ELSEVIER

The impact of aromatic ring count on compound developability – are too many aromatic rings a liability in drug design?

Timothy J. Ritchie and Simon J.F. Macdonald

Respiratory CEDD, GlaxoSmithKline Research Medicines Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK

The impact of aromatic ring count (the number of aromatic and heteroaromatic rings) in molecules has been analyzed against various developability parameters – aqueous solubility, lipophilicity, serum albumin binding, CyP450 inhibition and hERG inhibition. On the basis of this analysis, it was concluded that the fewer aromatic rings contained in an oral drug candidate, the more developable that candidate is probably to be; in addition, more than three aromatic rings in a molecule correlates with poorer compound developability and, thus, an increased risk of attrition in development. Data are also presented that demonstrate that even within a defined lipophilicity range, increased aromatic ring count leads to decreased aqueous solubility.

Introduction

Catalyzed by Lipinski's seminal 'rule of five' for absorption and permeability [1], there is now a substantial body of literature describing property space occupied by orally bioavailable small-molecule drugs [2,3]. This literature usually focuses on drug physicochemical properties – such as lipophilicity, H-bonding parameters (such as numbers of hydrogen bond donors and acceptors amongst others), polar surface area and molecular weight – and has lead to useful insights. One reason (amongst many) why Lipinski's rule is so widely used is that it is easily remembered; the medicinal chemist can consciously consider the rules during the design process, in contrast to design principles that require sophisticated *in silico* applications and/or esoteric molecular descriptors.

This analysis focuses on a somewhat more simplistic property: namely, the number of aromatic rings contained in the molecule. The terminology 'number of aromatic rings' (or aromatic ring count) is used generically and encompasses both benzenoid aromatic rings and heteroaromatics (including, e.g. pyridine and imidazole) – in essence, the Daylight definition of aromaticity (http://www.daylight.com/dayhtml/doc/theory/theory.mol.html). Each ring in a fused system is counted individually; thus, indole and naphthalene are each defined as having two aromatic rings.

We were initially prompted to investigate the impact of aromatic ring count *per se* on compound developability and drug-likeness after some preliminary analyses suggested that this descriptor was exerting a statistically significant (detrimental) influence in some *in vitro* developability screens and seemed in some cases to be more predictive than other properties, such as total ring count. Perhaps, intuitively, one might expect to see such trends, but we wanted to

Corresponding author: Macdonald, Simon J.F. (simon.jf.macdonald@gsk.com)

TIM RITCHIE

Tim Ritchie has over 20 years experience as a medicinal chemist in the pharmaceutical industry. After his PhD and post-doctoral studies, he worked for several years on neuroscience-related drug discovery programmes and early development projects at the Novartis (formerly Sandoz) Institute for Medical Sciences in London. In 2005, Tim moved to the Respiratory CEDD at GlaxoSmithKline in Stevenage. His role as a medicinal chemistry design expert was to increase the awareness and use of computational chemistry approaches within the medicinal chemistry community, and facilitate interactions between the medicinal and computational chemistry functions.
Tim has a keen interest in how calculated physicochemical properties of potential drug molecules can be used to predict their behaviour in screening assays and developability screens.

Simon has over 20 years experience as a medicinal chemist in the pharmaceutical industry and has spent his entire career at GlaxoSmithKline in its various incarnations. He is currently a director of medicinal chemistry in the Respiratory Centre of Excellence for Drug Discovery in Stevenage in the United Kingdom.

