Analysis of the Calculated Physicochemical Properties of Respiratory Drugs: Can We Design for Inhaled Drugs Yet?

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From an analysis of calculated physicochemical properties for 81 currently marketed respiratory drugs, compounds administered via the inhaled/intranasal routes have a higher polar surface area, a higher molecular weight, and a trend toward lower lipophilicity, when compared with their orally administered counterparts. Ranges of physicochemical space are described for the 29 drugs administered by the inhaled or intranasal routes.

INTRODUCTION

The focus of the Respiratory Centre of Excellence for Drug Discovery at GlaxoSmithKline is the discovery of medicines for the treatment of respiratory disease. In 2007, the worldwide respiratory market was valued at just over $52 billion and represented the sixth largest category of therapeutic sales.[1] One of the larger selling drugs in this category is Seretide/Advair, an inhaled treatment for asthma and chronic obstructive pulmonary disease with worldwide sales in 2007 of £3.4 billion.[2]

While some respiratory drugs are administered orally, there are distinct advantages in administration by either the inhaled or intranasal routes for the treatment of respiratory disease.

First, inhaled or intranasal delivery allows the therapeutic agent to be administered directly to the site of action. This offers the significant advantage that the efficacy of the drug can be achieved in the respiratory tract while systemic exposure of drug is reduced to a very low level. One example of this is by the long retention of the drug at the topical site of delivery.[3] Another example is the rapid metabolism or clearance of drug once it is absorbed from the lung or nose. In the ante[4a] or soft[4b] drug approach, the active agent is rapidly deactivated by metabolism. This has been used with notable success with extremely potent inhaled glucocorticoids.[5] However the low systemic concentrations of drug are achieved, the net result is an increased therapeutic index.

A second advantage is that delivering drug by the inhaled or intranasal routes for respiratory diseases avoids many of the physicochemical constraints on drug structure that a requirement for oral bioavailability can impose. Because the solving of pharmacokinetic issues associated with oral dosing is frequently problematic and time-consuming, it is likely that topical delivery leads to a more rapid drug *discovery* process.

Inhaled/intranasal drug administration can however represent significant challenges during the drug *development* phase. Such challenges may include obtaining a suitable crystalline form of the active component of the drug and its subsequent formulation. The development of an appropriate device for delivery of the drug to the patient can also represent a significant technical challenge.

Given our focus on respiratory drugs, we are particularly interested in establishing medicinal chemistry design principles for inhaled or intranasally administered drugs, and we are unaware of any literature that directly addresses this topic. In the first instance, we wished to define more clearly the physicochemical space occupied by this class of marketed drugs. How do the physicochemical and structural properties of inhaled respiratory drugs compare with orally administered respiratory drugs? Do the physicochemical properties of marketed inhaled drugs differ from those of intranasally delivered drugs ? Does an analysis of physicochemical properties provide insights into the medicinal chemical design of new respiratory drugs particularly those that would be administered topically ? When medicinal chemists were questioned on these topics, there was generally a lack of clarity about medicinal chemistry design principles for topical drugs although one common perception was that inhaled drugs tended to be more lipophilic and have a higher molecular weight than their oral counterparts. Is this perception actually correct?

Following Lipinski's seminal work in developing "the rule of 5", which describes physicochemical properties commensurate with poor oral absorption,[6] there is now extensive literature exploring the calculated properties of oral drugs and their application to oral drug design.[7−13] However, apart from a recent important review by Patton and Byron[14] on delivering drugs to the body through the lung and a brief analysis of inhaled drugs by Tronde et al.[15] in 2003, (as part of an elegant study on the pulmonary absorption rate and bioavailability of drugs in rats), we are unaware of any other published analyses of in silico properties of inhaled, intranasal, and orally administered respiratory drugs.

To answer the above questions and as part of our quest to identify more clearly medicinal chemistry design principles for topical drugs, we recently carried out an in silico analysis of currently marketed respiratory drugs up to May 2008 administered by the oral, inhaled, and intranasal routes. These

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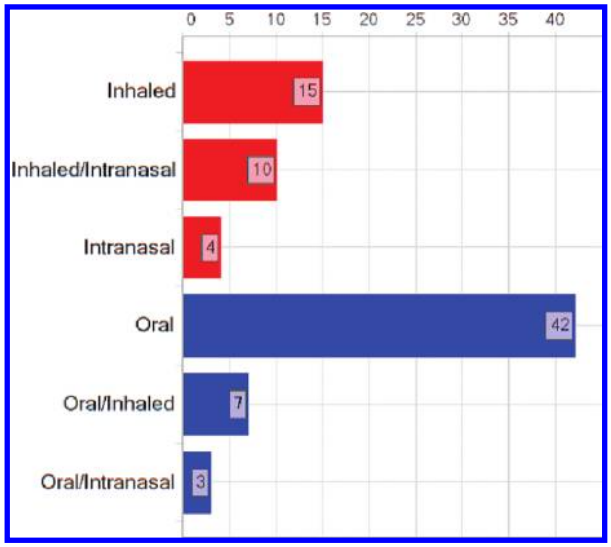

Figure 1. Number of the marketed drugs used in this analysis according to route of administration. Inhaled or intranasal drugs are in red, while those which are administered orally are in blue.

results, together with a discussion of their implications for topical drug design, are reported here.

