | 23 | 3.6 | 15 |
| penicillins | 14 | 413 | 1.4 | −2.4 | 149 | 39 | 2.8 | 8.5 |
| cephems | 28 | 452 | 0.1 | −3.0 | 210 | 51 | 4.1 | 10.8 |
| (carba)penems | 6 | 397 | −3.0 | −5.8 | 159 | 43 | 4.5 | 9 |
| sulfa drugs | 19 | 273 | 0.6 | −0.1 | 112 | 45 | 3.1 | 6.2 |
| fluoroquinolones | 24 | 371 | 1.3 | −0.8 | 82 | 25 | 2.1 | 6.5 |
| tetracyclines | 10 | 481 | −0.7 | −3.6 | 184 | 40 | 7.1 | 10.5 |
| aminoglycosides | 12 | 526 | −2.9 | −8.1 | 279 | 54 | 14.8 | 15.4 |

against *P. aeruginosa* is therefore of particular interest to us. As expected, this physicochemical property space is even more narrowly defined than the larger set of all Gram-negative antibacterials (Chart 2d). The MW cutoff is similar to that of the larger class of Gram-negative antibacterials (around 600 Da), but the lipophilicity requirement is shifted toward even higher polarity: for most compounds the $clogD_{7.4}$ values are well below 0, with difloxacin as most lipophilic compound at 1.2. Orally bioavailable compounds with *P. aeruginosa* activity are very narrowly distributed, and with the exception of the highly polar and low MW fosfomycin, they all belong to the fluoroquinolone class.

An interesting comparison can be made when differentiating between the broad spectrum fluoroquinolones (e.g., cipro- and levofloxacin) and the Gram-positive active oxazolidinones (e.g., linezolid). They differ only slightly in molecular weight, polar surface area, or clogp and consequently would be expected to behave similarly. However, most fluoroquinolones are zwitterionic in nature, a property that is captured by a substantially lower $clogD_{7.4}$ value (−1.35 and −1.41 for cipro- and levofloxacin, respectively, versus 0.29 for linezolid).

The polar surface area of compounds is another parameter that describes property requirements well and confirms differences between antibacterials and general drugs as outlined above (Chart 2e). The higher level of polarity is reflected in this plot, with most compounds containing more than 70 Å$^2$ of polar surface area. The exception is the FabI inhibitor triclosan that is known to possess additional biochemical activities and is speculated to be a membrane active agent.[32] Differences between antibacterials displaying activity solely on Gram-positive pathogens and those with activities encompassing Gram-negative bacteria are visible in this chart and illustrate the higher average amount of PSA per MW for the Gram-negative agents.

Finally, data can be analyzed as a function of relative polar surface area (PSA divided by total surface area) and MW (Chart 2f). This eliminates the obvious correlation between PSA and MW and separates the different compound classes. The difference between charged or uncharged functionalities is not captured by the relative PSA value, and this subtle difference is reflected in the space arrangement of compound classes. While sulfa drugs are distinctly separated from the bulk of CMC compounds (high relative polar surface area), the fluoroquinolones are positioned within the high probability zone of CMC compounds. This is in contrast to the ordering observed in the lipophilicity plot ($clogD_{7.4}$ vs MW, Chart 2b) where the charged state has an impact on this parameter and therefore separates compounds from the mainstream CMC data set.

Differences in the physicochemical property space are numerically represented by listing average (mean) values for each of the major compound classes (Table 2). The influence and importance of charges is best captured by comparing clogp and $clogD_{7.4}$ values; the higher the difference in these two parameters, the more the charges will contribute to an increase in polarity under neutral conditions. For example, this difference is only 0.7 for sulfa drugs but is 2.1 for fluoroquinolones,

indicating that for the latter compound class a charged species is the major component at pH 7.4.