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2009.07.014

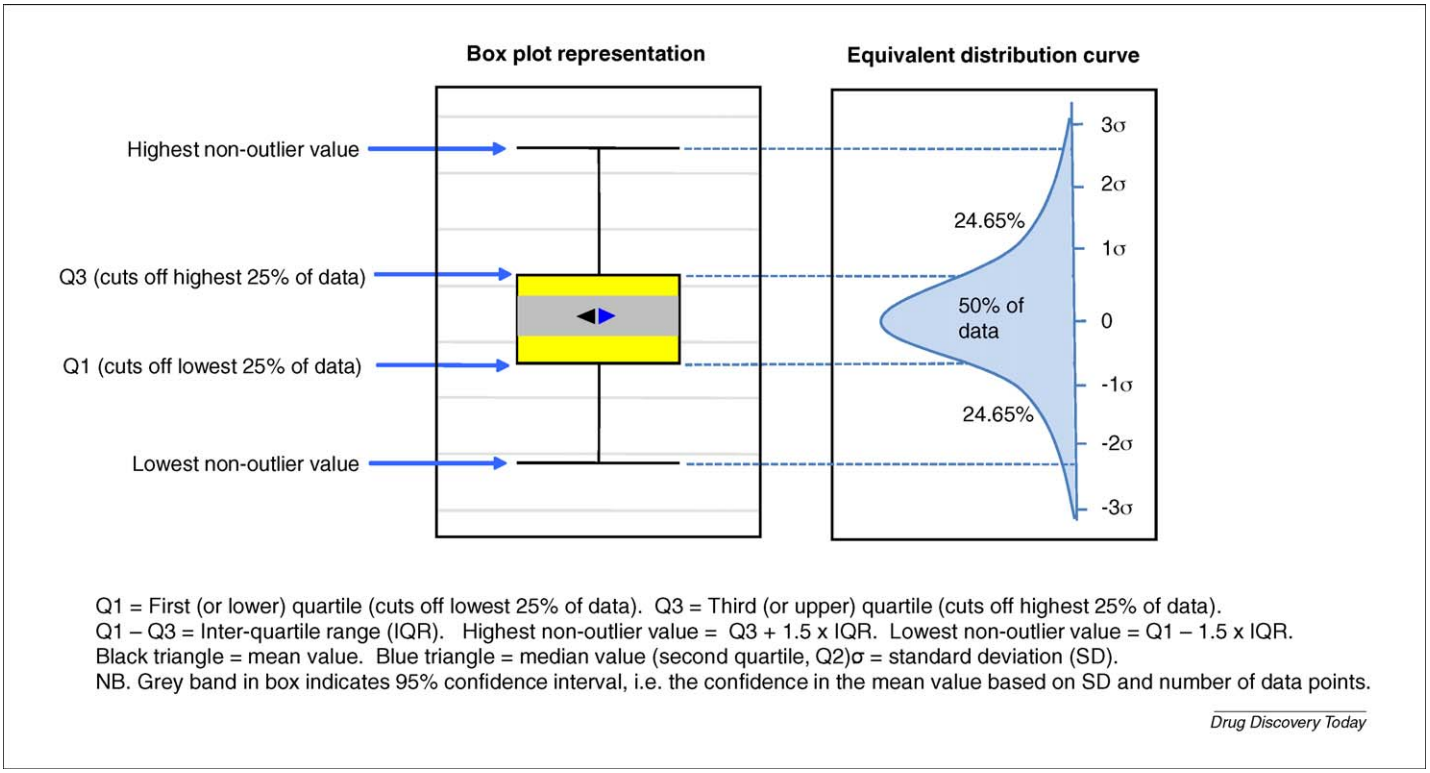


FIGURE 1

Box plots explained. Note that the grey bar in the box plot represents the 95% confidence interval in the mean value based on the standard deviation and number of data points. Generally speaking, grey bars that are not overlapping in adjacent box plots signify a statistically statistically significant difference between their mean values.

confirm and quantify this perception with concrete data. In addition, we are unaware of any similar analysis described in the literature.

Further attractions of carrying out a more in-depth analysis were: (i) that the addition or removal of an aromatic ring system (i.e. at least five or six atoms) should lead to a more perceptible change in the overall drug-likeness of a molecule than adding or removing a smaller functional group; (ii) the simplicity of any potential readouts – for example, 'the fewer the number of aromatic rings contained in a molecule, the more developable the compound is likely to be' or 'more than three aromatic rings correlates with poorer compound developability'; and (iii) the ease with which the property can be calculated and perceived. Other properties, such as lipophilicity or molecular weight (often crucial considerations in medicinal chemistry design), require a few moments of either computational time or mental arithmetic. By contrast, the number of aromatic rings in a molecule can be determined almost instantaneously with a glance at the structure. This, therefore, could act as a very simple mnemonic for the medicinal chemist during the compound or library design process. It could act as a constant reminder of the consequences of introducing further aromatic rings into potential drug molecules, namely their proclivity to reduce intrinsic developability.

From an evaluation of large numbers of compounds in the GlaxoSmithKline corporate collection that had undergone routine developability screening, this study does indeed show that increasing aromatic ring count has a detrimental impact on developability properties of drug molecules. Taken together, the data provide a consistent message, which is compelling.

TABLE 1

Mean aromatic ring count in compounds in the GSK pipeline

	CS	FTIH	P1	P2	POC
Count[a]	50	68	35	53	96
Mean aromatic ring count	3.3	2.9	2.5	2.7	2.3

Abbreviations: CS, preclinical candidate selection; FTIH, first time in human; P1, phase 1; P2, phase 2; POC, proof-of-concept.

[a] Count is the number of compounds in the category.

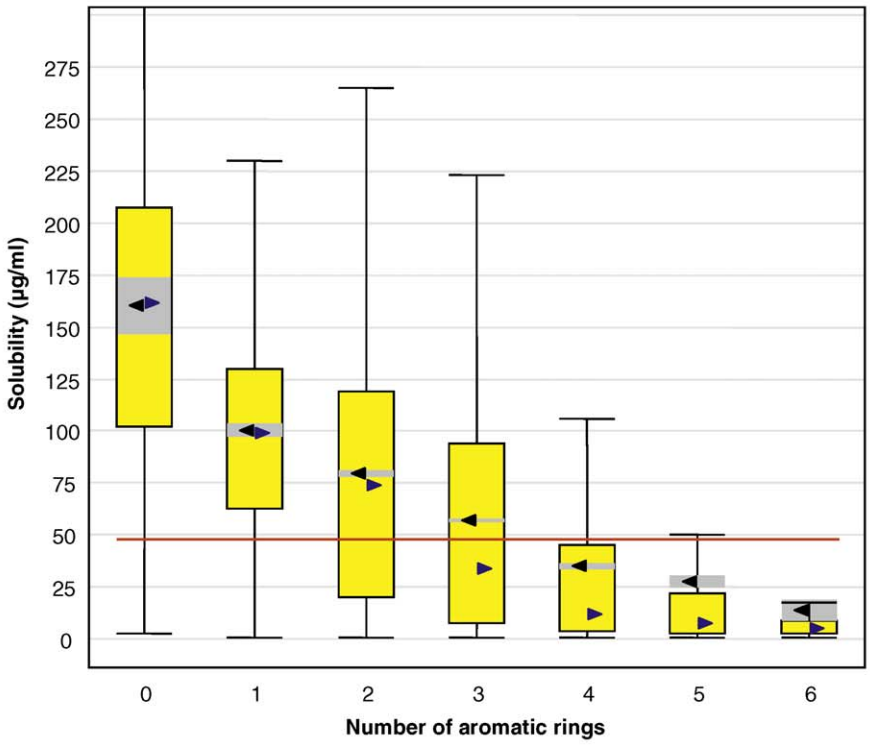
The data presented are shown in box plots [4], which are explained in Fig. 1.

Aromatic ring count and GSK pipeline attrition

The number of aromatic rings contained in 280 compounds in the GSK pipeline over a defined time period was analyzed. This snapshot covered compounds that had passed different development milestones, namely preclinical candidate selection, first time in human studies, clinical phase 1 and 2, and, finally, proof-of-concept trials (Table 1).

The average number of aromatic rings in preclinical candidate molecules is 3.3, in contrast to the average number of aromatic rings in those compounds that were still in the pipeline at POC, which is 2.3. In other words, there is a decrease in the average number of aromatic rings as compounds get closer to the market [5].[a] By this measure alone, the lower the number of aromatic rings

[a] Do other companies' pipelines look similar to ours? To the best of our knowledge, it is not known whether pipelines from other companies display the same trend, although Pfizer candidates are described as having an upward trend in lipophilicity over time.