RESULTS

Drugs Used in the Analysis. A list of 81 currently marketed respiratory drugs was identified from drug databases (GSK Marketed Drugs, PharmaProjects, World Drug Index, IMS Knowledge Link) and used as the basis for this analysis (for a table of structures, see the Supporting Information). Gases used as anesthetics, injected drugs, inhaled antibiotics, peptidic drugs and respiratory drugs administered into the eye (dioxopromethazine) were excluded. Bambuterol, ciclesonide, and oseltamivir are prodrugs. After the specific routes of administration were checked (in Martindale), 42 out of 81 drugs are administered orally *only* (Figure 1). A further 3 can be administered orally and intranasally (giving a running cumulative total of 45/81 respiratory drugs), and a further 7 can be adminstered orally and via the inhaled route (52/81) (Figure 1). There are 10 drugs that are only administered intranasally and via the inhaled route (62/81), a further 15 via the inhaled route only (77/81), and 4 intranasally (81/81) only. In other words, 29 (10 + 15 + 4) out of 81 respiratory drugs are only administered topically for respiratory diseases. Unless otherwise noted, those drugs that can be administered by the oral *and* the intranasal (3) or the oral *and* the inhaled routes (7) figures are grouped in the oral (42) classification (3 + 7+42 = 52 in total).

Mechanisms of action were compiled from the ISIS database records and checked in Martindale. It was not possible to determine the mechanism of action for certain drugs, for example, cough suppressants, mast cell stabilizers, or mucolytics. The most common mechanisms from the complete data set were short-acting β-agonists (SABAs, 20% of the data set), cough suppressants (11%), glucocorticoid agonists (11%), and histamine antagonists (10%). It is noteworthy that the inhaled/intranasal set of drugs are dominated by the glucocorticoid agonists (28%) and SABAs (24%) (Figure 2).

A principal components analysis was carried out using 21 calculated properties including Lipinski type parameters, 5 Abraham descriptors[16] and ACD clogP and ACD clogD 7.4 available from Adamantis (our in-house web portal for accessing in silico properties and ADME models). Classification of the mechanisms of action (Figure 3) suggests that the drug classes typically occupy distinct areas of the plot and possess class specific physicochemical properties. The exception is those drugs classed as mast cell stabilizers, which cover disparate mechanisms and structural classes and are scattered across the plot.

The data comparing various properties of inhaled/intranasal and oral drugs are presented using box plots (Figure 4). Statistical differences were determined using a Tukey Cramer

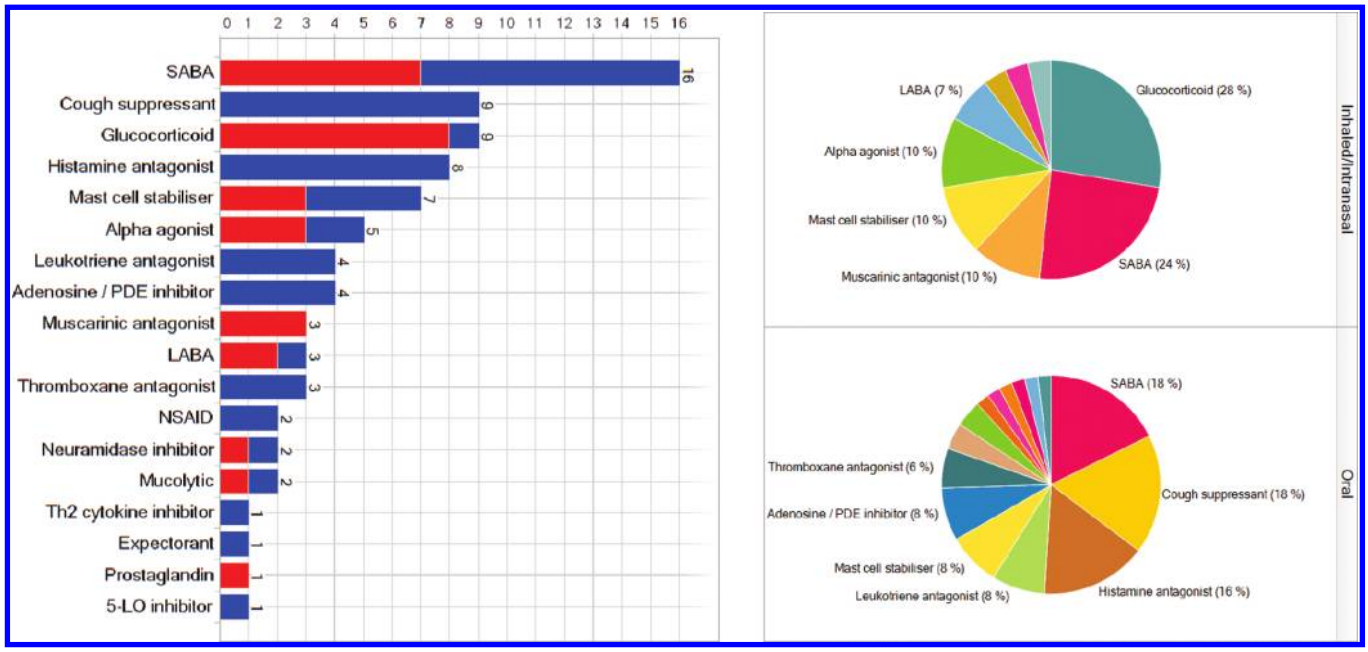

Figure 2. Number of respiratory marketed drugs broken down according to mechanism. SABA = short acting β-agonist, PDE = phosphodiesterase, LABA = long acting β-agonist, NSAID = nonsteroidal anti-inflammatory drug, LO = lipoxygenase. In the left panel, inhaled or intranasal drugs are in red, orally administered drugs are in blue.

