The impact of aromatic ring count on compound developability: further insights by examining carbo- and hetero-aromatic and -aliphatic ring types

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The impact of carboaromatic, heteroaromatic, carboaliphatic and heteroaliphatic ring counts and fused aromatic ring count on several developability measures (solubility, lipophilicity, protein binding, P450 inhibition and hERG binding) is the topic for this review article. Recent results indicate that increasing ring counts have detrimental effects on developability in the order carboaromatics ≫ heteroaromatics > carboaliphatics > heteroaliphatics, with heteroaliphatics exerting a beneficial effect in many cases. Increasing aromatic ring count exerts effects on several developability parameters that are lipophilicity- and size-independent, and fused aromatic systems have a beneficial effect relative to their nonfused counterparts. Increasing aromatic ring count has a detrimental effect on human bioavailability parameters, and heteroaromatic ring count (but not other ring counts) has increased over time in marketed oral drugs.

Introduction

A detailed account of the detrimental effects of increasing aromatic ring count on several developability measures has recently been described elsewhere by the authors of this review [1], concluding that the fewer the number of aromatic rings contained in an oral drug candidate, the more developable that candidate is likely to be – and that more than three aromatic rings in a molecule correlate with poorer compound developability and, therefore, an increased risk of compound attrition. The finding that increasing aromatic ring count has a detrimental effect on aqueous solubility was supported by the publication of a complementary approach [2], where the fraction of sp3 hybridized carbon atoms (Fsp3), in other words the fraction of carbon atoms that are saturated, correlates with solubility (i.e. compounds with fewer aromatic carbons, with respect to sp3 hybridized carbons, are more soluble). It has previously been shown that increasing 'aromatic proportion' in a molecule has a detrimental effect on solubility [3], and the simplistic summation of aromatic ring count and *c* log *D*7.4 has now been used as a simple but effective indicator of the solubility category [4]. A new parameter, aromatic atom count – sp3 atom count (Ar-sp3) – which describes aromatic–aliphatic balance, has also been introduced recently in an analysis of oral drugs and patented medicinal chemistry compounds [5].

As discussed previously, the descriptor 'aromatic ring count' is a generic term and encompasses benzenoid and heteroaromatic systems, as well as fused and nonfused aromatic groups. To gain more insight into the effects of aromatic ring count on developability, further analyses were conducted where: (a) the differentiation was made between carbon-only aromatic rings (carboaromatics) and heteroaromatic rings and (b) the fused aromatic ring count was investigated separately. The corresponding counts for carboaliphatic and heteroaliphatic rings were also included, because these had not been discussed previously elsewhere. All the above descriptors were readily generated using the topology analysis calculator plug-in available from ChemAxon (http://www.chemaxon.com/products/calculator-plugins/topology-analysis/). Both rings in bicyclic systems are counted. For example: 1*H*-indole is classified as containing one carboaromatic ring and one heteroaromatic ring; 2,3-dihydro-1*H*-indole contains one carboaromatic ring and one

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TABLE 1

Summary of effects of increasing ring counts on developability measures

	Carbo-Aromatics	Hetero-Aromatics	Carbo-Aliphatics[a]	Hetero-Aliphatics
CLND Solubility	↓↓ -0.37	↓ -0.10	↔ -0.01	↑ 0.16
CHI LogD7.4	↑↑ 0.36	↓ -0.17	↑ 0.06	↓ -0.05
HSA binding	↑↑ 0.39	↑ 0.08	↔ 0.00	↓ -0.29
AGP binding	↑↑ 0.43	↔ 0.04	↔ -0.02	↔ 0.03
CyP 3A4 inhibition	↑ 0.13	↑ 0.08	↔ -0.02	↔ 0.08
CyP 2C9 inhibition	↑ 0.26	↑ 0.12	↔ 0.01	↓ -0.13
CyP 2C19 inhibition	↑ 0.19	↔ 0.03	↔ 0.01	↓ -0.14
CyP 2D6 inhibition	↔ 0.06	↔ -0.04	↔ 0.02	↔ 0.00
CyP 1A2 inhibition	↓ -0.07	↔ 0.04	↔ -0.03	↓ -0.20
hERG inhibition	↑ 0.18	↔ 0.02	↔ -0.01	↑ [b]0.08

↓↓ or ↑↑ Strong, detrimental impact ↑ or ↓ Modest detrimental impact
↓ or ↑ Modest beneficial impact ↔ No significant impact

[a]Carboaliphatic rings are not a common ring type in the datasets.
[b]Effect driven by basic heteroaliphatics. Spearman's rank correlation coefficients are shown next to the arrows: values of >0.3 indicate a strong positive effect; values of <−0.3 indicate a strong negative effect. Effects that did not reach statistical significance ($P < 0.05$; Tukey–Kramer confidence circles) were classified as having no significant impact. *Abbreviations*: CLND, chemiluminescent nitrogen detection; CHI, chromatographic hydrophobicity index; HSA, human serum albumin; AGP, alpha-1-acid glycoprotein; CyP, Cytochrome P450; hERG, human ether-à-go-go-related gene.

heteroaliphatic ring, and so on. Although it is generally considered that a thiophene ring is more akin to a benzene ring with respect to its physicochemical properties [6], for the purposes of this review thiophene (and other sulfur-containing rings) is classified as hetero rings. In reality, <10% of the compounds studied contained a thiophene moiety, and excluding them did not significantly change the outcome of the analyses.