Aromatic ring count	0	1	2	3	4	5	6
Mean solubility	161	100	79	57	36	28	14
Median solubility	161	99	74	34	12	8	5
Q1	102	63	20	8	4	3	3
Q3	207	130	119	94	45	22	9
Number of compounds	184	1,379	8,711	13,204	6,127	1,725	195

Drug Discovery Today

FIGURE 2

Box plot and table of CLND solubility and aromatic ring count. The orange line in the graph indicates the 50 µg/mL solubility level.

contained in the compound, the further the compound is likely to progress in development, suggesting that higher aromatic ring count might correlate with poorer developability. In this context, it is interesting to note that the average number of aromatic rings in oral drugs is 1.6 [6], although it is not known whether this number is increasing over time.[b] It has also been shown that the average molecular weight and lipophilicity of orally administered drugs decrease as they pass through developmental phases [7].

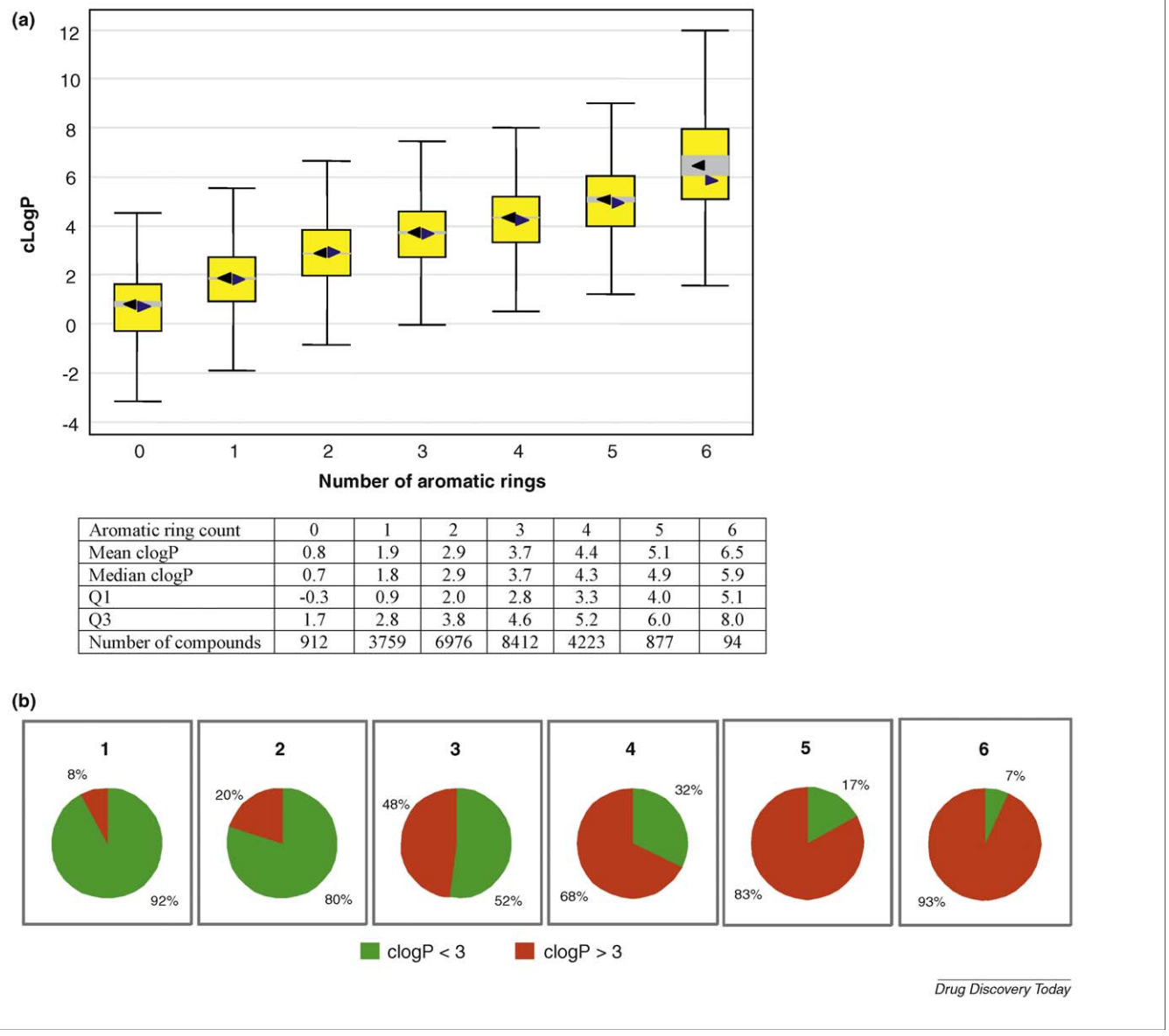
In an attempt to tease out the origins of these observations, in this study, the impact of higher ring count was investigated in relation to aqueous solubility, lipophilicity parameters, serum albumin binding, CyP450 inhibition and hERG inhibition.

Aromatic ring count and CLND solubility

Aqueous solubilities were determined by equilibrating a 5% dimethylsulfoxide (DMSO) solution (from a 10 mM stock solution) for one hour, filtering and then assaying the filtrate using chemiluminescent nitrogen detection (CLND). This is a rapid method of assessing approximate solubility but is likely to overestimate a compound's true solubility, particularly if that compound is highly crystalline and/or has a high melting point; it also takes no account of the compound's thermodynamic solubility or dissolution rate. CLND data from GSK databases for just more than 31,000 compounds were compared with aromatic ring count (Fig. 2). Mean CLND solubility dramatically decreases as ring count increases.[c] With four aromatic rings, the third quartile value is

[b] The mean number of rings (aromatic and non-aromatic) had increased by 13% when comparing launched drugs pre-1983 and 1983–2002. See Ref. [23].

[c] Even if acids or bases are removed from this analysis, the overall trends remain similar. We thank our colleague Rob Young for this observation.



