The Physicochemical Challenges of Designing Multiple Ligands

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Compounds designed to bind more than one target can provide a therapeutic benefit relative to highly target-selective ligands. The physicochemical properties of designed multiple ligands were found to be less druglike than those for preclinical compounds in general. These properties are controlled by the superfamily to which the targets belong and the lead discovery strategy that was followed. The properties for peptide G-protein-coupled receptor (GPCR) ligands were the least favorable for oral delivery, whereas transporter, monoamine GPCR, and oxidase ligands were the most druglike. The lead discovery strategy, framework combination or screening, exerts a profound influence on the property values. Combining the frameworks from two selective ligands often results in large, complex dual ligands, but druglike ligands can be achieved if the degree of framework overlap is maximized and the size of the selective ligands minimized. For some target combinations, a screening approach may provide a route to smaller, less complex leads.

Introduction

Despite record investment in drug discovery research by private and public institutions over the past few decades, many diseases remain inadequately treated. Recently, there has been a growing interest in the design of ligands that act specifically on multiple targets ("targeted polypharmacology") with the aim of enhancing efficacy or to improving safety relative to drugs that address only a single target. Compounds that are rationally designed with a well-defined multitarget profile have been classified as designed multiple ligands (DMLs) to distinguish them from nonselective (or "dirty") drugs that are discovered serendipitously and that often possess off-target activities irrelevant to the disease and that frequently give rise to deleterious side effects.[1,2] DMLs are of particular relevance to highly complex diseases, such as central nervous system disorders and cancer, where many reductionist single-target approaches have proved to be largely fruitless.[3,4]

It is fair to say that the field of designing ligands that possess predefined, well-balanced multitarget profiles is still in its infancy. Nonetheless, we felt that it would still be instructive to analyze the examples that have been published thus far to understand which factors have most heavily influenced success or lack of success in the area. It is well-known that physicochemical properties can have profound effects on the in vivo behavior of drugs, and these have been expressed in recent years in a number of seminal papers.[5−7] The current paper examines how the physicochemical properties of multiple ligands depend on both the lead discovery strategy that is followed and the protein superfamily to which the targets belong.

A database of 281 multiple ligands reported in the primary medicinal chemistry literature was compiled. For 264 of these ligands, the structures of the starting compound(s) were also available enabling an analysis of the changes in the physicochemical properties that occurred during the optimization process. The full database was subdivided into subsets on the basis of the target family enabling an analysis of the influence of target family on the properties (Figure 1).

We identified two distinctly different lead discovery strategies through which the DMLs present in the database were derived (Figure 2). The most common strategy was to start with a single molecule that, in most cases, had good activity at one of the targets of interest and at least some minimal activity at the other target(s). The starting compound was usually obtained via focused, or less commonly random, screening. During optimization, analogues were made in order to balance the desired activities at an appropriate level and, if necessary, to remove any undesired cross-reactivity. The second design strategy started with two compounds, one of which bound with high selectively to one of the targets and the other with high selectively to the other target. In this case, the first goal was to incorporate both activities into a single lead molecule by linking, fusing, or merging the frameworks of the two selective molecules (Figure 2). This is a knowledge-based combination strategy that effectively leverages SAR knowledge from historical selective ligand projects.

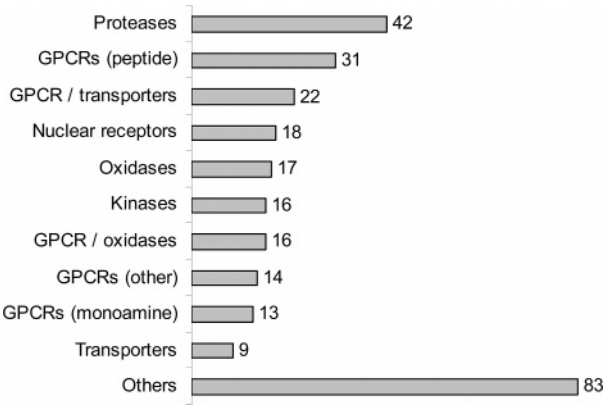

Figure 1. The main target families present in the DML database are also those of greatest interest in drug discovery. The number shown is the number of optimized compounds for each subgroup with these target families representing 70% of the full database. Where a single family is given, all targets in the combination belong to this same family. Where two families are given, there is at least one target in the combination from each family.

For each optimized compound from the full DML set, the main target family subsets and the discovery strategy subsets, six physicochemical properties were calculated: molecular weight (MW), cLogP, polar surface area (PSA), the number of

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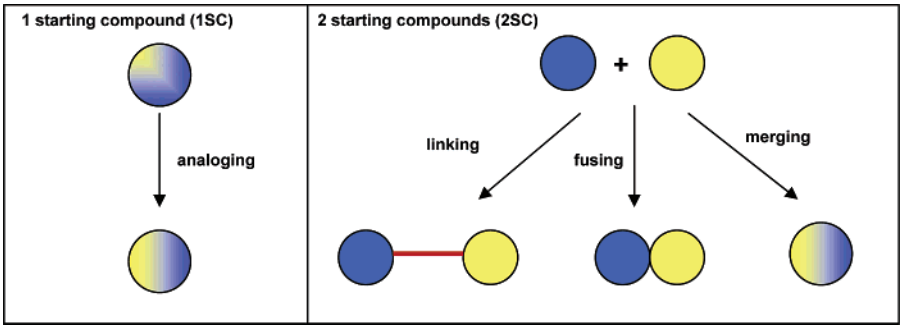

Figure 2. There are two principal strategies for generating ligands with multiple activity, represented by the blue color for the intensity of the first activity and yellow for the second activity. A single starting compound (1SC) approach may be followed with such compounds obtained via focused or random screening. Although already possessing multiple activity, analoging is required to balance the activities. Alternatively, a more rational, knowledge-based strategy may be followed whereby the frameworks from two selective starting compounds (2SC) may be linked, fused, or merged.