In this new study larger datasets (typically 10–100k) were collected from the panel of GlaxoSmithKline (GSK) developability assays, and in addition to the screens reported previously {e.g. aqueous solubility [measured by chemiluminescent nitrogen detection (CLND)], human serum albumin (HSA) binding, CyP 3A4 (cytochrome P450 3A4) inhibition and hERG channel binding} the effects of increasing ring counts on alpha-1-acid glycoprotein (AGP) binding [7] and CyP450 isozymes other than CyP 3A4 (namely 2C9, 2C19, 2D6 and 1A2) were examined. Lipophilicity was measured using the chromatographic hydrophobicity index (CHI) log *D*7.4 methodology [8], which has been shown to correlate well with classical octanol–water log *D*7.4 measurements and, importantly, does not suffer from the experimental limitations of the latter observed at high log *D* values [1,4]. Finally, the impact of aromatic ring count on some reported human bioavailability-related measures was investigated, and also whether ring counts have changed in oral drugs over time.

Compounds with the following properties were excluded from the analysis: macrolides and other macrocyclic (>10 atom rings) systems; molecules with obligate positive charge (e.g. quaternary ammonium species); molecules with four or more ionizable groups; molecules with no rings, seven or more aromatic rings, nine or more total rings; and polycyclic systems (six or more fused rings). These outliers amounted to ~10% of the data. As with the previous study [1], statistical significance was confirmed using box plots and Tukey–Kramer confidence circles as implemented in Tibco Spotfire v3.2 (http://spotfire.tibco.com/spotfire-for-you/by-industry/life-sciences/lead-discovery.aspx). Unless stated to the contrary in the text, all effects discussed were found to be statistically significant ($P < 0.05$) across the majority of the data.

Individual impacts of carboaromatic, heteroaromatic, carboaliphatic and heteroaliphatic ring counts on developability

Table 1 summarizes the overall impact of carboaromatic, heteroaromatic, carboaliphatic and heteroaliphatic ring counts on developability. Effects were categorized as being strong (two arrows) or modest (one arrow) based on the magnitude of the impact on each developability measure using the Spearman's rank correlation coefficient calculated in Tibco Spotfire: a Spearman's rank coefficient of >0.3 was classified as a strong positive effect and <0.3 as a modest positive effect; similarly a coefficient of <−0.3 was classified as a strong negative effect and >−0.3 as a modest negative effect. Where the increase in ring counts resulted in changes that were not statistically significant ($P > 0.05$, Tukey–Kramer confidence circles) this was categorized as having no impact.

It is clear from this study that the detrimental impact of increasing aromatic ring count *per se* is predominantly driven by the carboaromatic ring component. Carboaromatics (i.e. phenyl rings