Aromatic ring count	0	1	2	3	4	5	6
Mean clogP	0.8	1.9	2.9	3.7	4.4	5.1	6.5
Median clogP	0.7	1.8	2.9	3.7	4.3	4.9	5.9
Q1	-0.3	0.9	2.0	2.8	3.3	4.0	5.1
Q3	1.7	2.8	3.8	4.6	5.2	6.0	8.0
Number of compounds	912	3759	6976	8412	4223	877	94

FIGURE 3

Box plot, table and pie charts of aromatic ring count and *c* log *P* (Daylight). Pie charts show the ratio of lipophilicity for compounds with differing numbers of aromatic rings (one to six, left to right). Green segments represent the percentage of compound with *c* log $P < 3$, and red segments represent the percentage of compounds with *c* log $P > 3$. Abbreviations: Q1, quartile 1; Q3, quartile 3.

below 50 μg/mL, with a median value of only 12 μg/mL. When the distributions around the mean are examined, it is apparent that once a compound has at least two aromatic rings, there are many compounds with very low solubility (<5 μg/mL) (data not shown).

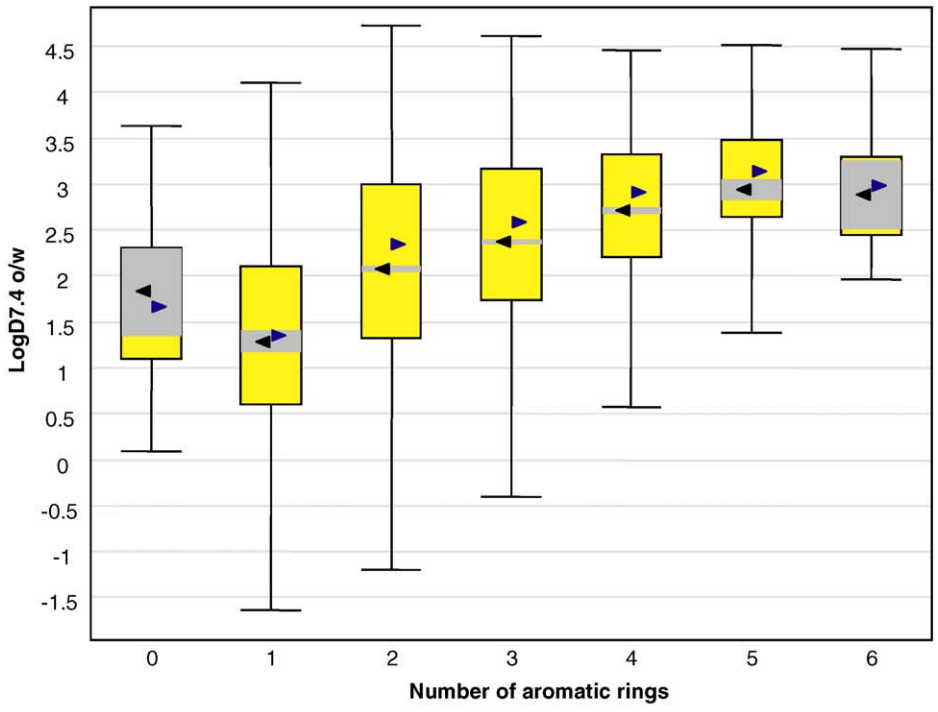
Aromatic ring count and *c* log *P*

A comparison was made between the number of aromatic rings contained in ~26,000 compounds registered into the GSK corporate collection in Stevenage (UK) during the early part of 2007 and their calculated Daylight lipophilicity (*c* log *P* v4.81) (Fig. 3). As can be seen, there is an excellent correlation between lipophilicity and aromatic ring count, indicating that the addition of an aromatic ring usually results in a discrete and statistically significant jump in *c* log *P*. As stated above, to keep the analysis simple, no differentiation was made between the atomic nature of each aromatic ring, and it should be noted, therefore, that carbon-only systems (e.g. phenyl substituents and benzo-fused groups), together with non-polar heterocycles, will have a greater impact on increasing *c* log *P* than more polar heterocyclic rings. Thus, the increases in *c* log *P* seen in Fig. 3 are averaged values, composed of many variations and permutations possible under the umbrella term 'aromatic ring'.

Another consequence of this correlation with lipophilicity is that as the aromatic ring count (and, hence, overall lipophilicity) increases, the percentage of compounds with lipophilicity commensurate with good oral bioavailability (shown for *c* log $P < 3$ in pie charts, Fig. 3) decreases.

Aromatic ring count and log *D*

A comparison was made between aromatic ring count and octanol-water log *D* (log $D_{o/w}$) values measured at pH 7.4 (10,464

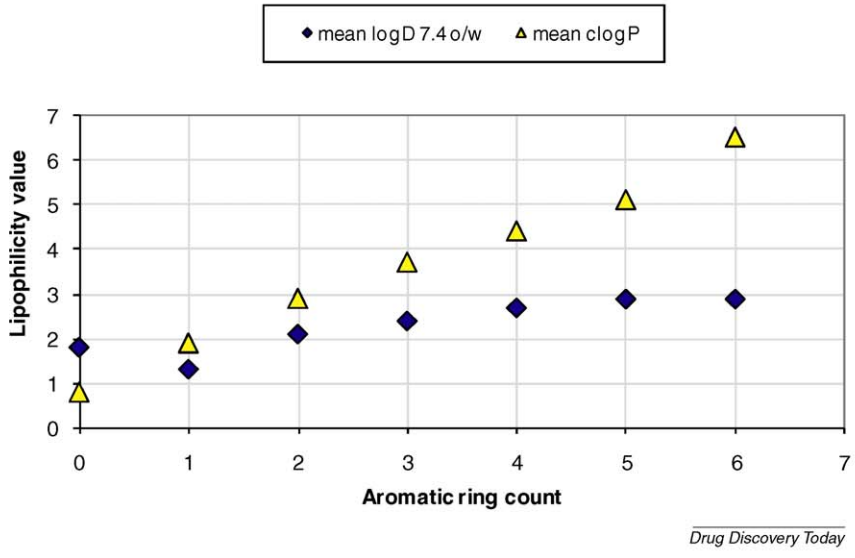


Aromatic ring count	0	1	2	3	4	5	6
Mean logD 7.4 $_{o/w}$	1.8	1.3	2.1	2.4	2.7	2.9	2.9
Number of compounds	17	329	2971	5184	1652	282	29

Drug Discovery Today

FIGURE 4

Box plot and table of aromatic ring count versus log *D* values. log *D* octanol-water are the values at pH 7.4.