Table 1. Molecular Weight (MW) Data[a]

target family subset	SC[b] median (mean) [*N*[e]]	OC[c] median (mean) [*N*[e]]	PC[d] median (mean) [*N*[e]]	Wilcoxon *p* value[f]	SCOPE OC[c] median (mean)	median difference from SCOPE set[g]	*p* value (difference from SCOPE set)[h]
full DML set	377 (398) [264]	450 (503) [281]	64 (110) [264]	**0**	422 (435)	37	**0**
GPCRs (all)	415 (455) [57]	549.5 (573) [58]	72 (121) [57]	**0**	433 (440)	116	**0**
GPCRs (monoamine)	360 (324) [12]	397 (410) [13]	73 (87) [12]	**0.009**	375 (377)	35	0.1265
GPCRs (peptide)	512 (509) [31]	636 (638) [31]	72 (129) [31]	**0**	510 (513)	123	**0**
GPCR/oxidases	400 (395) [16]	478 (502) [16]	99 (107) [16]	**0.014**			
GPCR/transporters	358 (356) [22]	426 (419) [22]	45 (63) [22]	**0**			
kinases	381 (411) [12]	523 (503) [16]	92 (103) [12]	**0.004**	392 (406)	107	**0**
nuclear receptors	383 (418) [15]	463 (482) [18]	55 (63) [15]	**0.007**	421 (431)	47	**0.0339**
oxidases	358 (346) [17]	352 (364) [17]	24 (17) [17]	0.118	357 (355)	2	0.9206
proteases	420 (468) [36]	454 (617) [42]	37 (180) [36]	**0**	467 (468)	−5	0.7862
transporters	297 (307) [9]	307 (331) [9]	28 (24) [9]	0.076	325 (335)	−5	0.8757

[a] Bold text shows significance at the 95% confidence level. [b] SC, starting compound. [c] OC, optimized compound. [d] PC, property change. [e] *N*, number of data points. [f] *p* value from 1-sample Wilcoxon signed rank test of the median. [g] Mann−Whitney point estimate for the difference in the population medians. [h] Mann−Whitney *p* value.

hydrogen bond acceptors (HBA), the number of hydrogen bond donors (HBD), and the number of rotatable bonds (RB).

Results

(A) Target Family Based Property Analysis. Molecular Weight. The median MW for the full set of optimized compounds was 450 (mean 503), and the median increase in MW during optimization was 64 (mean 110) (Table 1). We found considerable differences between the 11 target family subsets with the median ranging from 636 for peptide G-protein-coupled receptors (GPCRs) to 307 for transporters. The increase during optimization ranged from an increase of 99 for the GPCR/oxidase ligands to 24 for the oxidase ligands.

The target family subsets were divided into clusters by determining whether the median MWs of the optimized compounds showed statistically significant differences from each other (Figure 3).[8] In all cases, the target families within the same cluster were not significantly different from each other and in most cases were significantly different from the target families in the clusters above and below.[9] The uppermost cluster contained just one target family, the peptide GPCRs, with by far the highest median MW. This was followed by a large cluster containing the optimized compounds for proteases, nuclear receptors, GPCR/oxidases, the full set of GPCRs, and kinases. Two further clusters were identified, the first containing the monoamine GPCR and GPCR/transporter ligands, and the second containing the oxidase and transporter ligands with the lowest median MWs of all.

The median MW for the DMLs (450) was considerably higher than the median MW for oral drugs of 322 reported by Vieth et al.[10] However, since the DMLs were almost exclusively preclinical compounds, it was more relevant to make comparisons with other databases of preclinical compounds. Vieth et al. reported a median of 415 (mean of 448) for preclinical compounds, so clearly DMLs as a group appear to be considerably larger. To make a more detailed comparison across the individual target families, we compared the DML MWs with the MWs for those same target families present in a proprietary database (called SCOPE) of preclinical compounds reported in the medicinal chemistry literature.[11] The median MW during optimization for the full set of DMLs (450) was higher than that for the SCOPE ligands (422). The median MW increase during optimization for the full set of DMLs, 64, was broadly similar to the increases of 69 and 42 reported by Oprea[6] and Hann,[7] respectively, for a series of lead-drug pairs. Again, it was felt that it would be more relevant to draw a comparison with the predominantly preclinical compounds in the SCOPE database. For the SCOPE ligands, the median MW increase was 30, which was significantly lower than that for the full DML set (64).

The median MWs were higher for most of the DML target families compared to the comparable SCOPE target families except for oxidases, proteases, and transporters where there was no statistically significant difference between the two sets. The largest difference between the two sets was found for the full set of GPCRs, the peptide GPCRs, and the kinases. These differences were due to a combination of the larger size of the starting compounds and a larger increase during optimization for the DMLs.