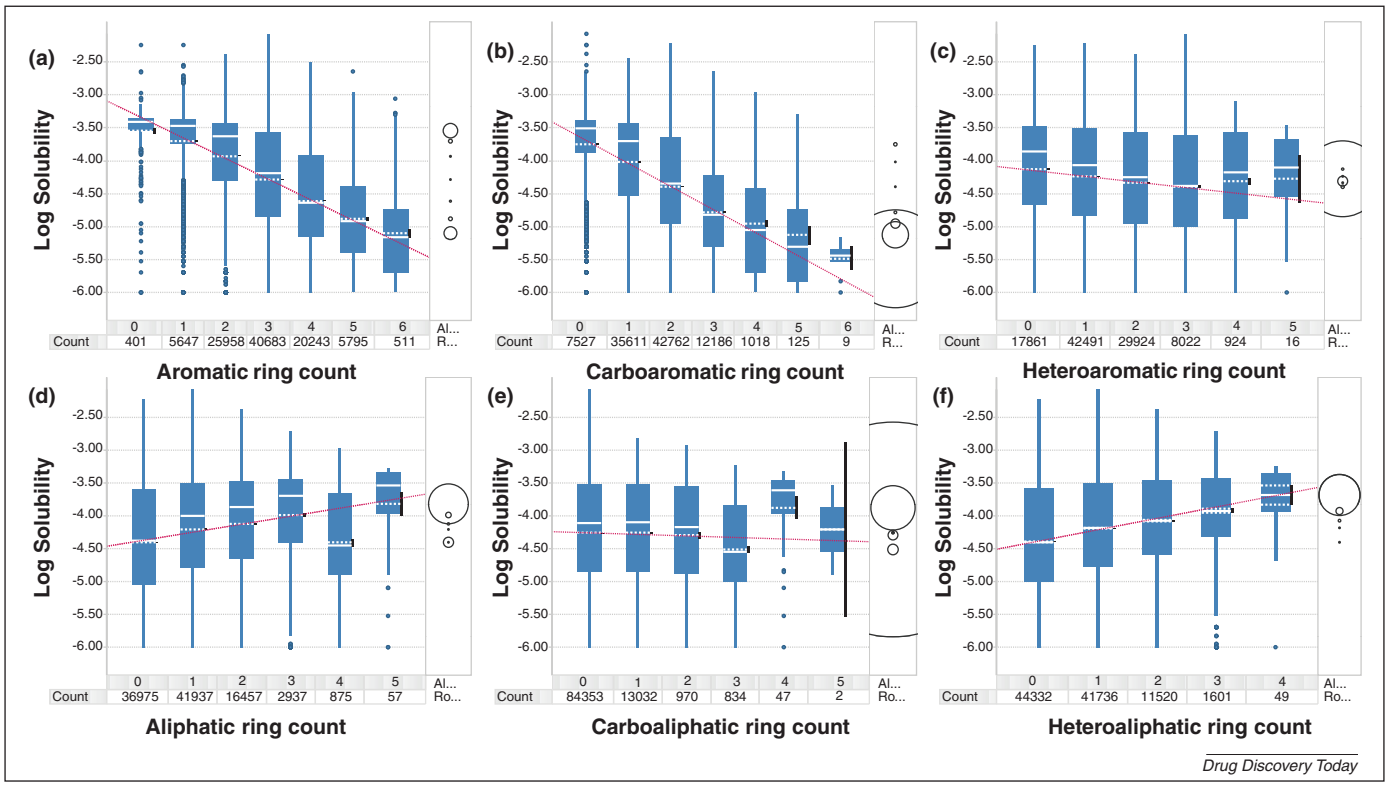

FIGURE 1

The effect of increasing ring counts on CLND solubility in μM (plotted on a logarithmic scale). The effect of total aromatic ring count (panel **(a)**) is driven mainly by the carboaromatic ring count component (**(b)**; Spearman $R = -0.39$) but also to some extent by the heteroaromatic ring count (**(c)**; $R = -0.10$). The apparent increase in solubility with increasing aliphatic ring count **(d)** is caused by the heteroaliphatic ring component (**(f)**; $R = 0.16$) rather than the carboaliphatic ring component (**(e)**; $R = -0.01$). The red lines are straight line fits to the data for each box plot. Non-overlapping circles (to the right of each plot) indicate that the mean values are significantly different ($P < 0.05$) from one another.

and benzo-fused ring systems) are inherently lipophilic and have strong deleterious effects on developability by lowering aqueous solubility (Fig. 1b), increasing lipophilicity (CHI log *D*7.4), and increasing HSA (Fig. 2b) and AGP binding. Increasing carboaromatic ring count also demonstrated detrimental effects on CyP 3A4, 2C9, 2C19 and hERG inhibition. A small beneficial effect (a reduction) was observed in CyP 1A2 binding as the carboaromatic ring count increased, presumably because of the size limitation of the narrow, planar active site in this enzyme [9]. Increasing carboaromatic ring count (or indeed any other ring count) in this study had no effect on CyP 2D6 inhibition.

The consequences of increasing heteroaromatic ring count, although not as dramatic as seen with carboaromatics, resulted in lower aqueous solubility (Fig. 1c), increased HSA binding (Fig. 2c) and increased CyP 3A4 and 2C9 inhibition. Increasing heteroaromatic ring count resulted in a reduction in CHI log *D*7.4; this might be expected to result in higher solubility but in reality this appears to be negated by the addition of a planar ring. Increasing heteroaromatic ring count had no effect on AGP binding, CyP 2C19 inhibition or hERG binding.

Increasing carboaliphatic ring count generally had little impact on developability measures, although there was a modest increase in lipophilicity. It is important to point out, however, that 85% of the compounds in the datasets had no aliphatic rings, with only 13% and 1% containing one or two carboaliphatic rings, respectively.

With regard to increasing heteroaliphatic ring count, it was interesting to note that in general this produced an improvement in developability, resulting in higher solubility (Fig. 1f), lower lipophilicity and lower HSA binding (Fig. 2f), as well as reduced CyP 2C9, 2C19 and 1A2 inhibition. There were no significant effects on AGP binding, or on CyP 3A4 inhibition. The beneficial effects were also observed when molecules possessing negatively or positively ionizable groups (e.g. carboxylic acids and protonatable amines) were excluded from the analysis (44% of the dataset), suggesting that the inclusion of neutral heteroaliphatics such as cyclic ethers, amides, sulfones and *N*-arylated, *N*-carbonylated or *N*-sulfonylated cyclic amines (e.g. pyrrolidine, piperidine, piperazine and morpholine) can exert a positive influence on developability measures. Increasing heteroaliphatic ring count resulted in a slight increase in hERG binding. Upon closer inspection, this increase was found to be absent in neutral molecules, consistent with the reported literature states that this effect is more associated with rings with basic amine functionality [10]. Recently, the concept of privileged saturated and aromatic heterocycle ring pairs in known drugs, or 'BioCores', has been discussed [11].

Importance of the carboaromatic:heteroaromatic ratio in developability

Because the separation of aromatic ring count into its carboaromatic and heteroaromatic components has yielded extra information, the data were analyzed to determine how the ratio of carboaromatic rings to heteroaromatic rings affects the overall developability profile. A summary of the findings is shown in Fig. 3, in this case for all compounds that have a total of three