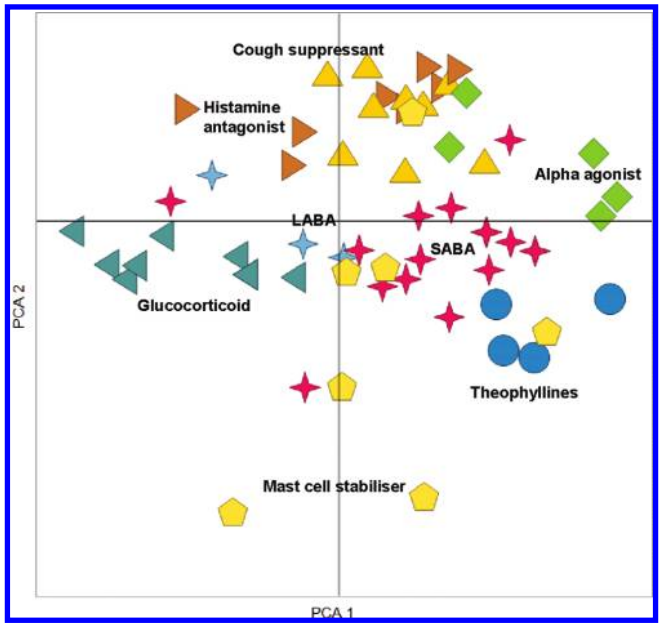

Figure 3. Principal components analysis of respiratory drug physicochemical properties using 19 calculated properties (see the Experimental Section for detail). See the table of Supporting Information for the list of drugs, structures and mechanism of action.

multiple comparison test using the Anova option and the comparison circle approach in Spotfire.[17]

H-Bonding and Polarity. Inhaled/intranasal respiratory drugs have a statistically significant higher mean hydrogen bond donor and acceptor count (Figure 5) compared with respiratory drugs administered by the oral route (8.3 vs 6.0, respectively). By comparison, the average H-bond acceptor and H-bond donor count for all marketed oral drugs is 6.6.[12] Other related physicochemical descriptors that measure H-bonding capacity (polar surface area,[18] Abraham's α and βH parameters[16]) show similar differences (Table 1). Note that this difference is *not* driven by the preponderance of drugs in the glucocorticoid or SABA classes.

Table 1. Comparison of H-Bonding Descriptors for Inhaled/Intranasal and Oral Respiratory Drugs

	HBDs[a]	HBAs[b]	PSA[c]	α[d]	βH[d]
inhaled/intranasal	2.7	5.6	89.2	0.7	2.0
oral	1.5	4.5	59.8	0.4	1.6

[a] Mean number of hydrogen bond donors. [b] Mean number of hydrogen bond acceptors. [c] Mean polar surface area. [d] Mean Abraham parameters.[17]

Molecular Weight. Inhaled/intranasal respiratory drugs have a statistically significant higher mean molecular weight (Figure 6) compared with those administered by the oral route (372.5 vs 306.7, respectively). By comparison, the average molecular weight for all marketed oral drugs is 333.[12] Other "size" descriptors such as heavy atom count or calculated molar refractivity (CMR) show similar differences (Table 2). However, in contrast to H-bonding and polarity, this difference appears to be associated with the glucocorticoid class of inhaled/intranasal drugs. If this class is removed, there is *no* significant difference in molecular weight (325.4 vs 304.8).

Lipophilicity. The average lipophilicity values for respiratory drugs administered via the inhaled/intranasal and oral routes as calculated by Daylight clogP are low with values of 1.7 and 2.5 respectively (Figure 7). Statistically, there is no significant difference between these values nor between the calculated ACD logP or logD values (Table 3). By comparison, the average clogP value for all marketed oral drugs is 2.5.[12] The difference in mean Daylight clogP values does however become statistically significant if the inhaled/intranasal glucocorticoid class is removed with the clogP lowered to 1.2. (There is no statistically significant difference if all the SABAs are removed.)