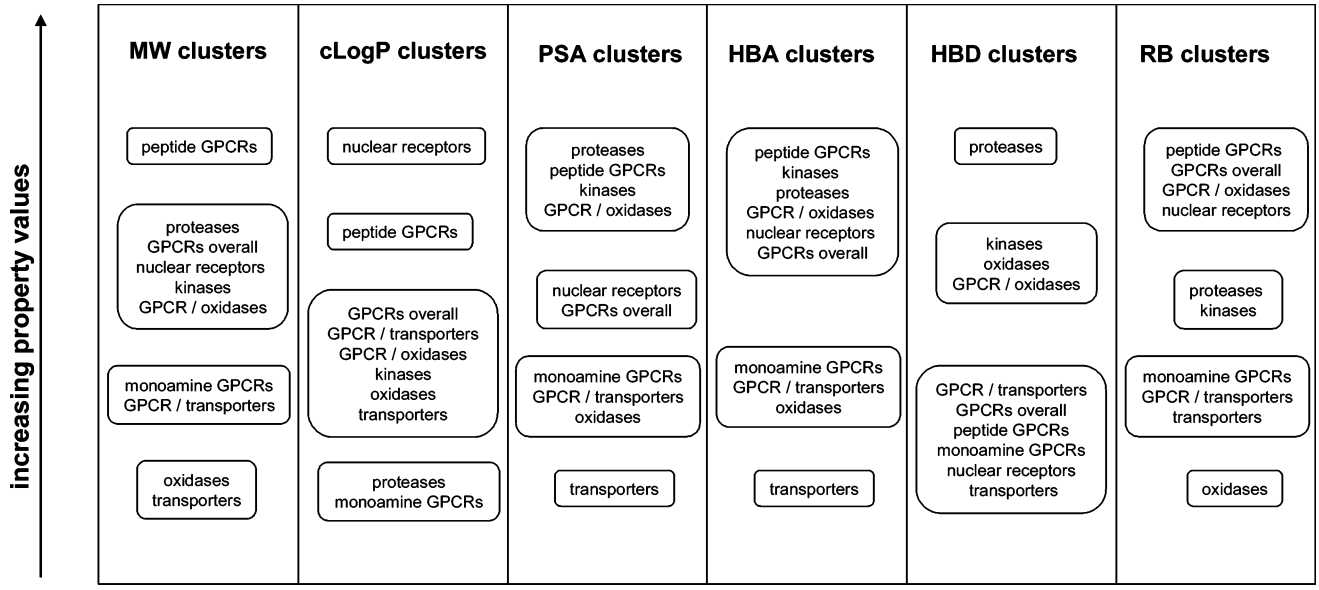

Figure 3. Classification of target families on the basis of six physicochemical properties for their optimized ligands: MW, cLogP, polar surface area (PSA), the number of hydrogen bond acceptors (HBA), the number of hydrogen bond donors (HBD), and the number of rotatable bonds (RB).

Table 2. cLogP Data[a]

target family subset	SC[b] median (mean) [*N*[e]]	OC[c] median (mean) [*N*[e]]	PC[d] median (mean) [*N*[e]]	Wilcoxon *p* value[f]	SCOPE OC[c] median (mean)	median difference from SCOPE set[g]	*p* value (difference from SCOPE set)[h]
full DML set	3.5 (3.6) [264]	4.4 (4.2) [281]	0.7 (0.7) [264]	**0**	4 (4)	0.3	**0.0425**
GPCRs (all)	4.4 (4.1) [57]	4.8 (4.8) [58]	0.9 (0.7) [57]	**0.001**	4.4 (4.3)	0.4	0.1149
GPCRs (monoamine)	2.55 (2.6) [12]	3.4 (3.6) [13]	1.35 (1.1) [12]	**0.013**	3.8 (3.7)	−0.1	0.6557
GPCRs (peptide)	5.1 (5) [31]	5.7 (5.6) [31]	0.7 (0.6) [31]	0.086	5 (5)	0.6	0.0556
GPCR/oxidases	4.5 (4.1) [16]	4.8 (4.9) [16]	0.6 (0.9) [16]	0.074			
GPCR/transporters	3.65 (3.7) [22]	4.6 (4.5) [22]	0.65 (0.9) [22]	**0.007**			
kinases	4.8 (4.7) [12]	4.85 (4.4) [16]	−0.25 −0.1) [12]	0.969	3.8 (3.5)	0.9	**0.0417**
nuclear receptors	6.2 (6) [15]	6.9 (6.9) [18]	0.7 (1.1) [15]	0.065	5.1 (5.3)	1.7	**0.0004**
oxidases	4.6 (4.7) [17]	4.5 (4.3) [17]	−0.5 (−0.4) [17]	0.185	4.2 (4.2)	0.2	0.7459
proteases	2.5 (2.2) [36]	3.05 (3.2) [42]	0.9 (1) [36]	**0.004**	3.2 (3)	0.2	0.4454
transporters	4.3 (4.1) [9]	4.2 (4.1) [9]	−0.3 (0.1) [9]	0.767	3.7 (4)	0.4	0.4206

[a] Bold text shows significance at the 95% confidence level. [b] SC, starting compound. [c] OC, optimized compound. [d] PC, property change. [e] *N*, number of datapoints. [f] *p* value from 1-sample Wilcoxon signed rank test of the median. [g] Mann−Whitney point estimate for the difference in the population medians. [h] Mann−Whitney *p* value.

cLogP. The median log *P* value for the full set of optimized compounds of the 281 DMLs was 4.4 (mean 4.2), and the median change in cLogP during optimization was +0.7 (mean +0.7) (Table 2). There were considerable differences between target families, with nuclear receptor ligands being the most lipophilic by far (median 6.9) and protease DMLs the least lipophilic. The largest increase in lipophilicity during optimization was shown by the monoamine GPCR ligands, whereas oxidase, kinase, and transporter ligands showed no change.

The target families were clustered in a similar manner as for the MW above (Figure 3).[9] The nuclear receptor ligands had significant higher cLogP values than any of the other target families, but this finding has to be qualified by the fact that all the examples were peroxisome proliferator-activated receptor (PPAR) ligands. Next came a cluster containing the full set of GPCRs, GPCR/transporters, transporters, GPCR/oxidases, and oxidases. Occupying the lowest lipophilicity cluster were the protease and monoamine GPCR ligands.