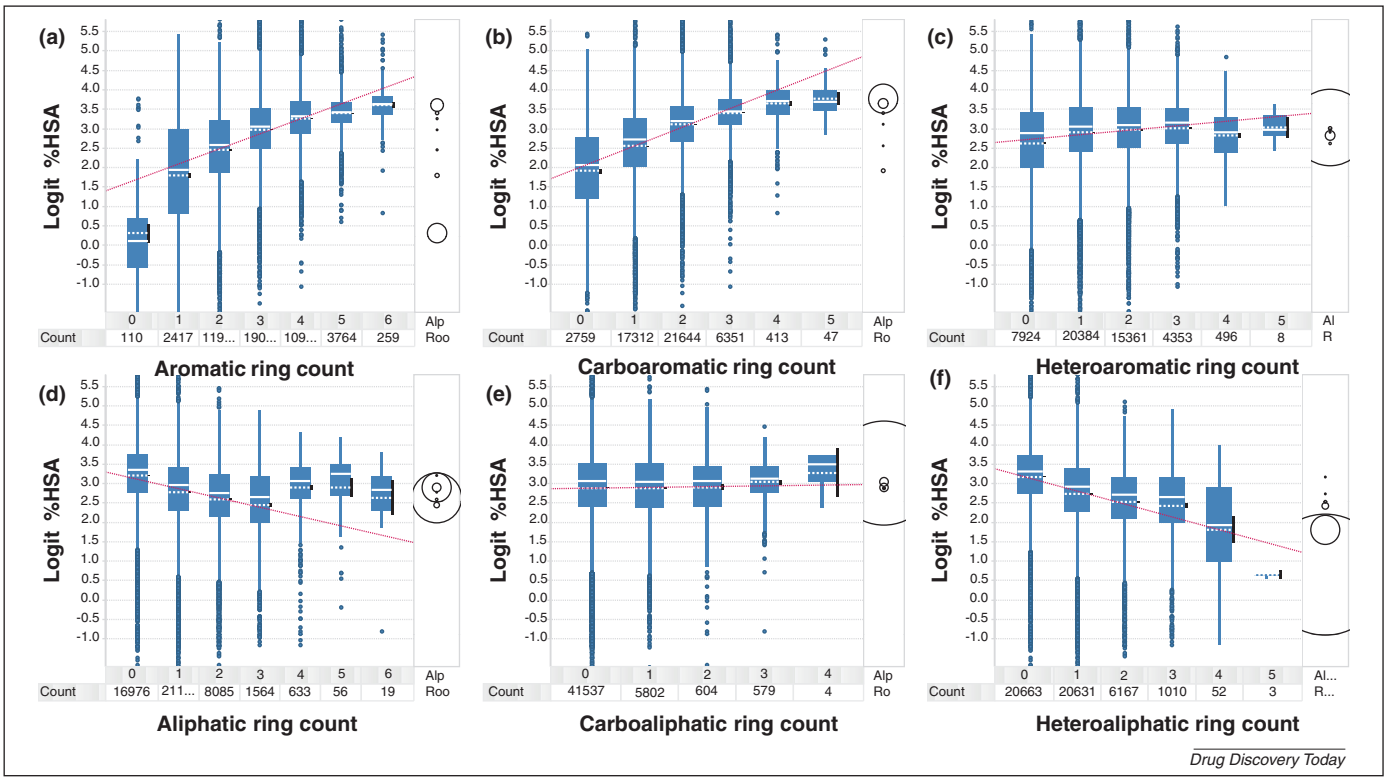

FIGURE 2

The effect of increasing ring counts on human serum albumin (HSA)% binding. The effect of total aromatic ring count (panel **(a)**) is driven mainly by the carboaromatic ring count component (**b**; Spearman $R = 0.39$) but also to some extent by the heteroaromatic ring count (**c**; $R = 0.08$). Carboaliphatic ring count (**e**; $R = 0.00$) has no effect on HSA, whereas increasing heteroaliphatic ring count (**f**; $R = -0.29$) lowers HSA binding. Binding is expressed as the logit function (the natural logarithm of the % bound:% unbound ratio, Ln[%HSA/(100 − %HSA)].

aromatic rings and any number of aliphatic rings ($n = 40,683$; solubility dataset). Thus, compounds in this subset contain: three heteroaromatic and no carboaromatic rings ($n = 2187$); two heteroaromatic and one carboaromatic ring ($n = 13,875$); one heteroaromatic and two carboaromatic rings ($n = 20,762$); or no heteroaromatic and three carboaromatic rings ($n = 3859$). It can be seen that there is a gradual deterioration in developability profile as the proportion of carboaromatic character increases;

	3 Het + 0 Car	2 Het + 1 Car	1 Het + 2 Car	0 Het + 3 Car
Mol Wt	392	387	415	459
Solubility (uM)	242	184	128	83
Daylight clogP	2.5	3.25	4.19	5.14
CHI logD7.4	1.59	2.21	2.81	3.27
HSA (% binding)	87	92	94.7	95.7
AGP (% binding)	75.4	80.6	85.2	88.5
CyP 3A4 (pIC50)	4.71	4.8	4.91	4.98
CyP 2C9 (pIC50)	4.7	4.95	5.18	5.4
CyP 2C19 (pIC50)	4.55	4.72	4.87	5.1
CyP 2D6 (pIC50)	4.71	4.74	4.78	4.91
CyP 1A2 (pIC50)	4.51	4.6	4.56	4.39
hERG (pIC50)	5.04	5.17	5.35	5.48

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FIGURE 3

Effect of heteroaromatic/carboaromatic ring ratio on developability measures. Average data shown for compounds with a total of three aromatic rings and any number of aliphatic rings; increasing carboaromatic ring content negatively impacted all developability parameters (except CyP 1A2 inhibition). *Abbreviations*: Mol Wt, molecular weight; *c* log *P*, calculated logarithm of the partition coefficient; CHI, chromatographic hydrophobicity index; HSA, human serum albumin; AGP, alpha-1-acid glycoprotein; CyP, Cytochrome P450; hERG, human ether-à-go-go-related gene.