Ring count and rotatable bond count. There is no statistically significant difference in average ring count (aromatic *and* nonaromatic rings) between respiratory drugs administered via the inhaled/intranasal route (mean value of

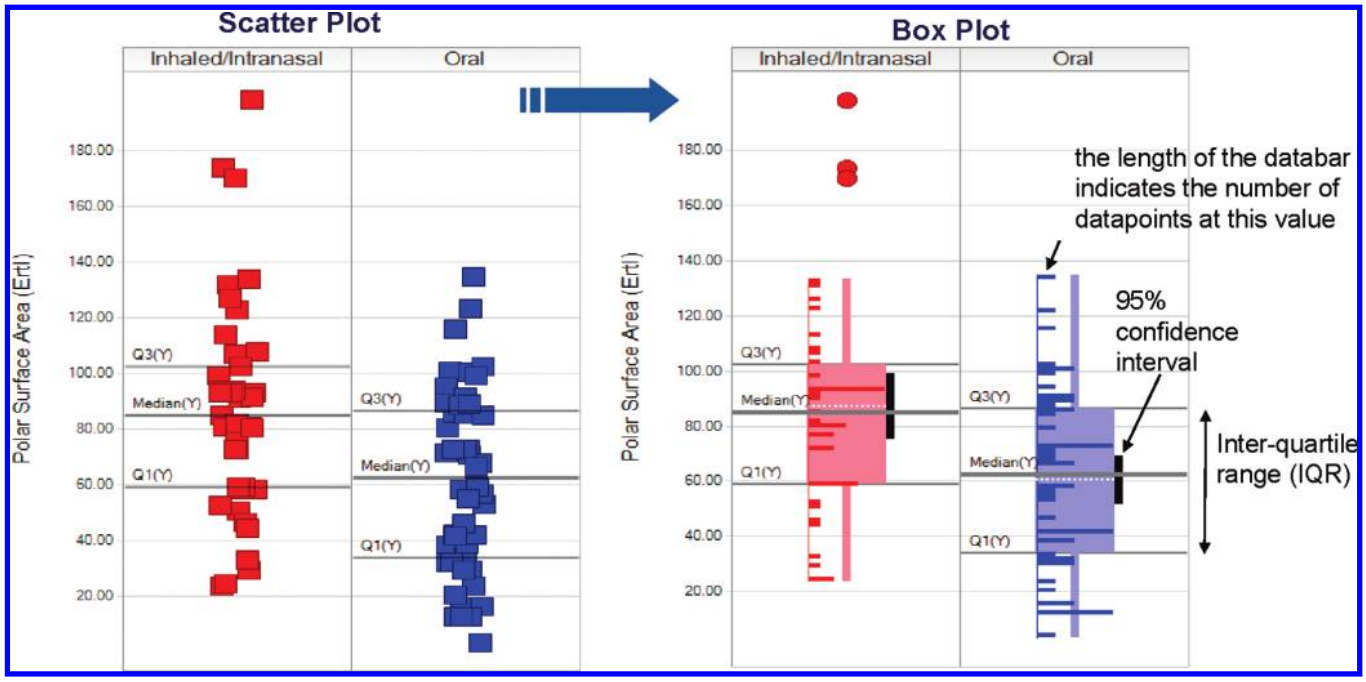

Figure 4. Box plots explained. To provide a clearer presentation of the data, box plots of the data (right-hand panel) rather than the usual scatter plots (left-hand panel), are used. Q1(Y) = quartile 1 dividing line on the *y*-axis and Q3(Y) similarly.

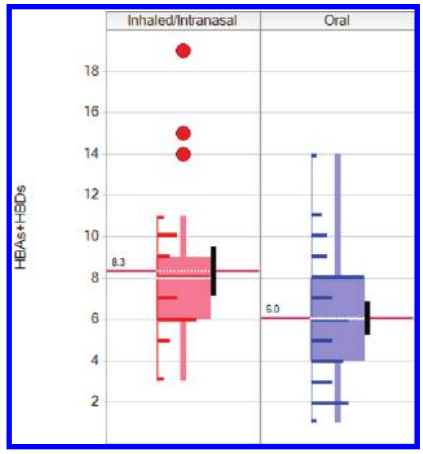

Figure 5. Plot of the sum of H-bond acceptors and donors for inhaled/intranasal and oral respiratory drugs.

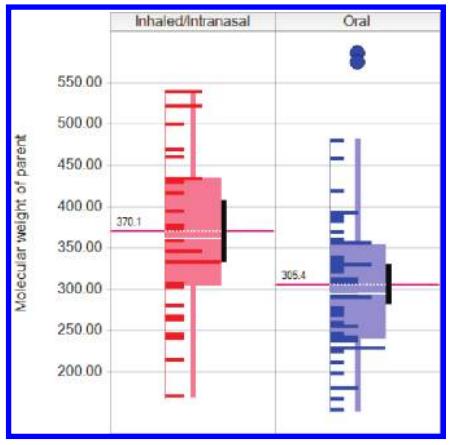

Figure 6. Plot of the molecular weight of the parent for inhaled/intranasal and oral respiratory drugs.

Table 2. Comparison of "Size" Descriptors for Inhaled/Intranasal and Oral Respiratory Drugs

	MWt[a]	heavy atoms[b]	CMR[c]
inhaled/intranasal	370.1	25.9	9.7
oral	305.2	21.5	8.5

[a] Mean molecular weight. [b] Mean heavy atom count (non-hydrogen atoms). [c] Mean calculated molar refractivity.