When the DML data were compared with the SCOPE data, it was apparent that cLogP was higher for DMLs by 0.4. This was due to a much larger increase in cLogP during optimization, since the lipophilicity was no different for the starting compounds. For the peptide GPCR, nuclear receptor, and kinase subsets, the DMLs were significantly more lipophilic.

PSA. The median PSA of the full set of DML optimized compounds was 67 Å^2, with a median increase of 9 during optimization (Table 3). The ligands with the highest PSA values were those for the proteases (87 Å^2), and once again, the transporter ligands had the lowest values (19 Å^2). There was a significant increase in PSA for the full set of GPCRs, peptide GPCR, kinase, nuclear receptor, and GPCR/oxidase families. Interestingly, the high PSA values for the protease optimized compounds were due entirely to the high PSA of the starting compounds and there was no evidence for an increase during optimization.

When the target families were compared directly with each other, there was no significant difference between the peptide GPCR, protease, kinase, and GPCR/oxidase families, so these formed the uppermost cluster (Figure 3).[9] The monoamine GPCR, GPCR/transporter, and oxidase families were equivalent in terms of PSA but had lower values than the nuclear receptor and full set of GPCRs subsets. The transporters had a significant lower PSA than any of the other subsets.

The median PSA for the DMLs was higher than that for the SCOPE ligands by 9 Å, and this was predominantly due to a larger increase during optimization.

HBA. The analysis showed that the DMLs possessed on average five HBAs and that the median increase was one HBA

Table 3. Polar Surface Area (PSA) Data[a]

target family subset	SC[b] median (mean) [*N*[e]]	OC[c] median (mean) [*N*[e]]	PC[d] median (mean) [*N*[e]]	Wilcoxon *p* value[f]	SCOPE OC[c] median (mean)	median difference from SCOPE set[g]	*p* value (difference from SCOPE set)[h]
full DML set	54 (60) [264]	67 (80) [281]	9 (21) [264]	**0**	58 (63)	9	**0**
GPCRs (all)	49 (53) [57]	65 (74) [58]	10 (21) [57]	**0**	51 (56)	12.	**0.0034**
GPCRs (monoamine)	30 (33) [12]	35 (42) [13]	2 (9) [12]	0.139	41 (43)	−1	0.8018
GPCRs (peptide)	56 (58) [31]	79 (83) [31]	13 (24) [31]	**0**	62 (65)	13	**0.0139**
GPCR/oxidases	62 (61) [16]	75 (77) [16]	13 (16) [16]	**0.008**			
GPCR/transporters	40 (41) [22]	42 (46) [22]	4 (4) [22]	0.173			
kinases	62 (55) [12]	75 (78) [16]	16 (26) [12]	**0.006**	65 (71)	10	**0.036**
nuclear receptors	58 (53) [15]	62 (65) [18]	4 (12) [15]	**0.015**	52 (54)	12	**0.0235**
oxidases	42 (49) [17]	49 (52) [17]	0 (3) [17]	0.534	43 (46)	6	0.2673
proteases	79 (100) [36]	87 (136) [42]	0 (46) [36]	**0.028**	89 (90)	−5	0.3403
transporters	19 (21) [9]	19 (24) [9]	0 (3) [9]	0.834	22 (28)	−1	0.7903

[a] Bold text shows significance at the 95% confidence level. [b] SC, starting compound. [c] OC, optimized compound. [d] PC, property change. [e] *N*, number of data points. [f] *p* value from 1-sample Wilcoxon signed rank test of the median. [g] Mann−Whitney point estimate for the difference in the population medians. [h] Mann−Whitney *p* value.

Table 4. Hydrogen Bond Acceptor (HBA) Data[a]

target family subset	SC[b] median (mean) [*N*[e]]	OC[c] median (mean) [*N*[e]]	PC[d] median (mean) [*N*[e]]	Wilcoxon *p* value[f]	SCOPE OC[c] median (mean)	median difference from SCOPE set[g]	*p* value (difference from SCOPE set)[h]
full DML set	4 (4.4) [264]	5 (5.9) [281]	1 (1.6) [264]	**0**	4 (4.4)	1	**0**
GPCRs (all)	4 (4.1) [57]	5 (5.6) [58]	1 (1.5) [57]	**0**	4 (4.2)	1	**0**
GPCRs (monoamine)	2.5 (2.7) [12]	3 (3.3) [13]	0.5 (0.6) [12]	0.063	3 (3.4)	0	0.9632
GPCRs (peptide)	5 (4.5) [31]	6 (6.3) [31]	1 (1.8) [31]	**0**	5 (4.8)	1	**0.0005**
GPCR/oxidases	4 (4.3) [16]	5 (5.7) [16]	1 (1.3) [16]	**0.014**			
GPCR/transporters	3 (3.3) [22]	3 (3.7) [22]	0 (0.4) [22]	0.069			
kinases	4.5 (4.4) [12]	6 (5.7) [16]	1.5 (1.5) [12]	**0.025**	4 (4.6)	1	**0.0036**
nuclear receptors	5 (4.5) [15]	5 (5.6) [18]	1 (1.2) [15]	**0.009**	3 (3.8)	2	**0.0002**
oxidases	3 (3.2) [17]	3 (3.5) [17]	0 (0.3) [17]	0.327	3 (3.3)	0	0.4851
proteases	4 (6.8) [36]	5 (9.6) [42]	0 (3.6) [36]	**0.032**	5 (5.4)	0	0.2594
transporters	2 (2.3) [9]	2 (2.2) [9]	0 (−0.1) [9]	0.855	3 (2.6)	0	0.3897

[a] Bold text shows significance at the 95% confidence level. [b] SC, starting compound. [c] OC, optimized compound. [d] PC, property change. [e] *N*, number of datapoints. [f] *p* value from 1-sample Wilcoxon signed rank test of the median. [g] Mann−Whitney point estimate for the difference in the population medians. [h] Mann−Whitney *p* value.