Drug Discovery Today

FIGURE 5

Graph of lipophilicity measures against aromatic ring count.

compounds) using the traditional shake-flask method. (In contrast to log *P*, which is the partition coefficient of a compound between octanol and water, log *D* is the distribution coefficient and is frequently used to describe the lipophilicity of ionizable compounds.) From these data (Fig. 4), the $\log D_{o/w}$ values increase significantly as the number of aromatic rings increases, as seen with the *c* log *P* values. The exception seems to be those compounds that possess no aromatic rings, which are more lipophilic than compounds with one ring. However, this difference is not statistically significant, and the number of compounds with no rings is small ($n = 17$).

Although direct comparison between these measured log *D* data and the calculated log *P* data shown above is not possible because the compound sets are different, there is a difference in that the log *D* values tend to plateau out at approximately 3 at higher aromatic ring counts, in contrast to the *c* log *P* data (data plotted together in Fig. 5). This phenomenon is attributed to the limitations of the $\log D_{o/w}$ measurement, whereby it becomes difficult to measure highly lipophilic compounds accurately because of low solubility and, thus, low concentrations of compound in the aqueous phase. The presence of ionizable groups in compounds will also skew the data.

Although the increased lipophilicity that results from increased aromatic ring count can be offset by the inclusion of heteroatom functionality (often in the ring itself), this will increase the polar surface area and might result in exceeding the recognized limits for permeability/absorption [8,9]. For example, from the set of compounds in this study that contain two aromatic rings, 52% have *c* log $P < 3$ and the mean polar surface area is 77 Å^2. For those compounds containing four aromatic rings, only 17% have *c* log $P < 3$ and the mean polar surface area has increased to 95 Å^2. For those with six aromatic rings, 3% have *c* log $P < 3$ with a mean polar surface area of 115 Å^2.

The liabilities associated with increased lipophilicity are now widely known; Lipinski's original rule of five paper, published in 1997, had been cited more than 2000 times as of February 2009. More recent literature correlates increased molecular lipophilicity with the risk of adverse toxicological events [2,10]. Although the drugability of current targets is often lower than that of historical targets, and there are examples of highly lipophilic drugs on the market, this analysis suggests (and others suggest [2]) that adding more lipophilicity by adding more aromatic rings to a lead structure (particularly when there are already three aromatic rings in the molecule) is likely to increase the risk of attrition in development.

Lipophilicity and solubility

Because solubility is inversely proportional to lipophilicity [11], we examined the data further to determine whether aromatic ring count was exerting an effect on solubility, which was independent of hydrophobicity. Thus, the solubility data were plotted in relation to the number of aromatic rings in *c* log *P* 'bins' (Fig. 6). Within a narrow lipophilicity range (*c* log *P* bin), increasing the aromatic ring count leads to a decrease in CLND solubility. For example, in the *c* log *P* 2–3 bin, approximately

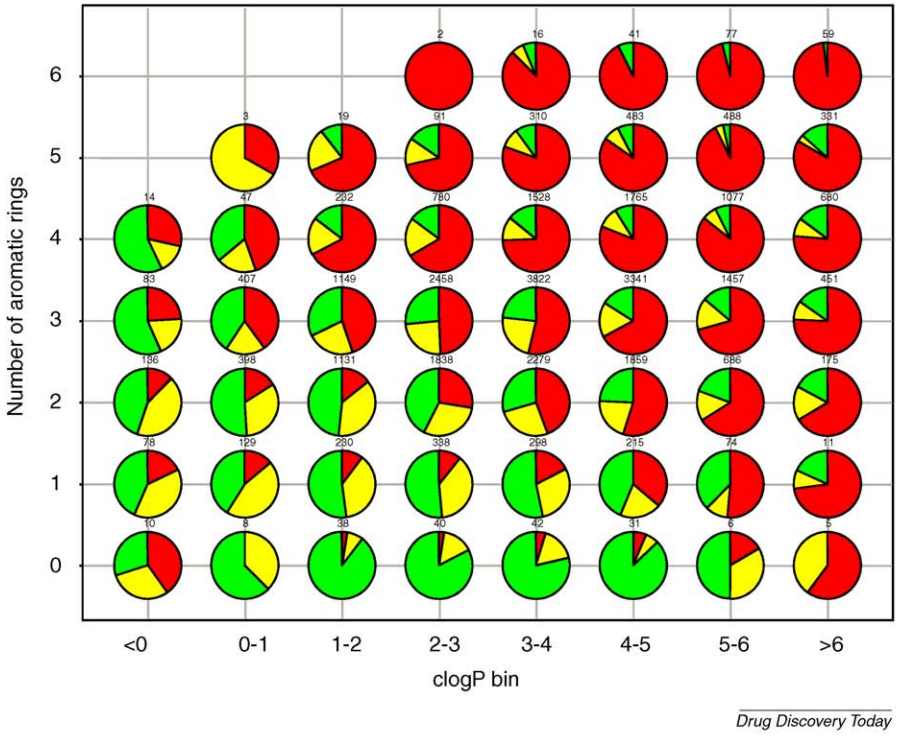
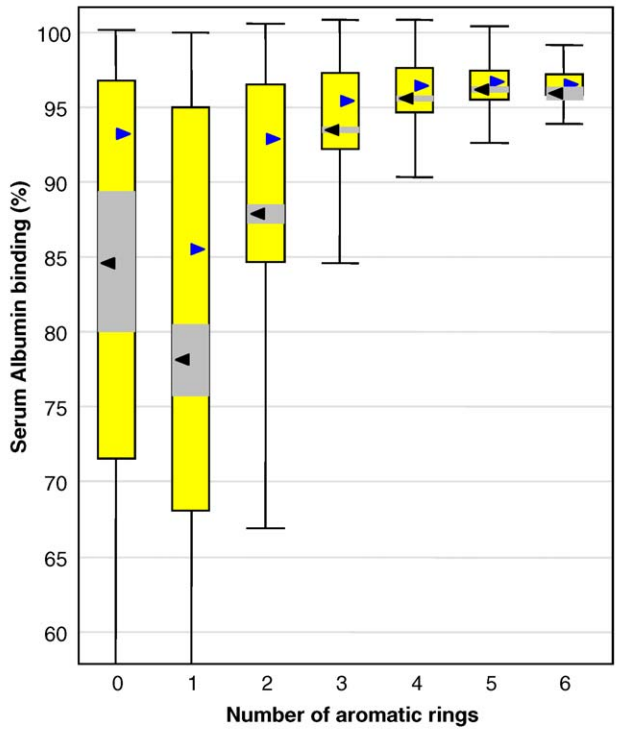