2.9) and the oral routes (mean value of 2.3) (Figure 8). (Counting aromatic and nonaromatic rings separately does give a significant result).[19] By comparison, the average ring count for marketed oral drugs is 2.7.[11] Similarly there is no statistically significant difference in average rotatable bond count between respiratory drugs administered via the inhaled/intranasal and oral routes (5.1 vs 5.0 respectively) (Figure 8). By comparison, the average rotatable bond count for all marketed oral drugs is 5.9.[9] The mean values do not change when the glucocorticoids or short acting β2 agonists sets are removed.

Inhaled Drugs versus Intranasal Drugs. The data set was reclassified to separate compounds that can be delivered *via* oral, inhaled and intranasal routes. Comparisons similar to those described above for polar surface area, ring count, molecular weight, clogP values, and rotatable bond count, indicate that there are no significant differences between inhaled and intranasal drugs (see the Supporting Information). Comparison of inhaled or intranasal drugs as separate classes with oral drugs show the same differences as described above. The glucocorticoid subclass has the same effects on this data set as seen previously.

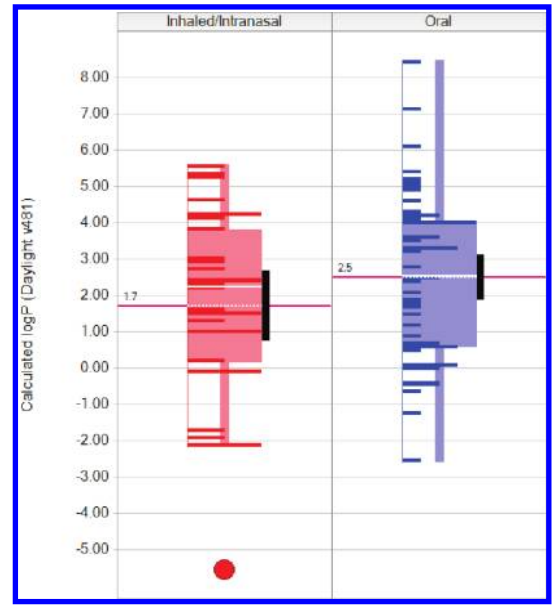

Figure 7. Plot of clogP for inhaled/intranasal and oral respiratory drugs.

Table 3. Mean Lipophilicity Values for Inhaled/Intranasal and Oral Respiratory Drugs

	clogP (day)[a]	clogP (ACD)[b]	clogD (ACD)[c]
inhaled/intranasal	1.7	1.9	0.5
oral	2.5	2.6	1.1

[a] Calculated logP using Daylight software. [b] Calculated logP using ACD/Laboratories software. [c] Calculated logD using ACD softeware.

Comparison of Short-Acting and Long-Acting β2-Agonists. Comparison of the seven inhaled short-acting and three long-acting (LABA) β2-agonists (Figure 9) shows that although the mean molecular weight of LABAs is significantly higher than SABAs, the mean values of their polar surface area, clogP, and ring count are similar.

DISCUSSION

The focus of this study was the analysis of all marketed drugs used for respiratory diseases classified according to oral, intranasal, or inhaled routes of administration. We omitted anesthetics, inhaled antibiotics, and peptidic drugs as being outside our parameters of interest.[20] Pro-drugs were included in the analysis in the pro-drug form (that is, their active metabolites were not also included) on the basis of analyzing what is actually therapeutically administered. The aims were to (i) establish the ranges of calculated physicochemical properties for respiratory drugs; (ii) to study the differences in these properties according to route of administration, and (iii) to establish whether there are inhaled or intranasal design principles. First however, we comment on the structural diversity of the drugs that make up the data set.

Structural Diversity. The principal components analysis highlights that drugs targeted at specific mechanisms tend to have similar structural and, often, physicochemical features. For example, marketed glucocorticoid receptor (GR)

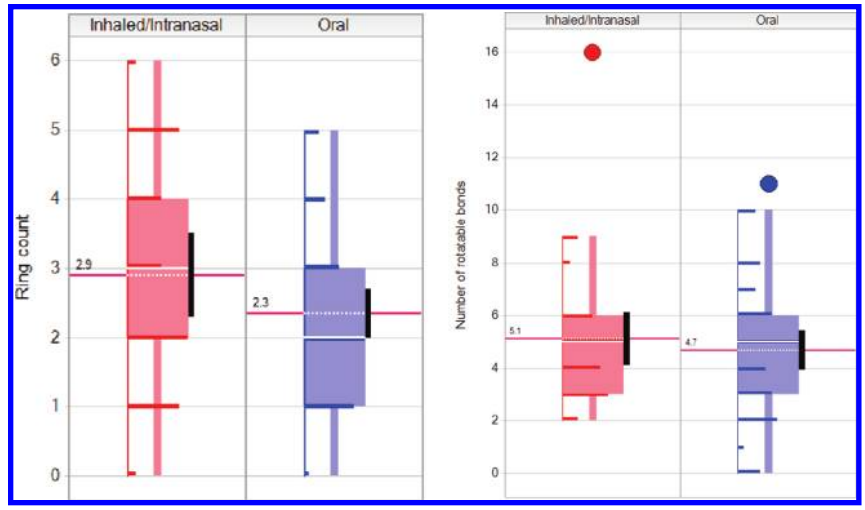

Figure 8. Plots of ring count (left panel) and number of rotatable bonds (right panel) for inhaled/intranasal and oral respiratory drugs.