Table 5. Hydrogen Bond Donor (HBD) Data[a]

target family subset	SC[b] median (mean) [*N*[e]]	OC[c] median (mean) [*N*[e]]	PC[d] median (mean) [*N*[e]]	Wilcoxon *p* value[f]	SCOPE OC[c] median (mean)	median difference from SCOPE set[g]	*p* value (difference from SCOPE set)[h]
full DML set	2 (4.3) [264]	2 (2.2) [281]	0 (−2.1) [264]	0.139	1 (1.9)	0	**0.0227**
GPCRs (all)	1 (4) [57]	1 (1.9) [58]	0 (−2.1) [57]	0.915	1 (1.5)	0	0.6734
GPCRs (monoamine)	1.75 (7.6) [12]	1 (1.1) [13]	−0.75 (−6.4) [12]	**0.025**	1 (1.2)	0	0.8253
GPCRs (peptide)	1 (1.5) [31]	1 (2) [31]	0 (0.6) [31]	0.104	1 (1.7)	0	0.9358
GPCR/oxidases	1.5 (1.7) [16]	2 (1.8) [16]	0 (0.1) [16]	0.683			
GPCR/transporters	2 (1.7) [22]	2 (1.5) [22]	0 (−0.2) [22]	0.532			
kinases	2 (12.1) [12]	2 (2.1) [16]	0 (−9.9) [12]	0.5	2 (2.6)	0	0.2177
nuclear receptors	1 (7.4) [15]	1 (1.1) [18]	0 (−6.3) [15]	0.225	1 (1.2)	0	0.7603
oxidases	1.5 (1.7) [17]	2 (1.8) [17]	0 (0.1) [17]	0.838	1 (1)	1	**0.0054**
proteases	3 (7.4) [36]	3 (4.1) [42]	0 (−3.1) [36]	0.327	3 (3.3)	0	0.7535
transporters	1 (0.7) [9]	1 (1) [9]	0 (0.3) [9]	0.181	1 (0.9)	0	0.5163

[a] Bold text shows significance at the 95% confidence level. [b] SC, starting compound. [c] OC, optimized compound. [d] PC, property change. [e] *N*, number of data points. [f] *p* value from 1-sample Wilcoxon signed rank test of the median. [g] Mann−Whitney point estimate for the difference in the population medians. [h] Mann−Whitney *p* value.

(Table 4). During optimization, the number of HBAs increased significantly for five subsets, the full set of GPCRs, peptide GPCR, nuclear receptor, kinase, and GPCR/oxidase ligands. There was no statistically significant difference between the peptide GPCRs, kinases, proteases, GPCR/oxidases, nuclear receptors, and the full set of GPCRs, so these can be regarded as constituting the uppermost cluster.[9] Once more, the transporter ligands had a uniquely low median value for the number of acceptors (two). The number of HBAs for the DMLs was higher than for the SCOPE ligands, and this was found to be due to a higher increase for the DMLs during optimization. This trend was maintained with significance for four of the subsets, the full set of GPCRs, kinases, nuclear receptors, and peptide GPCRs.

HBD. The protease optimized compounds had the highest number of donors (median 3) (Table 5). Comparison of the protease subset with the other subsets showed that this target family constituted a statistically distinct upper cluster.[9] Below came the GPCR/oxidase, oxidase, and kinase subsets with the remaining target families constituting the lowest cluster (Figure 3). There was no statistically significant increase in the number of HBDs for any of the individual target families. Monoamine

Table 6. Rotatable Bond (RB) Data[a]

target family subset	SC[b] median (mean) [*N*[e]]	OC[c] median (mean) [*N*[e]]	PC[d] median (mean) [*N*[e]]	Wilcoxon *p* value[f]	SCOPE OC[c] median (mean)	median difference from SCOPE set[g]	*p* value (difference from SCOPE set)[h]
full DML set	6 (6.6) [264]	8 (9) [281]	1 (2.5) [264]	**0**	6 (6.7)	2	**0**
GPCRs (all)	7 (6.9) [57]	9 (9.5) [58]	1.5 (2.7) [57]	**0**	6 (6.6)	3	**0**
GPCRs (monoamine)	5 (5.2) [12]	6 (6.6) [13]	1.25 (1.5) [12]	**0.033**	5 (5.2)	1	0.0557
GPCRs (peptide)	8 (7.5) [31]	10 (10.4) [31]	1 (2.9) [31]	**0**	7 (7.9)	3	**0.0003**
GPCR/oxidases	7 (8) [16]	10 (10.6) [16]	2.5 (2.6) [16]	0.028			
GPCR/transporters	5.25 (5.6) [22]	6 (5.9) [22]	0 (0.3) [22]	0.594			
kinases	5 (6.1) [12]	7 (8.2) [16]	1 (1.8) [12]	0.059	5 (5.5)	2	**0.0005**
nuclear receptors	10 (9.3) [15]	10 (10.4) [18]	1 (1.3) [15]	**0.023**	4 (5.3)	6	**0**
oxidases	4 (4.4) [17]	3 (4.3) [17]	0 (−0.1) [17]	0.859	4 (4.2)	0	0.7696
proteases	7 (8.7) [36]	7.5 (13.3) [42]	1 (5.5) [36]	**0.012**	8 (8.2)	1	0.3322
transporters	6 (5.4) [9]	6 (5.4) [9]	0 (0) [9]	1	3 (4.5)	1	0.197

[a] Bold text shows significance at the 95% confidence level. [b] SC, starting compound. [c] OC, optimized compound. [d] PC, property change. [e] *N*, number of datapoints. [f] *p* value from 1-sample Wilcoxon signed rank test of the median. [g] Mann−Whitney point estimate for the difference in the population medians. [h] Mann−Whitney *p* value.