FIGURE 6

Chart of the number of aromatic rings in *c* log *P* bins. Pie charts are divided into three solubility segments: <50 μg/mL in red, 50–100 μg/mL in yellow and >100 μg in green. The numbers above the pie charts are the number of compounds in that pie chart.



Aromatic ring count	0	1	2	3	4	5	6
% mean albumin binding	85	78	88	93	96	96	96
Number of compounds	52	311	1,832	3,197	1,726	559	201

Drug Discovery Today

FIGURE 7

Box plot and table of serum albumin binding and aromatic ring count.

80% of compounds containing no aromatic rings have CLND solubility >100 μg/mL. In the same log *P* 2–3 bin, approximately 55% of compounds containing one aromatic ring have solubility >100 μg/mL, as do approximately 40% of compounds containing two aromatic rings and approximately 25% of compounds containing three aromatic rings. Thus, aromatic ring count seems to be affecting aqueous solubility, even when the *c* log *P* value is relatively constant.

This is striking and found consistently within this dataset of solubility for more than 31,000 compounds. It is supported by an elegant model described by Maccari and coworkers [12] for discarding insoluble compounds, which is based only on molecular weight and aromatic proportion (the ratio of aromatic atoms to the total number of heavy atoms in the molecule). These solubility differences are probably because of a combination of factors: increased molecular rigidity, melting point phenomena and the capacity for π–π stacking with increased aromaticity *inter alia*. Given the importance of aqueous solubility on permeability and oral absorption [1,5], however, if a compound in lead optimization is known to have poor solubility (or poor absorption), reducing the number of aromatic rings in the compound is likely to be beneficial.

Aromatic ring count and serum albumin binding

Aromatic ring count and serum albumin binding (as determined by high-performance liquid chromatography, or HPLC [13]) was analyzed for 7856 GSK compounds (Fig. 7). There is a statistically significant increase in albumin binding as the number of aromatic rings increases in the compound from one ring to four rings, with ~75% of compounds with four aromatic rings having binding values of >95%. In this assay, binding values level out at approximately 96%. As seen with the solubility analysis above, the affinity for albumin increases as aromatic ring count increases, even when the *c* log *P* data are binned and examined in discrete ranges (data not shown). This might be expected, given that there are domains in human serum albumin that have a high affinity for lipophilic and particularly anionic aromatic compounds [14].

In-house experience (data not shown) also unfortunately suggests that the percentage binding as judged by this HPLC assay is usually an underestimate of the value obtained when plasma protein binding is experimentally determined. The origin of the plateauing phenomenon of the percentage of compound bound when the compound contains four or more aromatic rings is unclear, but compound solubility might be a factor.

Plasma protein binding of drug substances is now recognized [15] in many instances to effectively reduce drug potency *in vivo*. In other words, in the absence of data to the contrary, the non-bound (free) fraction of drug in plasma represents the drug available to interact with the biological target [15]. Clearly, therefore, reducing plasma protein binding by reducing the aromatic ring count in the compound is likely to lead to a greater free fraction of circulating drug, which might enable reduction of the therapeutic dose that is administered, provided that the compound is stable to normal phase I and phase II metabolic processes.

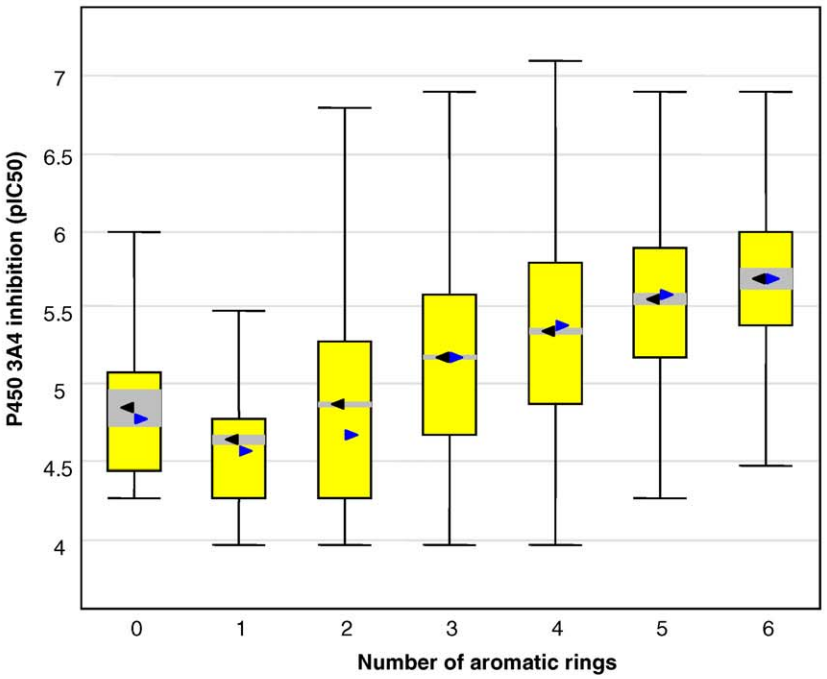
Aromatic ring count and P450 3A4 inhibition

Aromatic ring count and inhibitory activity for cytochrome P450 3A4 was analyzed for 15,178 compounds from the GSK collection (Fig. 8). There is a statistically significant trend for increased inhibition of 3A4 as aromatic ring count increases [16]. This behaviour is also seen with other P450 isoenzymes (data not shown).