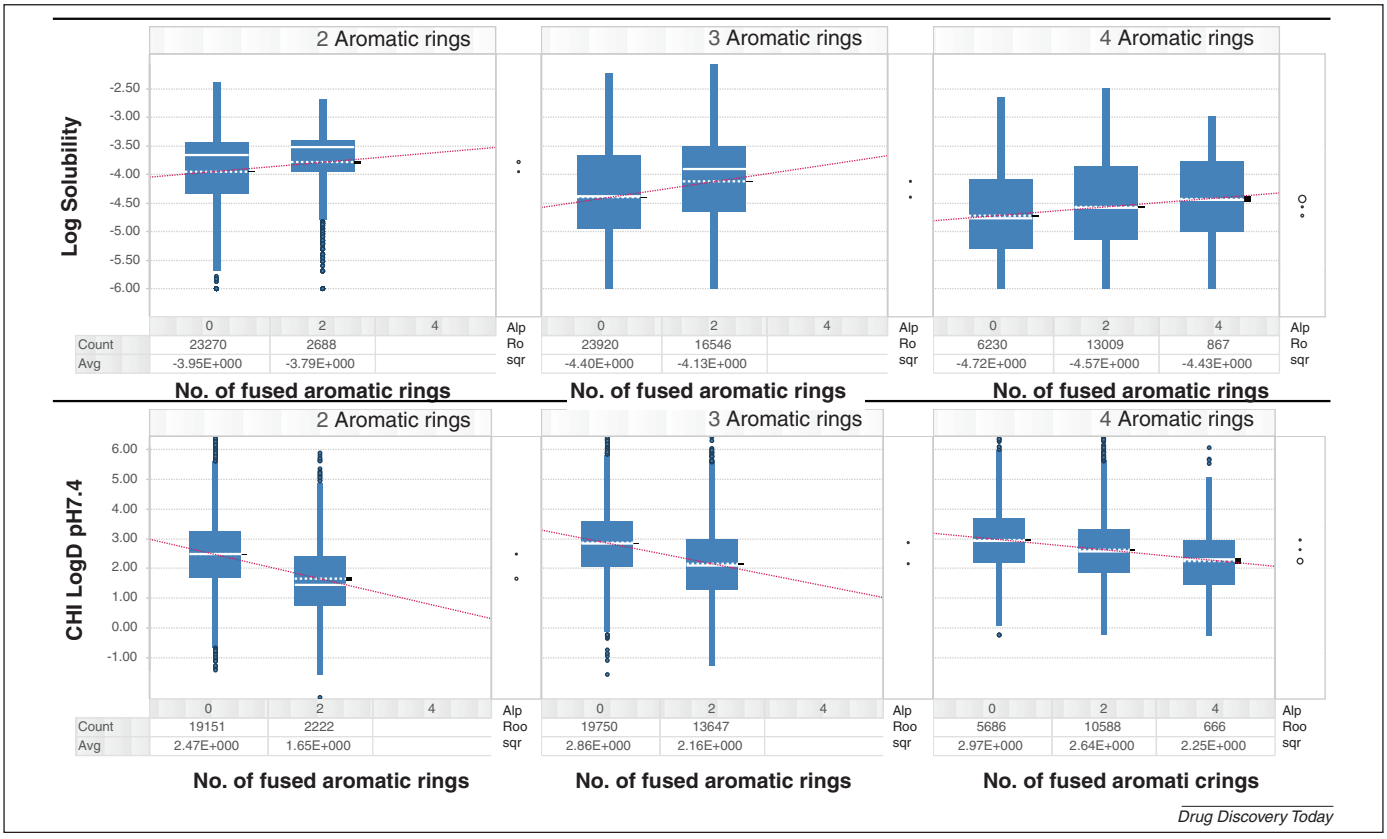

FIGURE 4

Effect of fused versus nonfused aromatic rings on solubility and lipophilicity. For a given number of aromatic rings, molecules with fused aromatic rings are more soluble and less lipophilic than analogous nonfused systems; the effect on solubility is small but significant; the effect on CHI log *D*7.4 is more pronounced. *Abbreviation*: CHI, chromatographic hydrophobicity index.

the replacement of heteroaromatic rings with carboaromatic rings increases molecular weight (MW) (presumably owing to the increase in six-membered rings and the additional positions available for substitution on carbon rings) and lipophilicity (Daylight *c* log *P* and CHI log *D*7.4), resulting in reduced aqueous solubility and higher protein binding. CyP450 inhibition and hERG binding also increased although the effects were less dramatic but still statistically significant, except for CyP 1A2 inhibition. When this analysis was repeated for compounds with a total of four aromatic rings, a similar pattern of deterioration in developability was observed as the proportion of carboaromatic content increased relative to heteroaromatic content. Thus, it is advisable to replace carboaromatic rings with heteroaromatic rings where possible. A recent survey has suggested that there are many synthetically tractable heteroaromatic ring systems that have not been synthesized to date [12].

Fused versus nonfused aromatic rings

The effect of fused and nonfused aromatic ring counts was also examined. For example, compounds with two aromatic rings can have two independent aromatic rings or both rings can be in one fused aromatic system; compounds with three aromatic rings can have three independent aromatic rings, one independent ring and two rings in a fused system, or all three rings fused together, and so on. Because of the low numbers of tricyclic aromatic systems in the data, these were not included in the analysis.

Because fused aromatic ring systems, by definition, have fewer heavy atoms and contain more heteroaromatic rings than their corresponding nonfused congeners, one might expect to see some differences in the developability screens, and indeed this was found to be the case. Molecules with fused aromatic ring systems exhibited improved developability properties when compared with their nonfused-ring counterparts. The effects observed on aqueous solubility (log Sol) and lipophilicity (CHI log *D*7.4) are shown in Fig. 4 for compounds with a total of two, three and four aromatic rings. In all cases, replacing individual aromatic rings with fused aromatic ring systems resulted in an increase in solubility and a decrease in lipophilicity. This would suggest that fusing aromatic rings can improve developability characteristics. For example, a new hit or lead series might be selected that contains more fused aromatic rings; rather than another with an equal number of separate aromatic rings. When compounds with two aromatic rings joined by a single bond (e.g. biphenyl) were analyzed separately they generally displayed improved developability profiles when compared with compounds with two separated aromatic rings, but not when compared with compounds with two aromatic rings fused in a bicyclic system.