Table 7. Physicochemical Property Data for the Two Starting Compound Subsets[a]

subset	SC[b] median (mean) [*N*[e]]	OC[c] median (mean) [*N*[e]]	PC[d] median (mean) [*N*[e]]	*p* value[f]	median difference between OCs[g]	*p* value (difference between OCs)[h]	median difference between PCs[g]	*p* value (difference between PCs)[h]
MW								
2SC set	328 (365) [85]	471 (599) [85]	153 (234) [85]	**0**	40	**0.0172**	121	**0**
1SC set	393 (413) [179]	443 (465) [179]	38 (51) [179]	**0**				
cLogP								
2SC set	2.8 (2.6) [85]	3.6 (3.5) [85]	1 (0.9) [85]	**0**	−1.0	**0.0006**	0.4	0.0576
1SC set	4.1 (4) [179]	4.6 (4.6) [179]	0.5 (0.5) [179]	**0**				
PSA								
2SC set	53 (65) [85]	78 (114) [85]	26 (50) [85]	**0**	19	**0**	23	**0**
1SC set	55 (57) [179]	62 (65) [179]	1 (8) [179]	**0**				
HBA								
2SC set	4 (4.8) [85]	6 (8.5) [85]	2 (3.7) [85]	**0**	1	**0.0001**	1.5	**0**
1SC set	4 (4.1) [179]	5 (4.7) [179]	0 (0.6) [179]	**0**				
HBD								
2SC set	1.5 (3.1) [85]	2 (2.9) [85]	0.5 (−0.2) [85]	**0**	0	0.0762	0.5	**0**
1SC set	2 (4.8) [179]	2 (1.9) [179]	0 (−3) [179]	0.179				
RB								
2SC set	5.5 (6.1) [85]	9 (12) [85]	3.5 (5.9) [85]	**0**	2	**0.0002**	3	**0**
1SC set	6 (6.8) [179]	7 (7.7) [179]	0 (0.9) [179]	**0**				

[a] Bold text shows significance at the 95% confidence level. [b] SC, starting compound. [c] OC, optimized compound. [d] PC, property change. [e] *N*, number of data points. [f] *p* value from 1-sample Wilcoxon signed rank test of the median. [g] Mann−Whitney point estimate for the difference in the population medians. [h] Mann−Whitney *p* value.

GPCRs showed a statistically significant decrease of −0.75 according to the Wilcoxon method. There was no statistically significant difference in the number of HBDs between the DML and SCOPE target family subsets except in the case of the oxidase DMLs, for which there was a higher number of donors than the equivalent SCOPE target family.

RBs. The full set of DML optimized compounds contained a median of 8 rotatable bonds, and there was a substantial increase during optimization (median 1; mean 2.5) (Table 6). Statistical clustering gave four groups with peptide GPCRs, GPCR/oxidases, nuclear receptors, and full set of GPCRs ligands having the highest number of RBs (Figure 3).[9] The second cluster contained the protease and kinase, and the third cluster contained the monoamine GPCR, transporter, and GPCR/transporter ligands. The oxidases had the most rigid ligands of all. The highest increase in the flexibility of the ligands during optimization was observed for the peptide GPCR and GPCR/oxidase subsets.

There was a marked difference between the numbers of RBs typically found in the SCOPE ligands compared to the DMLs. This difference for the full set was 2 RBs, and this was due to both a higher number in the starting compounds and a higher increase during optimization. There was an increase of 3 RBs for the full set of GPCRs and the peptide GPCR subset compared to the SCOPE ligands. For the nuclear receptors, the difference was very high (6 RBs), although again this might be a PPAR specific effect.

(B) Discovery Strategy-Based Property Analysis. The median and mean MWs for the two starting compound (2SC) set, 471 and 599, respectively, were higher than those of the one starting compound (1SC) set, 443 and 465, respectively (Table 7). For both the 1SC and 2SC scenarios, there was a significant increase in MW during optimization. The magnitude of this increase was much higher for the 2SC set with a median increase of 153. Interestingly, the median MW of the starting compounds was significantly lower for the 2SC set, 328, compared to the 1SC set, 393. Thus, the higher MW for the 2SC set was entirely dictated by the higher MW change during optimization.

The median cLogP for the optimized compounds for the 2SC set, 3.6, was roughly an order of magnitude lower than that for the 1SC set, 4.6. Similarly, the lipophilicities of the optimized compounds were also lower for the 2SC set with a median of 2.8. There was a statistically significant increase in cLogP for the 1SC and 2SC sets of 1 and 0.5, respectively.

The median PSA for the optimized compounds from the 2SC set, 78, was significantly higher than those from the 1SC set, 62. There was, however, little difference in the median values

for the starting compounds, so the higher PSA for the 2SC set of optimized compounds was due to a higher increase during optimization of 26. There was no statistically significant increase in PSA for the 1SC set.

The trends observed for the number of acceptors mirrored those seen for PSA, with the number being higher for the optimized compounds from the 2SC set, median of 6. This was due to a higher degree of increase during optimization. The starting compounds in the 1SC and 2SC sets had the same number of acceptors, with a median of 4.

The optimized compounds from both the 1SC and 2SC sets had a median of 2 HBDs. There was no increase in the number of donors for the 1SC set, whereas there was an increase of 0.5 for the 2SC set.