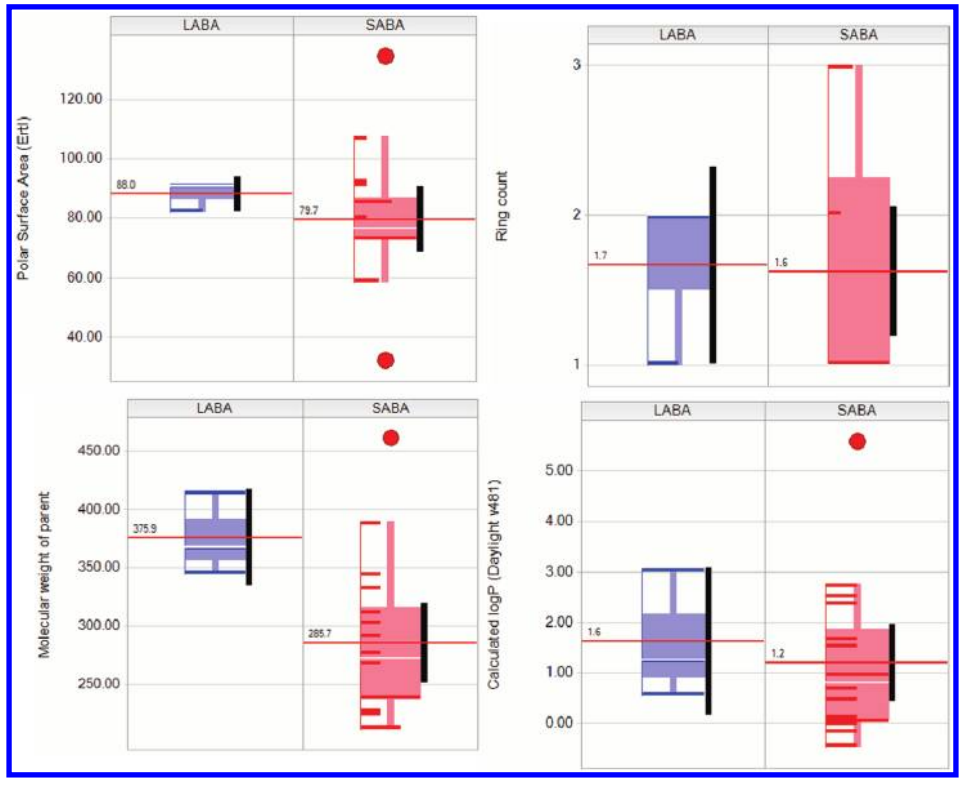

Figure 9. Plot of long-acting vs short-acting β-2 agonists for polar surface area (top left panel), ring count (top right panel), molecular weight of parent (bottom left panel)m and clogP (Daylight) (bottom right panel).

agonists are structurally steroidal; histamine antagonists tend to be lipophilic amines. Several factors are likely to be responsible for this. In part, it is a reflection of the functionality and structural topography of the active site in the receptor/enzyme and whether the receptor/enzyme is intra- or extracellular. Another factor is that in designing a new chemical entity for a particular mechanism, the medicinal chemist is naturally drawn to the structures of endogenous ligands or the structures of marketed drugs as potential starting points. Again GR agonists are an example of this, the first marketed compounds were based on the structure of cortisol (the endogenous ligand for GR), which is steroidal in structure.[21] Since then, all marketed GR agonists have been steroids, and it is only very recently that nonsteroidal GR agonist templates have been discovered, which have yet to reach the market.[22] This raises an interesting question. In the context of designing new inhaled or intranasal drugs with a defined duration of action, does this mean that one set of medicinal chemistry design strategies are likely to be used in one discovery program (say GR agonists where the receptor is located within epithelial cells) whereas another, different, set of design strategies are used in another disease program (say β2 agonists where the receptor is located in the cell membrane in the smooth muscle)? This will be discussed later.

Physicochemical Differences between Inhaled/Intranasal Drugs and Oral Respiratory Drugs. The results of this analysis of respiratory drugs, the average, median, standard deviation, quartile, and 10th and 90th percentile, are sum-

Table 4. Summary of Values for Various Properties for Inhaled/Intranasal Respiratory Drugs (Lightface) and Oral Respiratory Drugs (Boldface)

property	average	stand. dev.[a]	median	Q1[b]	Q3[c]	P10[d]−P90[e]	
HBAs[f] & HBDs[g]	8.31	3.25	8.00	6.00	9.00	5.80–11.60	Inh/Int[h]
	6.04	**2.92**	**6.00**	**4.00**	**8.00**	**2.00–9.90**	**oral**
PSA[i]	89.20	38.65	84.86	59.06	93.81	51.30–135.47	Inh/Int
	60.37	**32.27**	**62.35**	**33.84**	**86.31**	**16.13–98.69**	**oral**
MWt[j]	370	103	360	303	434	243–521	Inh/Int
	305	**91**	**294**	**239**	**354**	**212–392**	**oral**
clogP[k]	1.70	2.65	2.21	0.15	3.80	−1.99–4.74	Inh/Int
	2.50	**2.27**	**3.51**	**0.58**	**4.03**	**−0.03–5.05**	**oral**
clogD[l]	0.48	3.22	0.30	–1.60	3.10	−2.42–4.06	Inh/Int
	1.41	**2.10**	**1.75**	**0.03**	**2.78**	**−1.10–3.70**	**oral**
Rot. bonds[m]	5.10	2.76	5.00	3.00	6.00	3.00–8.20	Inh/Int
	4.69	**2.69**	**5.00**	**2.00**	**6.00**	**2.00–8.00**	**oral**
R count[n]	2.90	1.65	3.00	2.00	4.00	1.00–5.00	Inh/Int
	2.35	**1.27**	**2.00**	**1.00**	**3.00**	**1.00–4.00**	**oral**