Aromatic ring count and developability within narrow lipophilicity and size ranges

In our previous study [1] it was highlighted that increasing aromatic ring count reduced aqueous solubility even when the

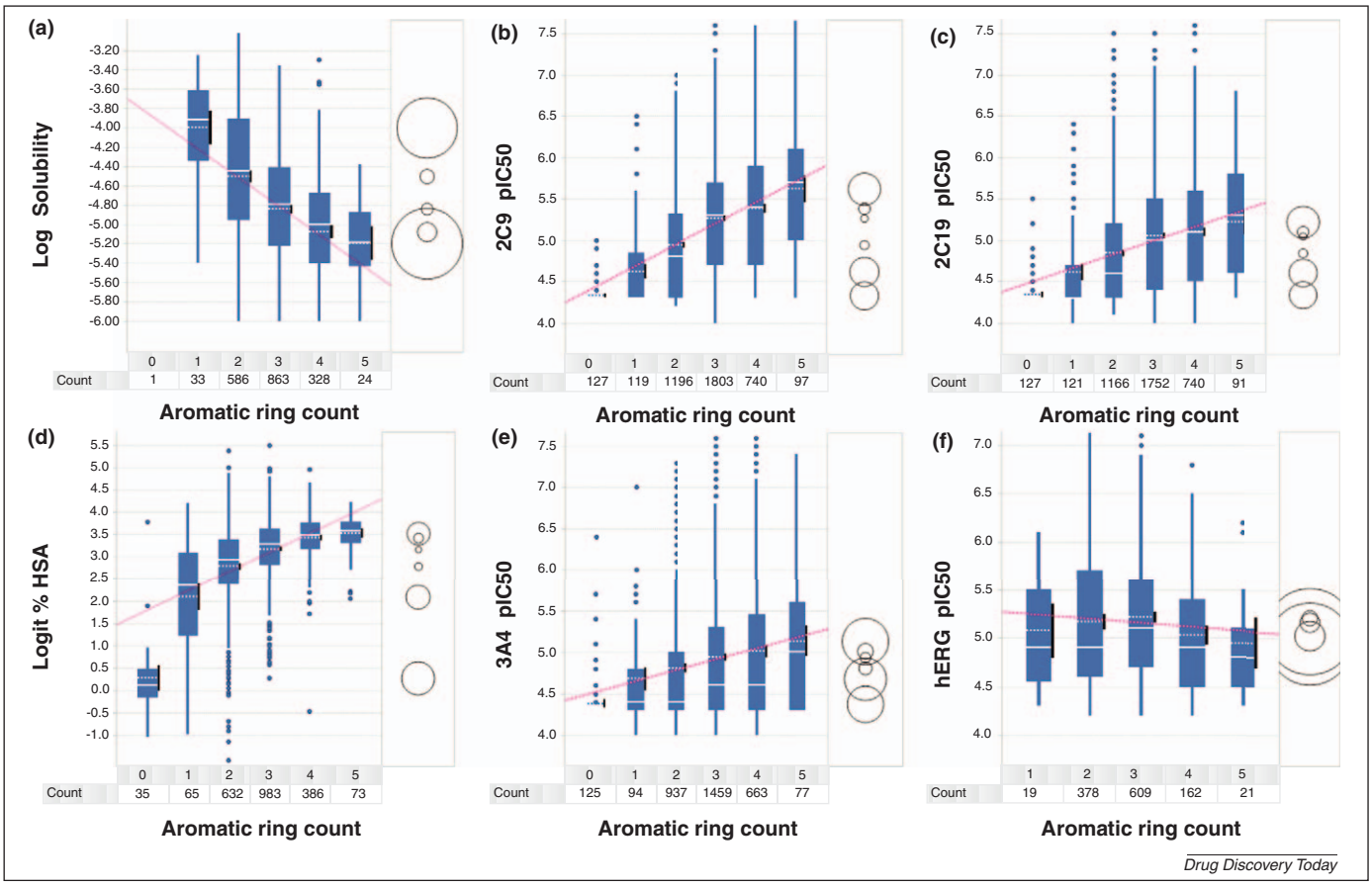

FIGURE 5

Lipophilicity- and size-independent effects of increasing aromatic ring count on developability measures. The decrease in solubility (panel **(a)**) and increase in HSA binding **(d)** and CyP 2C9 **(b)**, 2C19 **(c)** and 3A4 **(e)** inhibition is still apparent within narrow ranges of CHI log *D*7.4 (3.5–4.0) and MW (350–400 Da). Increasing aromatic ring count does not affect hERG inhibition **(f)** in a lipophilicity- and size-independent manner. *Abbreviations*: HSA, human serum albumin; Ln[%HSA/(100 − %HSA)], logit function (the natural logarithm of the % bound:% unbound ratio).

lipophilicity was restricted to a narrow range. This effect has now been investigated further by also restricting the range of MW. Thus, in a representative subset of compounds with MWs between 350 and 400 Da, and a CHI log *D*7.4 value between 3.5 and 4.0, increasing aromatic ring count still exhibited significant effects in reducing aqueous solubility (Fig. 5a) and increasing HSA binding (Fig. 5d), which appeared to be independent of lipophilicity and size. This effect was observed in all similarly sized narrow bins across the MW range 200–500 Da and CHI log *D*7.4 range 2.0–5.0. Similar lipophilicity- and size-independent effects were also seen with CyP 2C9 (Fig. 5b), 2C19 (Fig. 5c) and 3A4 inhibition (Fig. 5e), but not with hERG binding (Fig. 5f). It has been shown that increasing lipophilicity will result in higher HSA binding [13], so it is interesting that aromatic ring count had an influence in this case – even when the lipophilicity was held relatively constant.