Inhibition of P450 function and particularly irreversible inhibition is associated with a higher risk of compound toxicity [17] and can lead to deleterious drug–drug interactions, which can lead to restrictions in the use of the compound clinically [18]. As a consequence, oral lead optimization programmes usually reject compounds with inhibitory activity less than 1–10 μM against P450 isoforms. The data in the plot (Fig. 8) show that compounds containing four or more aromatic rings have mean inhibitory values for 3A4 in the low micromolar range; therefore, constraining the aromatic ring count might be advantageous.

Aromatic ring count and hERG inhibition

Aromatic ring count and hERG activity were analyzed for 11,105 compounds (Fig. 9). There is a trend for increased activity with increased ring count up to four aromatic rings, after which the hERG values decrease. This bell-shaped behaviour might be because of the underestimation [19] of hERG inhibition for compounds with aqueous solubility <5 μg/mL – such as those with higher aromatic ring count – or the inability of larger compounds to bind effectively to the hERG channel for steric reasons.



Aromatic ring count	0	1	2	3	4	5	6
Mean pIC_{50} P450 3A4	4.9	4.7	4.9	5.2	5.4	5.6	5.7
Number of compounds	68	842	3,950	5,825	3,282	923	275

Drug Discovery Today

FIGURE 8

Box plot and table of the negative log IC_{50} of inhibition of P450 3A4 and aromatic ring count.

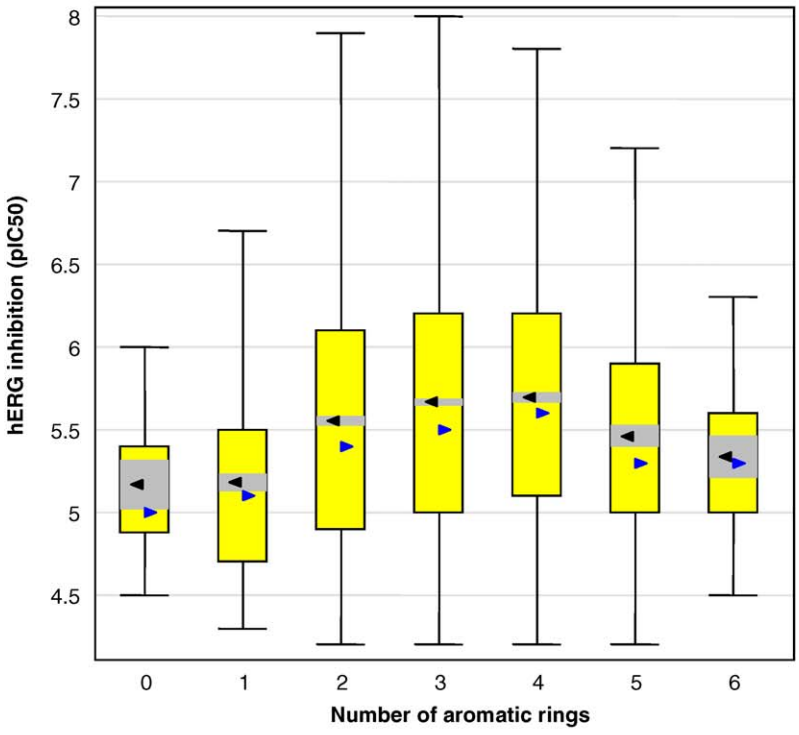
Marketed drugs have recently been withdrawn owing to hERG inhibition [19], and as a consequence, establishing the hERG profile of a compound series in lead identification or optimization has now become important (for an excellent example where hERG liabilities were addressed in a medicinal chemistry programme, see Ref. [20]). The π stacking and hydrophobic interactions of aromatic residues in the hERG channel with aromatic rings in drug molecules are some of the structural factors that can lead to inhibition of hERG activity [19]. There is an increase in the mean observed hERG activity to just less than micromolar as aromatic ring count increases up to three rings (Fig. 9). Compounds containing four or more rings have similar or lower activity than compounds with three rings, albeit with the caveat regarding low solubility mentioned above. This analysis suggests that limiting aromatic ring count might be beneficial in limiting hERG inhibition.

Discussion

The purpose of this study was to investigate the impact of the number of aromatic rings contained in a molecule on its developability properties and, if possible, to determine a limit above which the number of rings would significantly impact developability. The properties investigated were aqueous solubility, calculated and measured lipophilicity (*c* log *P*, log *D*7.4), serum albumin binding, cytochrome P450 3A4 isoform inhibition and hERG inhibition. As has been shown above, these data do indicate that an increased number of aromatic rings have a detrimental impact on compound developability.

However, aromatic and heteroaromatic rings are ubiquitous features in small-molecule drugs. Why are aromatic and heteroaromatic rings so prevalent in drug molecules? There are numerous possible reasons; we discuss two here. First, as a structural feature, aromatic rings always possess fewer degrees of freedom than chains. This generally increases the ligand–receptor binding energy (by reducing the entropy term), thus leading to increased compound potency. As a consequence, the medicinal chemist will often seek to introduce a ring into the lead structure in an attempt to increase its potency. However, in the context of orally administered drugs and in terms of developability criteria in drug discovery, the addition of an aromatic ring – for example, a phenyl substituent – increases the molecular weight by 78 and the lipophilicity (*c* log *P*) by 2.14 units. These values represent a statistically significant component of a molecule's overall properties in the context of the limits advised by Lipinski's rule of five [1]. And as previously mentioned, the average number of aromatic rings in oral drugs is 1.6!

In seeking to reduce the number of rings in a lead compound, a recent example describes transforming rigid cyclic templates (cyclohexane and piperidine rings embedded in a lead structure) into conformationally stabilized acyclic alternatives, albeit with



Aromatic ring count	0	1	2	3	4	5	6
Mean pIC_{50}	5.2	5.2	5.6	5.7	5.7	5.5	5.3
Number of compounds	36	392	3,216	4,802	2,181	416	61

Drug Discovery Today

FIGURE 9

Box plot and table of the negative log IC_{50} of inhibition of hERG and aromatic ring count.

an increase in the number of chiral centres [21,22]. It remains to be seen whether such an approach will find application in the replacement of aromatic rings, particularly in those circumstances in which the conformationally constrained acyclic motifs are not readily available.