The optimized compounds from the 2SC set were more flexible than those from the 1SC set, with a median number of 9 and 7 RBs, respectively. There was no statistically significant change in flexibility for the 1SC set during optimization, but for the 2SC set there was a large increase from 5.5 to 9 rotatable bonds. As with MW and cLogP, the starting compounds from the 2SC set had a lower number of RBs, but it was the large increase during optimization that reversed the order of the subsets for the optimized compounds.

Discussion

(A) Target Family Based Property Analysis. It is clear from the data that we present in this paper that there are significant differences between the various target families studied with respect to the properties of their optimized DMLs. The target family that consistently gave the highest values was the peptide GPCRs. For example, the optimized compounds for peptide GPCRs had a median MW of 636 and a median cLogP of 5.1, figures in excess of those defined in the "rule-of-5" for druglikeness.[5] At the other extreme, the transporter inhibitors had an exceptionally low median MW of 307. The optimized compounds for monoamine GPCRs, oxidases, and GPCR/transporters were the most druglike after the transporters.

The position of peptide GPCRs as the single most challenging family in terms of obtaining druglike properties is consistent with many of the published examples having been reported to possess poor oral bioavailability. On rare occasions, reducing the size and complexity of the lead compounds was possible in order to achieve acceptable pharmacokinetics while retaining or increasing potency and selectivity. For example, the structures of complex dual NK_1/NK_2 antagonists and AT_1/ET_A antagonists were simplified by Murugesan et al.[12] and Mah et al.,[13] respectively, to give derivatives that possessed good oral bioavailability. In many other examples, the combination of a desirable in vitro profile with the pharmacokinetic profile required for the development of an oral drug was not achievable, but nevertheless, these ligands may represent useful pharmacological tools. Indeed, an important goal for future research in this field, particularly in academic institutions, will be to develop high-quality pharmacological tools to explore the potential therapeutic value of novel target combinations. Here, less attention can be paid to oral exposure and overall developability criteria. More important will be the wider selectivity profile of these pharmacological tools.

The conclusions of this paper are relevant only for the discovery of oral drugs. The use of alternative routes of administration, such as intravenous and transdermal, is applicable for some DML applications. High MW DMLs (conjugates), containing a linker group separating the frameworks of the two selective ligands, have been successfully employed as intravenously administered drugs.[14]

The rank order of the target families, shown in Figure 3, bears a close resemblance to that reported previously for a diverse set of preclinical compounds, the majority of which were designed to possess high selectivity for a single target.[11] However, the average property values for the DMLs are typically higher than those reported for preclinical compounds in general. Given the need to satisfy two or more sets of stringent pharmacophoric requirements, might we expect that DMLs would be larger and more structurally complex than ligands that are selective for a single target?

The goal of a medicinal chemist working on a DML project is to find a molecular framework or "anchoring group" that satisfies a basic pharmacophoric requirement of each target. By modification of this basic template, a common finding is that some groups are crucial for activity at one of the targets but are merely tolerated by the other target(s). It is conceivable that such "tolerated regions" may be buried deep within the active site of one target but exposed to solvent in the other. DMLs containing groups that are merely tolerated by one of the targets without contributing much binding energy are likely to be larger and less efficient than selective ligands. It might be expected that designing druglike DMLs with high efficiency would be most feasible for targets that possess similar binding sites where there is less need for functionality that is only relevant for binding to one of the targets. Where the targets are fundamentally different, it may be very difficult indeed to integrate the pharmacophoric requirements of both binding sites into a small, compact molecule.

The large difference in the median MWs between the DML and SCOPE ligands binding to peptide GPCRs is notable (Table 1). This can be explained, at least partly, by the fact that the SCOPE set contained a larger number of small opioid agonists that served to lower the median MW of the optimized compounds.[11] However, the difference could also be partially explained by the binding sites of individual peptide GPCRs being more diffuse and more dissimilar to each other compared to members of some other families. The degree of overlap of the frameworks, and underlying pharmacophores, that can routinely be achieved might be lower than for other families, and the resulting presence of substantial "tolerated regions" would result in lower binding efficiency.

In contrast, for the oxidases, proteases, and transporters, the optimized compounds were of similar size for the SCOPE and DML data sets (Table 1). For these three families, this may be because the binding sites for the target combinations in our DML data set are more conserved. Possibly the DMLs for these families contain anchoring groups that contribute a large proportion of the binding energy, thereby allowing the size of the remainder of the molecule to be minimized while still retaining acceptable potency. For many of the protease inhibitors, this conserved anchoring group is a warhead that binds zinc as in omapatrilat **1** (Figure 4). An additional explanation may be that the availability of biostructural and mechanistic information for proteases enables medicinal chemists to merge the frameworks of selective ligands with high efficiency. In the case of the transporters, the binding sites are also likely to be highly similar by virtue of binding similar monoamine neurotransmitters. It is thought that the conserved anchoring group is an aspartate residue in the first transmembrane domain of monoamine transporters that is involved in binding the endogenous substrates and presumably also inhibitors such as duloxetine **2** (Figure 4).[15]

While the property values for the GPCR/transporter ligands were typically higher than those for transporters alone, they were

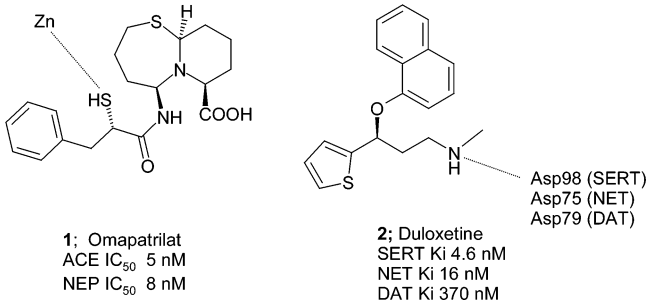

Figure 4. Structures of DMLs for proteases and transporters containing conserved anchoring groups: ACE, angiotensin converting enzyme; NEP, neutral endopeptidase; SERT, serotonin transporter; NET, norepinethrine transporter; DAT, dopamine transporter.