Ring counts in oral drugs

A recent publication reported several bioavailability measures in humans for around 300 orally administered drugs [14]. Although it has been suggested that using simple molecule properties to predict accurate oral bioavailability is difficult [15], it was nevertheless decided to examine total aromatic ring count against these measures to see if there was any correlation. In this case, the average bioavailability readouts of compounds with two or fewer aromatic rings ($n = 263$) were compared against those with three or more aromatic rings ($n = 40$); the fact that only 13% of the compounds in this dataset have three or more aromatic rings supports the premise that successful oral drugs tend to have low numbers of aromatic rings. The results are shown in Fig. 6: the fraction of unbound drug in human plasma was on average 40% for compounds with two or fewer aromatic rings; when three or more rings were present the fraction of unbound drug dropped significantly to 11%. The fractions escaping intestinal extraction (Fg) were 86% and 75%, respectively, for these two groups. Compounds with two or fewer aromatic rings also exhibited trends towards a higher fraction escaping hepatic extraction (Fh), lower hepatic clearance (CLh) and higher overall oral bioavailability (F), when compared to compounds with three or more rings; however, these trends failed to reach statistical significance, in part because of the small number of drugs with three or more aromatic rings. The overall absorption (Fa) was similar in both groups. Thus, it appears that limiting the number of aromatic rings in potential drug molecules is likely to have a beneficial effect on human bioavailability-related parameters as well as general developability measures.

A collection of 1200 marketed oral drugs was also analyzed to see whether the ring counts discussed above have changed over time. It has previously been shown that MW and H-bond acceptor (HBA) count have both increased over time in oral drugs, with

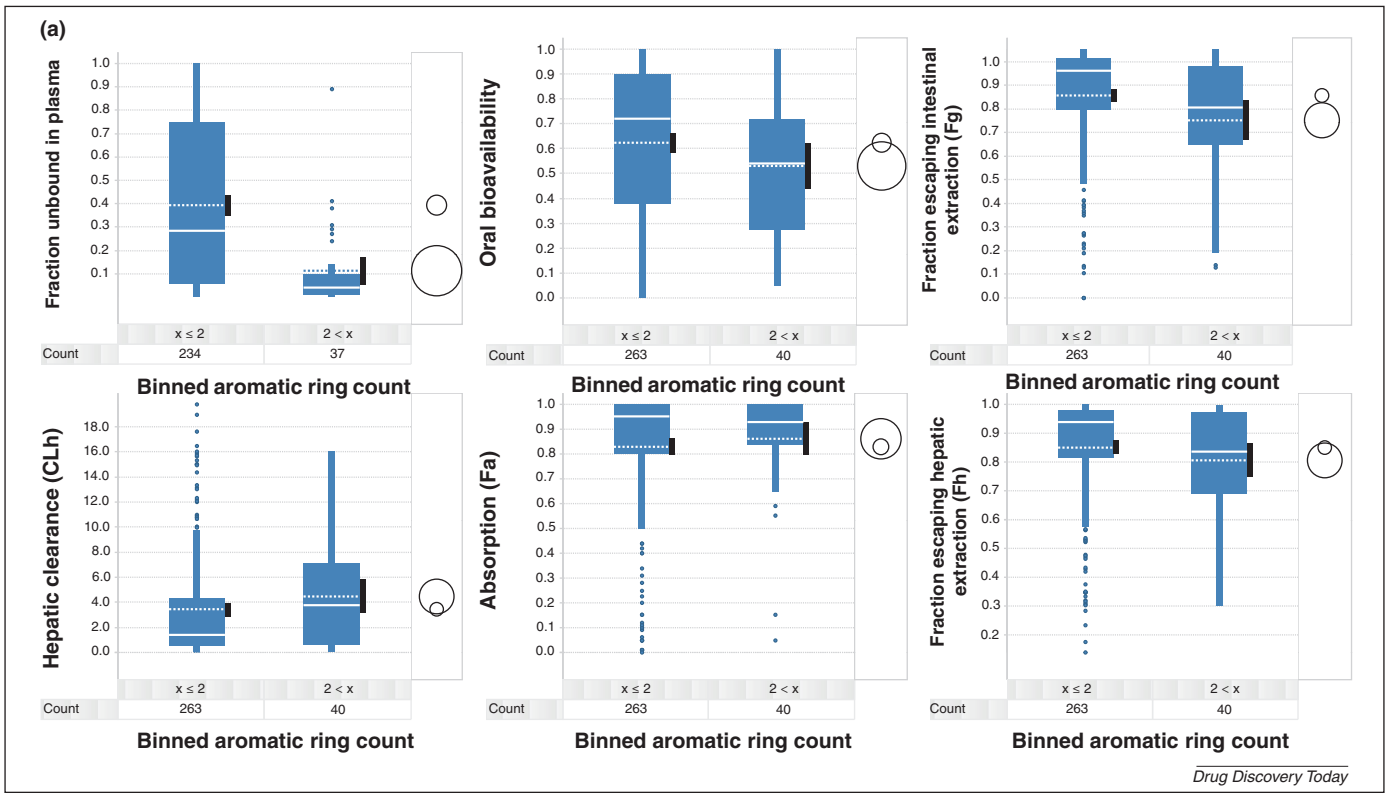

FIGURE 6

Effect of aromatic ring count on human absorption parameters. Data published [12] for *ca.* 300 oral drugs: drugs with three or more aromatic rings (right hand box in each plot) have significantly lower fraction unbound in plasma and lower fraction escaping intestinal extraction (Fg) than drugs with two or fewer aromatic rings; other parameters [oral bioavailability (F), hepatic clearance (CLh), fraction escaping hepatic extraction (Fh)] show similar trends but are not statistically significant (at the $P < 0.05$ alpha level).