## Discussion

Antibacterial drugs occupy a unique property space that is remarkably different compared to drugs of other therapeutic areas. This fact has been long recognized, and general rules such as Lipinski's rules of five do not apply to these compounds. The most likely reason for this observed divergence is the different cell architecture of bacteria that, in turn, greatly affects permeability and efflux of compounds. While different groups have addressed the property space of antibacterial drugs as a whole and established algorithms to predict activity, to the best of our knowledge a rigorous distinction between compounds with Gram-positive and Gram-negative activity has to date been lacking. We propose that this differentiation is necessary for a significant analysis because of large differences in the cell wall structure of these organisms.

Two major differences between antibacterial and "normal" drugs, as seen in our CMC reference set, are MW and lipophilicity. The latter is reflected in multiple parameters such as clog$D_{7.4}$, clogp, number of H-donors and -acceptors, and relative PSA. Drugs with activity only against Gram-positive bacteria have much less restriction in MW, especially if the target is located in the peptidoglycan matrix or on the outer surface of the underlying lipid bilayer (e.g., glycopeptides such as vancomycin) and permeation through the inner lipid membrane is not required to kill the pathogens. Compared to the set of reference compounds, polarity is slightly increased, as demonstrated with an average 36% higher relative PSA and decrease in clog$D_{7.4}$ by almost 2 log units. Compounds with oral bioavailability are in compliance with the general rules established by Lipinski[33] with the exception of macrocyclic compounds (macrolides, rifampin, and rifalazil) and fusidic acid that are believed to possess high cellular permeability and carrier-mediated transport mechanism that facilitate oral bioavailability despite large MWs.[28–30]

Compounds with activity against Gram-negative organisms must overcome further barriers to function, namely, the penetration of the outer lipid membrane and evasion of efflux pumps. These additional requirements appear to result in even more dissimilar physicochemical properties compared to the reference drug set, with a larger MW (but a quite strict MW cutoff at 600 Da[20]) and an increase in polarity, as reflected by the low average clog$D_{7.4}$ value of −2.8 and more than double the relative PSA. Both parameters are partially believed to be driven by the properties of porin proteins that serve as a major entry pathway in Gram-negative bacteria. These proteins form cylinder-shaped openings ($\beta$-barrels) in the outer membrane with polar amino acid side chains lining the inside of the opening. For a molecule to enter through these hydrophilic channels, the hydration sphere of the channel-lining amino acids has to be removed and replaced temporarily by the drug molecule. The required activation energy for lipophilic molecules to pass this channel is too high, and these molecules are consequently prevented from crossing the outer membrane and subsequently entering the relevant target-containing compartments of either the periplasmic space or the cytoplasm. Permeability works in coordination with efflux to generate the intrinsic drug resistance of Gram-negative bacteria, and this analysis reflects the overall difference between Gram-positive and Gram-negative bacteria that is influenced by both parameters.

The regions of physicochemical space required to achieve both Gram-negative activity (high polarity to ensure porin permeability) and oral bioavailability (reasonable level of lipophilicity to guarantee lipid membrane permeability) seem to be largely nonoverlapping. Fluoroquinolones, however, fulfill both these requirements. Key to meeting both requirements is the capability of molecules to exist in both charged (mostly zwitterionic) and noncharged form, the former to penetrate porins and the latter to be absorbed in the gut. The mostly zwitterionic fluoroquinolones are the best exemplars of these properties. Essential is the capability of charged and noncharged species to coexist at neutral pH, requiring the p$K_a$ values to be close to pH 7.4 (e.g., the experimental p$K_a$ values for ciprofloxacin are 6.15 and 8.66[34]), an observation that would seem to place strict limits on the types of functionality allowed.

In conclusion, the unique physicochemical property space required for antibacterially active compounds, and especially Gram-negative antibacterials, must be taken into account during high-throughput screening to identify hits with whole cell activity. In the context of previously low-yielding screening campaigns,[9] this uncovers at least one important parameter that was partially responsible for failure: the trend to high lipophilicity for molecules included in modern corporate compound collections. The combination of synthetic convenience and combinatorial chemistry resulted in a steady shift of compounds toward lower polarity,[11,35,36] farther away from the ideal property space for antibacterials.