[a] Standard deviation. [b] Quartile 1. [c] Quartile 3. [d] 10th percentile. [e] 90th percentile. [f] HBAs = hydrogen bond acceptors. [g] HBDs = hydrogen bond donors. [h] Inh/Int = inhaled/intranasal. [i] PSA = polar surface area.[18] [j] MWt = molecular weight. [k] clogP = calculated logP (Daylight v4.81). [l] clogD = calculated log D (pH 7.4 ACD). [m] Rot. bonds = number of rotatable bonds. [n] R count = ring count.

marized in Table 4.[23] In general, when compared with oral drugs, marketed inhaled/intranasal drugs have

- significantly *higher* H-bonding/polarity measures (although these are still within the usual oral limits)
- a trend toward *lower* lipophilicity (clogP) and related lipophilicity parameters (which becomes significant when glucocorticoids are excluded)
- significantly *higher* molecular weight/size (although this is not significant when glucocorticoids are excluded)
- no difference in rotatable bond and total ring counts.

It is perhaps unsurprising that given inhaled/intranasal drugs possess significantly higher H-bonding/polarity measures there is a trend toward lower lipophilicity. However, with the exception of hydrogen bond acceptor/donor count and rotatable bond count, it can be stated that the 10th−90th percentile range is broader for inhaled/intranasal drugs than for oral respiratory drugs (Table 4). In comparison to the orally administered values, the broader inhaled/intranasal ranges perhaps reflect that a topical compound has only to distribute to a local site of action whereas an oral compound has to distribute systemically, crossing an increased number of membranes and with sufficient drug remaining to have the desired effect after clearance mechanisms. However it is striking how much overlap there is between the physical property ranges of oral and inhaled/intranasal drugs and as described earlier many orally available drugs are also given by the inhaled or intranasal routes. An interesting question (which we will address elsewhere) is whether this overlap is a result of specific design for inhaled/intranasal administration or a consequence of oral drugs being given topically.

As mentioned in the results section, there are no significant differences between inhaled and intranasal respiratory drugs although it is worth repeating that this analysis is based on a small data set of 15 drugs administered only by the inhaled route and 3 drugs administered only by the intranasal route.

Design Principles? This data set is small; just 29 drugs are administered only via the intranasal or inhaled routes. So in contrast with Lipinski, who used over 2000 orally administered drugs as the basis for deriving his "rule of 5",[6] formulating design principles based on these data for intranasal or inhaled drugs is inappropriate.

However several comments on medicinal chemistry design of inhaled drugs can be made. A substantial portion of an inhaled drug is swallowed leading to the possibility of oral absorption and systemic exposure. There is therefore a significant benefit in designing inhaled compounds to occupy the physicochemical space outside that defined by Lipinski's rules as such compounds are more likely to suffer from poor oral absorption. One caveat however, is that substantial regions of this physicochemical space are unprecedented territory for marketed respiratory drugs according to this analysis. It is difficult to assess whether clinical candidates destined for inhaled delivery which contravene Lipinski's rules will therefore carry additional risk of attrition during the development process.[24]

A further area of medicinal chemistry design of inhaled drugs that is worth comment relates to duration of action. A common objective in the design of a respiratory medicine is to prolong its duration of action. This may be achieved in several ways. One way is to adjust the kinetics of the binding of the compound to its target such that the off-rate is slow.[25] However this approach may have limited use as designing particular kinetic profiles into compounds is often difficult. Another way, which may facilitate increased duration of action, is to prolong the retention of the compound in the lung or, in other words, to retard its rate of absorption from the lung. This is often achieved through manipulation of the compound's physicochemical properties. On the basis of numerous studies,[26,27] this is often achieved by increasing the molecular weight or the lipophilicity. Salmeterol (clogD 1.2, clogP (Daylight) 3.06. molecular weight 416) is an example where a longer acting β-agonist (LABA) has increased lipophilicity over a shorter acting β-agonist such as salbutamol (clogD −1.8, clogP 0.06, molecular weight 239), although there are clearly many other factors that might contribute to salmeterol's extended duration of action.[28] In contrast, formeterol and bambuterol are LABA's (with clogD values of 0.1 and −1.1, clogP values of 1.26 and 0.56, and molecular weights of 344 and 368 respectively), which have a long duration of action but with significantly lower lipophilicity and molecular weight when compared with salmeterol. In fact, from the limited set of marketed LABAs (3) and SABAs (16), the LABAs have higher molecular weight than SABAs, but similar polarity, lipophilicity and ring counts (Figure 9). Nonetheless, in the preclinical phase, the literature ascribes increased duration in the lung of

potential LABAs to increased lipophilicity[14] and this strategy[29−32] has been shown to lead to extended duration of action in animal models.