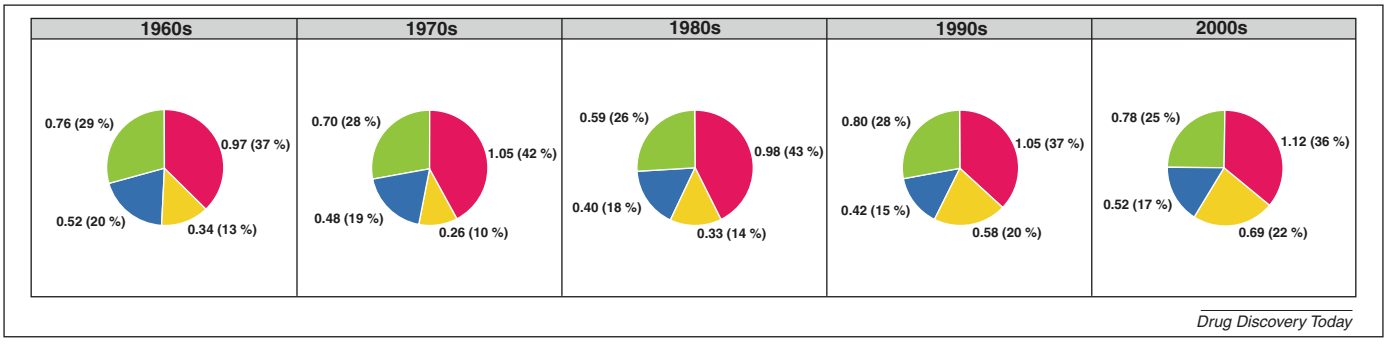

FIGURE 7

Increase in heteroaromatic ring count over time in marketed oral drugs. The heteroaromatic ring count (yellow segment) has increased from 0.34 rings in the 1960s to 0.58 and 0.69 rings in the 1990s and 2000s, respectively. Carboaromatic (red), carboaliphatic (blue) and heteroaliphatic (green) ring counts have remained relatively constant.

c log *P* values and H-bond donor count remaining constant [16]. From the current analysis of oral drugs, this increase in MW and HBA count could be caused by an increase in the heteroaromatic ring count, which has increased from 0.34 rings in the 1960s to 0.58 and 0.69 rings in the 1990s and 2000s, respectively (Fig. 7). Carboaromatic (*ca.* 1.0), carboaliphatic (*ca.* 0.5) and heteroaliphatic (*ca.* 0.8) ring counts have remained relatively constant over the same period (Fig. 7).

Where now?

At GSK many, if not most, structural starting points for lead optimization feature aromatic cores (or templates). There are good reasons for this. First, is the abundant availability and variety of aromatic starting materials. Second, there is a plethora of robust tractable aromatic chemistry that can be used with confidence. Both of these factors generally mean there is a high preponderance of aromatic cores among the compounds that are screened as starting points for a new programme. Third, aromatic rings provide the opportunity to display binding functionality from a rigid core in numerous vectors without introducing new stereocentres. By contrast, a starting point that features a chain or a saturated ring as the core has disadvantages including multiple conformations and frequently difficult synthetic chemistry to substitute at the desired position, which also often introduces a new stereocentre. A

further consideration relates to the selection of the core for lead optimization. When a GSK project is in the hit-to-lead phase it is often the case that relatively little synthetic resource is assigned – so simple synthetic transformations from an aromatic core are attractive in comparison to, say, a saturated core. Thus, on the one hand, aromatic rings appear to be attractive from a synthetic and SAR point of view but, on the other hand, too many in any one molecule will impact developability in a negative manner. Therefore, any insights from the current analysis perhaps emphasize the importance of the type of ring that is appended to an aromatic core. These should be carefully selected with an increased willingness to accept any extra synthetic effort that might be required for their introduction, in the knowledge that there are positive developability benefits that are likely to be gained.

Concluding remarks

The separation of 'aromatic ring count' into its components: carboaromatic ring count and heteroaromatic ring count, has highlighted the former as the most important contributor to the drop-off observed in developability parameters. Also, for a given number of aromatic rings, it is clear that higher carboaromatic content in a molecule with respect to heteroaromatic content will significantly impact developability. It is therefore advisable not only to limit the number of overall aromatic rings in a molecule but also, where possible, to replace carboaromatic rings with heteroaromatic congeners (while keeping in mind general oral drug-like limits for polar surface area and H-bonding groups, among others). The analysis of carboaliphatic and heteroaliphatic ring counts has identified the ambivalent nature of the former, and the generally beneficial nature of the latter, on developability measures, which is seen in neutral molecules as well as those with positively or negatively ionizable groups. In summary, the detrimental effects on developability measures of increasing ring counts are in the order carboaromatics $\gg$ heteroaromatics $>$ carboaliphatics $>$ heteroaliphatics. It should be considered that the use of heteroaliphatic rings with basic amine functionality could have the potential to introduce unwanted effects into molecules such as hERG inhibition [9] or increased target promiscuity [17]. Increasing aromatic ring count exhibits effects on several developability parameters that are independent of lipophilicity and size, and molecules possessing fused aromatic systems appear to show improved developability over their nonfused counterparts. Although, in many cases, the SAR in chemical series might not allow the replacement of two independent aromatic rings with a fused system, the selection of a new hit or lead series with fused aromatic systems rather than separate aromatic rings at an early stage could be worthy of consideration.

In the context of marketed oral drugs, increasing aromatic ring count appears to exert a deleterious effect on human bioavailability-related parameters and, over time, heteroaromatic ring count has increased, whereas carboaromatic ring count and aliphatic ring counts have remained constant.

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