A better understanding of the antibacterial property space is one of multiple parameters that are essential to improve the future success rate for the identification of novel antibacterial drugs, especially the badly needed compounds with activity against multi-drug-resistant Gram-negative pathogens that are becoming more prevalent in nosocomial and community based infections. This analysis also suggests that natural products should be increasingly investigated again to identify novel antibacterial hits. Besides their high level of structural diversity, they are likely to better cover the required physicochemical property space for antibacterial compounds compared to synthetic molecules because of an increased density of polar functionalities.[37,38] *In addition, we believe the understanding of required property space to be important for the further improvement of existing hits or leads and that this parameter should be taken in consideration during the designing process in order to achieve or improve whole cell activity and/or oral bioavailability.*

## Methods

**Set of Antibacterial Drugs.** A total of 147 compounds were used consisting of either approved human drugs or compounds that are still in clinical evaluation, using parent compounds for prodrug molecules. The compounds were distributed in three major bins of drugs active only against Gram-positive bacteria (Gram-positive only antibacterials, *S. aureus* $MIC_{50}$ value, and/or MIC against ATCC 29213), drugs active against Gram-negative organisms (Gram-negative antibacterials, *E. coli* $MIC_{50}$ value, and/or MIC against ATCC 25922), and a subset of drugs with activity against *P. aeruginosa* ($MIC_{50}$ values or MIC against ATCC 27853). Activity was defined as MIC of ≤8 $\mu$g/mL. Compounds with >100-fold difference between Gram-positive and -negative MIC values were declared inactive against Gram-negative bacteria, even if their MIC value is 8 or lower (e.g., rifampin), as it indicated a major impact by permeability and/or efflux. Exceptions were made for the well established sulfa drugs that have MIC values slightly higher than the chosen threshold level.

Most MIC data were compiled from either Lorian[39] or the Integrity database (Prous Science). Not all values could be extracted from the literature to complete some of the graphs, and compounds were omitted if data were inaccessible (e.g., oral bioavailability of

sulfa drugs or some candidates under clinical investigation). The following compounds were used as listed within individual classes.

**Aminoglycosides:** amikacin, arbekacin, dibekacin, gentamicin, isepamicin, kanamycin A, neomycin, netilmicin, paromomycin, sisomicin, streptomycin, tobramycin.

**Carbapenems:** doripenem, ertapenem, imipenem, meropenem, tomopenem.

**Cephems:** cefaclor, cefadroxil, cefamandole, cefazolin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmetazole, cefoperazone, cefotaxime, cefotetan, cefoxitin, cefpirome, cefpodoxime, cefprozil, ceftazidime, cefibuten, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cephalexin, cephalothin, cephradine, ceftaroline.

**Dihydrofolate reductase inhibitors:** iclaprim, trimethoprim.

**Quinolones:** **2**,[40] ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, **3**,[41] enoxacin, fleroxacin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, nadifloxacin, nalidixic acid, norfloxacin, pefloxacin, rufloxacin, sitafloxacin, sparfloxacin, temafloxacin, trovafloxacin.

**Glycopeptides:** dalbavancin, oritavancin, teicoplanin, telavancin, vancomycin.

**Lincosamides:** clindamycin, lincomycin.

**Macrolides:** azithromycin, cethromycin, clarithromycin, dirithromycin, **4**,[42] erythromycin, roxithromycin, telithromycin.

**Oxazolidinones:** linezolid, ranbezolid.

**Penems:** faropenem.

**Penicillins:** amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, methicillin, mezlocillin, nafcillin, oxacillin, penicillin G, penicillin V, piperacillin, ticarcillin.