Number of aromatic rings	1	2	3	4	5
clogP	1.9	2.9	3.7	4.4	5.1
$LogD_{7.4}$	1.3	2.1	2.4	2.7	2.9
Serum albumin binding (%)	78	88	93	96	96
Aqueous solubility (ug/ml)	100	79	57	36	28
P450 3A4 inhibition (pIC_{50})	4.7	4.9	5.2	5.4	5.6
hERG inhibition (pIC_{50})	5.2	5.6	5.7	5.7	5.5

Drug Discovery Today

FIGURE 10

A summary of the data presented in this analysis. Green shading represents increased developability, and red shading represents decreased developability.

A second possible reason for the prevalence of aromatic and heteroaromatic rings in drug molecules is that the chemical methodology available to assemble aryl–aryl systems is very broad with many metal-mediated couplings known. The robustness of these transformations, the ready commercial availability of both substrates and building blocks and the lack of time and resource usually available to pursue novel or less validated synthetic methodologies make aryl–aryl couplings particularly attractive for use in drug discovery programmes.

So ultimately, where does this analysis lead? It suggests that limiting the number of aromatic rings in a drug candidate will make it broadly more developable and more 'drug-like' (Fig. 10). In particular, the following mnemonic is suggested for oral drug discovery programmes:

'The fewer the number of aromatic rings contained in an oral drug candidate, the more developable that candidate is likely to be; specifically, more than three aromatic rings in a molecule correlates with poorer compound developability and, therefore, an increased risk of compound attrition.'

Furthermore, the addition of aromatic heterocycles will have a lesser effect on increasing lipophilicity than carbon-containing aromatics but will increase polar surface area and might begin to reduce oral absorption and/or cell penetration.

Finally, the simplicity of determining aromatic ring count in a compound enables this parameter to be continually borne in mind whilst designing the next iteration of compounds and might be particularly useful in promoting awareness of the potential developability issues that seem to be associated with increasing aromatic ring count.

Acknowledgements

We thank Alan Hill for helpful discussions and Rob Young and Robin Carr for their crucial reading of this manuscript and their helpful comments.

References

1 Lipinski, C.A. *et al.* (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 46, 3–26
2 Leeson, P.D. and Springthorpe, B. (2007) The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discov.* 6, 881–890
3 Muresan, S. and Sadowski, J. (2008) Properties guiding drug- and lead-likeness. In *Methods and Principles in Medicinal Chemistry*. Wiley InterScience pp. 439–461
4 Spotfire DXP 2.0 or DecisionSite 8.2.1
5 Lipinski, C.A. (2000) Drug-like properties and the causes of poor solubility and poor permeability. *J. Pharmacol. Toxicol. Methods* 44, 235–249
6 Hann, M.M. *et al.* (2001) Molecular complexity and its impact on the probability of finding leads for drug discovery. *J. Chem. Inf. Comput. Sci.* 41, 856–864
7 Wenlock, M.C. *et al.* (2003) A comparison of physicochemical property profiles of development and marketed oral drugs. *J. Med. Chem.* 46, 1250–1256
8 Palm, K. *et al.* (1997) Polar molecular surface properties predict the intestinal absorption of drugs in humans. *Pharm. Res.* 14, 568–571
9 Veber, D.F. *et al.* (2002) Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* 45, 2615–2623
10 Hughes, J.D. *et al.* (2008) Physiochemical drug properties associated with *in vivo* toxicological outcomes. *Bioorg. Med. Chem. Lett.* 18, 4872–4875
11 Ran, Y. and Yalkowsky, S.H. (2001) Prediction of drug solubility by the general solubility equation (GSE). *J. Chem. Inf. Comput. Sci.* 41, 354–357
12 Lamanna, C. *et al.* (2008) Straightforward recursive partitioning model for discarding insoluble compounds in the drug discovery process. *J. Med. Chem.* 51, 2891–2897
13 Valko, K. *et al.* (2003) Fast gradient HPLC method to determine compounds binding to human serum albumin. Relationships with octanol-water and immobilized artificial membrane lipophilicity. *J. Pharm. Sci.* 92, 2236–2248
14 Sudlow, G. *et al.* (1975) Characterization of two specific drug binding sites on human serum albumin. *Mol. Pharmacol.* 11, 824–832
15 Trainor, G.L. (2007) The importance of plasma protein binding in drug discovery. *EODC* 2, 51–64
16 Lewis, D.F.V. and Dickins, M. (2002) Substrate SAR in human p450s. *Drug Discov. Today* 7, 918–925
17 Blagg, J. (2006) Structure activity relationships for *in vitro* and *in vivo* toxicity. *Annu. Rep. Med. Chem.* 41, 353–358
18 Hop, C.E.C.A. *et al.* (2006) Importance of early assessment of bioactivation in drug discovery. *Annu. Rep. Med. Chem.* 41, 369–381
19 Jamieson, C. *et al.* (2006) Medicinal chemistry of hERG optimizations: highlights and hang-ups. *J. Med. Chem.* 49, 5029–5046
20 Wood, A. and Armour, D. (2005) The discovery of the CCR5 receptor antagonist, UK-427,857, a new agent for the treatment of HIV infection and AIDS. *Prog. Med. Chem.* 43, 239–271
21 Santella, J.B. *et al.* (2008) From rigid cyclic templates to conformationally stabilized acyclic scaffolds. Part I: the discovery of CCR3 antagonist development candidate BMS-639623 with picomolar inhibition potency against eosinophil chemotaxis. *Bioorg. Med. Chem. Lett.* 18, 576–585
22 Gardner, D.S. *et al.* (2008) From rigid cyclic templates to conformationally stabilized acyclic scaffolds. Part II: acyclic replacements for the (3*S*)-3-benzylpiperidine in a series of potent CCR3 antagonists. *Bioorg. Med. Chem. Lett.* 18, 586–595
23 Leeson, P.D. and Davis, A.M. (2004) Time-related differences in the physical property profiles of oral drugs. *J. Med. Chem.* 47, 6338–6348