Decreased solubility (and also slow dissolution) is another physicochemical attribute which is suggested to increase lung retention and thence duration of action. In fact decreased solubility is often (although not always) a consequence of increased lipophilicity.[33] Anti-inflammatory glucocorticoid agonists such as fluticasone propionate have very low aqueous solubility (~100 ng/mL[3,34]), are reasonably lipophilic (Daylight clogP 3.8) and, as microcrystals, take a long time to dissolve in human bronchial fluid (>8 h).[35] Thus fluticasone propionate has a reasonably long mean absorption time of 5−7 h from the lung which has been correlated with greater pulmonary residence time.[36]

From our own work with a series of highly polar zanamivir (Relenza) derivatives with grossly similar physicochemical properties, dramatic increases in the concentrations of compounds in rat lungs correlated with significantly reduced aqueous solubility and delivered very long durations of action.[27]

These approaches to extended duration of action/lung retention illustrate one advantage of topical lung delivery over oral delivery where the consequences of increasing lipophilicity and/or significantly reducing aqueous solubility can severely attenuate oral bioavailability.

CONCLUSION

This analysis of 81 marketed respiratory drugs suggests that inhaled/intranasal administered compounds have

- significantly higher hydrogen bonding and polar surface area
- significantly higher molecular weight (although the significance disappears if glucocorticoids are excluded)
- a trend toward lower lipophilicity (which becomes significant if glucocorticoids are excluded)
- no difference in rotatable bond or total ring count

when compared with oral compounds. Further, although the data set is small, LABAs have higher molecular weight than SABAs, but have similar polarity, lipophilicity and total ring count. Using these physicochemical parameters as medicinal chemistry design principles for inhaled/intranasal drug discovery is inappropriate because of the small size of the data set. However, there are advantages in deliberately contravening Lipinski's rules to minimize the risk of systemic exposure occurring through oral absorption following the swallowing of the majority of an inhaled/intranasal dose. Further, it is clear there are medicinal chemistry design principles which are particular to individual mechanistic classes; we will review this in more detail elsewhere.

EXPERIMENTAL SECTION

Identification of the Drugs Used in This Analysis. The list of marketed respiratory drugs was constructed from the following searches. (i) A GSK in-house database MARKETED_DRUGS_GSKCHEM.DB ISIS database was searched using RESPIRATORY in Major Therapeutic Class field; (ii) PHARMASTRUCTURES (PJB.DB) ISIS database (PJB Publications Ltd., Richmond, Surrey UK) was searched using Antiasthma in ACT1 field + "L" in Status field; (iii) WORLD DRUG INDEX (WDI-CBIS.DB) ISIS database (Thomson Scientific) searched using %RESPIRATORY% in Indications/usage field; (iv) IMS KNOWLEDGE LINK (IMS Health Inc.), therapeutic code R (Respiratory System drugs).

Chemical structures were retrieved from the World Drug Index (Thomson Scientific) or Available Chemicals Directory 2007.2 (MDL Information Systems Inc.) using their CAS numbers. The full list of drugs used in this analysis is provided in the Supporting Information.

Principal Components Analysis. The principal components analysis was carried out in Spotfire using the following calculated molecular properties: molecular weight, clogP (Daylight v4.8.1), hydrogen bond acceptors (as defined by Lipinski[6]),hydrogen bond donors (as defined by Lipinski[6]), polar surface area,[18] molar volume (Schrodinger), number of aromatic rings, number of nonaromatic rings, number of halogen groups, number of heavy (non-hydrogen) atoms, number of negatively ionisable groups, number of positively ionisable groups, number of rotatable bonds, calculated molar refractivity (Daylight v4.8.1), clogP (ACD v8.0), clogD7.4 (ACD v8.0), and α, βH, π, R2,and Vx Abraham descriptors.[16]

Box Plots. Box plots were generated in Spotfire DXP 2.0 or DecisionSite 8.2.1. Statistical significance was determined using (i) the Tukey Cramer multiple comparison test visualized by the comparison circle approach in DecisionSite 8.2.1[37,38] or (ii) the Anova option in the column relationships feature in DecisionSite 8.2.1 (or data relationships feature in DXP 2.0).

Polar Surface Area. Polar surface area was calculated by the method of Ertl et al.[18]

Lipophilicity. LogP values were calculated using ACD prediction algorithm (version 8.0) and Daylight prediction algorithm (version 4.81). LogD values were calculated using ACD.

Ring Count and Number of Rotatable Bonds. Ring count and number of rotatable bonds were calculated using in-house algorithms.

Intranasal Only Drugs. There are only four intranasal only drugs in this analysis, one mast cell stabilizer (spaglumic acid) and three α-agonists (oxymetazoline, phenylephrine, and xylometazoline).

Long-Acting β-Agonists. The three β-agonists that are classified as long acting are bambuterol, formeterol, and salmeterol.

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Supporting Information Available: Full details of the structures of the drugs used in this analysis are provide together with other box plots as detailed in the main text. This information is available free of charge via the Internet at http://pubs.acs.org.

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