**Rifamycins:** rifalazil, rifampin.

**Streptogramins:** dalfopristin, quinupristin.

**Sulfa drugs:** sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfadiazine, sulfadimethoxine, sulfaguanidine, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethoxazole, sulfamethoxypyridazine, sulfamonomethoxine, sulfanitran, sulfaphenazole, sulfapyridine, sulfaquinoxaline, sulfathiazole, sulfisoxazole.

**Membrane active agents:** gramicidin, polymyxin B1, triclosan (also a FabI inhibitor).

**Tetracyclines:** chlortetracycline, demeclocycline, doxycycline, meclocycline, methacycline, minocycline, oxytetracycline, **1**,[43] tetracycline, tigecycline.

**Miscanelous agents:** chloramphenicol, loracarbef, chlorobiocin, novobiocin, pseudomonic acid A, daptomycin, aztreonam, fosfomycin, fusidic acid.

**CMC Data Set.** The commercially available CMC database (containing oral and parenteral drugs) was reduced to a set of 4623 druglike compounds as outlined below. Only compounds were used that contain an INN and/or a USAN number. Compounds were removed that contained one or more of the following words in the class field: antibacterial, antibiotic, antimicrobial, antiinfective, antifungal, antituberculosis, antimalarial, antihelmintic, antiamebic, antiprotozoal, antitrypanosomal, parasiticide, insecticide, or radiopaque. Chemical groups that were judged to be not stable enough under physiological conditions were searched by the following substructures, and corresponding compounds were eliminated: $-CH_2COOCH_2-$, $-COCH_2Cl$, $-CHO$, oxirane with one unsubstituted ring carbon, and tetrapeptides. In addition, the following classes of compounds were eliminated as well: diagnostics, antidotes, pigments, blood substitutes, coagulants, pharmaceutic aids, UV light adsorbers, surgical aids, vitamins, nutrients, dental products, chelating agents, radioactive agents, antiacids, dermatological agents, detergents, sweeteners, and detoxicants. All salts were removed, and the final compound set was freed from duplicates (some drugs are sold as free and salt form and therefore have multiple listings). For drugs with both a racemic and enantiomerically pure form only one was included in the final data set (e.g., dexi- and mepivacaine).

Both the antibacterial and CMC sets of compounds were compiled and manipulated using Scitegic's Pipeline Pilot software and then subject to analysis by both the ACD Laboratories LogD software suite (version 10.0) and Pipeline Pilot (version 5.0) in order to obtain the calculated physicochemical properties described therein. All cLogD values and solubilities were calculated at pH 7.4 using the ACD Laboratories software suite.

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## Biographies

**Rosemarie O'Shea** received her B.Sc. (Hons) from Manchester University in 1994. She then worked at Cold Spring Harbor Laboratory, New York, using combinatorial chemistry to identify inhibitors of farnesyl transferase. She joined Advanced Medicine (now Theravance) in 1998 working in multiple therapeutic areas but predominantly in antibiotics and then later joined Gilead Sciences (2001) working on novel antivirals of HIV and HCV. Since 2005, she has been in charge of informatics at Achaogen.

**Heinz E. Moser** received his Ph.D. degree in Natural Sciences from the Federal Institute of Technology (ETH) in Zürich (1985). After postdoctoral studies at California Institute of Technology, he worked in various functions and therapeutic areas at Ciba-Geigy and later at Novartis in Basel, Switzerland, and Horsham, U.K. (1987–1999). He joined Genesoft, later Oscient (1999–2004), as CTO and VP of Chemistry, working initially on DNA-binding molecules as antibacterials and antiproliferative agents and later on antibiotics in general. Since 2005, he is in his current position as SVP of Chemistry at Achaogen, a company focused on the drug discovery and development of antibacterial agents with primary focus on highly resistant pathogens.

**Supporting Information Available:** Data sets as Excel worksheet and, for the antibacterial drugs (where available), data on oral bioavailability, protein binding, selected MIC values, and additional calculated parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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