still in the druglike range being similar to those for monoamine GPCRs. Most of these ligands were dual monoamine transporter inhibitors/monoamine GPCR antagonists. Similarities in the antagonist binding sites in the transmembrane regions of monoamine GPCRs and transporters will likely facilitate the discovery of druglike ligands.[15] The property values for the GPCR/oxidase ligands were consistently higher than those for the GPCR/transporter ligands, and this almost certainly reflects lower similarity of the GPCR and enzyme active sites. The significantly larger size and complexity of the kinase DMLs compared to SCOPE were somewhat surprising given that the binding sites share a common ligand (ATP). A caveat here is that the kinase DML data set was relatively small and more examples will be required to establish if this trend is real. For the nuclear receptors, there were also large differences between the DML and SCOPE property medians, but these differences should be treated with particular caution because all the DMLs in the data set came from a single subclass, the PPAR receptors.

Previously we reported that the principal influence on the druglikeness of the SCOPE optimized compounds was the properties of the starting compounds because the degree of change in those properties during optimization was rather consistent across the different target families.[11] In the case of the DMLs, there were profound differences between the target families with respect to the degree of increase of these properties during optimization. As a result, the properties of the optimized compounds were influenced to a much greater extent by the increases in properties during optimization. For MW, the increases were generally higher for the DMLs compared to the SCOPE ligands, and these larger increases were predominantly responsible for the larger size of the ligands of the DMLs. For those families where the median MW of the optimized compounds was similar for the SCOPE and DML sets, oxidases, proteases, and transporters, this was due to the change during optimization also being similar. Although there were some exceptions, there was a trend for those target families with the lowest property values for the starting compounds (transporters, monoamine GPCRs, oxidases, and GPCR/transporters) to also have the lowest increases during optimization. On the other hand, the peptide GPCR family usually had both the highest property values for the starting compounds and the highest increases during optimization. For example, the median MW increase was +72 for the peptide GPCR ligands but only +24 for the oxidase ligands.

For the peptide GPCRs, the starting compounds were considerably larger than their SCOPE equivalents. Again, the larger number of relatively low MW opioid agonists in the SCOPE set is likely to be a contributory factor here.[11]

The increases in lipophilicity during optimization were also generally higher for DMLs compared to the SCOPE ligands. One example of the strong influence of the change during optimization is the high cLogP increase (+1.35) for monoamine GPCR ligands. Unusually the monoamine GPCR ligands also showed a decrease in the number of HBDs during optimization. These two observations may be explained by the way in which the frameworks from two monoamine GPCR ligands are often merged with the overlapping of a common secondary or tertiary amine and retention in the optimized compound of lipophilic groups from both starting compounds as in compound **8** (Figure 5).

(B) Lead Discovery Strategy-Based Property Analysis. We have found strong evidence that the discovery strategy exerts an even more profound influence than the target family on the changes in properties during optimization and consequently on the properties of the optimized DMLs. The 2SC strategy, which comprises the merging of two selective ligands, results in dual ligands that are larger and more complex than those resulting from a 1SC strategy (Figure 2). This effect is predominantly the result of larger increases in the physicochemical properties during optimization, caused by the fact that a high degree of merger is often difficult to achieve. For the 1SC strategy, the starting compound was typically obtained by focused or random screening and multitarget activity was usually already present to some extent. In such cases, optimization then proceeded along the lines of "balancing" the activities by adding modestly sized groups or modifying the existing functionality. This typically had less of an effect on the overall size and physicochemical properties of the molecule than the merging of two frameworks.

This Achilles' heel of the 2SC framework combination strategy is illustrated by the example in Figure 5 wherein the framework of a selective gastrin ligand **3** was combined with that of a histamine H_2 ligand **4**.[16] Compound **5** is a classic example of a "fused" DML (Figure 2) because the degree of overlap that was possible was just a single carbon atom. The incompatibility of the hydrophobic gastrin pharmacophore with the hydrophilic H_2 pharmacophore produces "tolerated regions" that are only relevant for binding at one of the targets, having the effect of lowering the overall efficiency of binding and compromising oral absorption. If the 2SC framework combination strategy is to be successfully employed to produce druglike multiple ligands (MW < 500), it is imperative to start from small fragments (MW < 250) if the degree of overlap that is expected is very low or to use "leadlike" (MW < 400) starting compounds if the expected overlap is considerably higher. Interestingly, the properties of the starting compounds from the 2SC set tended to be lower than those for the one starting compound and SCOPE sets. Perhaps this indicates a tendency for medicinal chemists to preselect the smallest starting compounds, knowing that large increases in MW and flexibility will inevitably result from the 2SC framework combination approach.

A successful application of the 2SC approach was the combination of the frameworks of the $5HT_2$ ligand **6** with dopamine **7**.[17] Again, the degree of overlap of the frameworks was just a single atom, but this example of a fused DML **8** was much smaller by virtue of the very low MW of the two starting compounds. It may be possible to use somewhat larger fragments, as with the merger of the $5HT_{1A}$ and SERT ligands **9** and **10** to give compound **11**, providing the frameworks can be highly merged.[18] This requires high similarity in the pharmacophores of the two targets, as is the case here for the $5HT_{1A}$ receptor and the serotonin transporter, which share the same endogenous ligand. In this case, the sulfonamide group could be deleted, which helped to further reduce the MW. Since the overall goal of the 2SC strategy is to reduce the property values

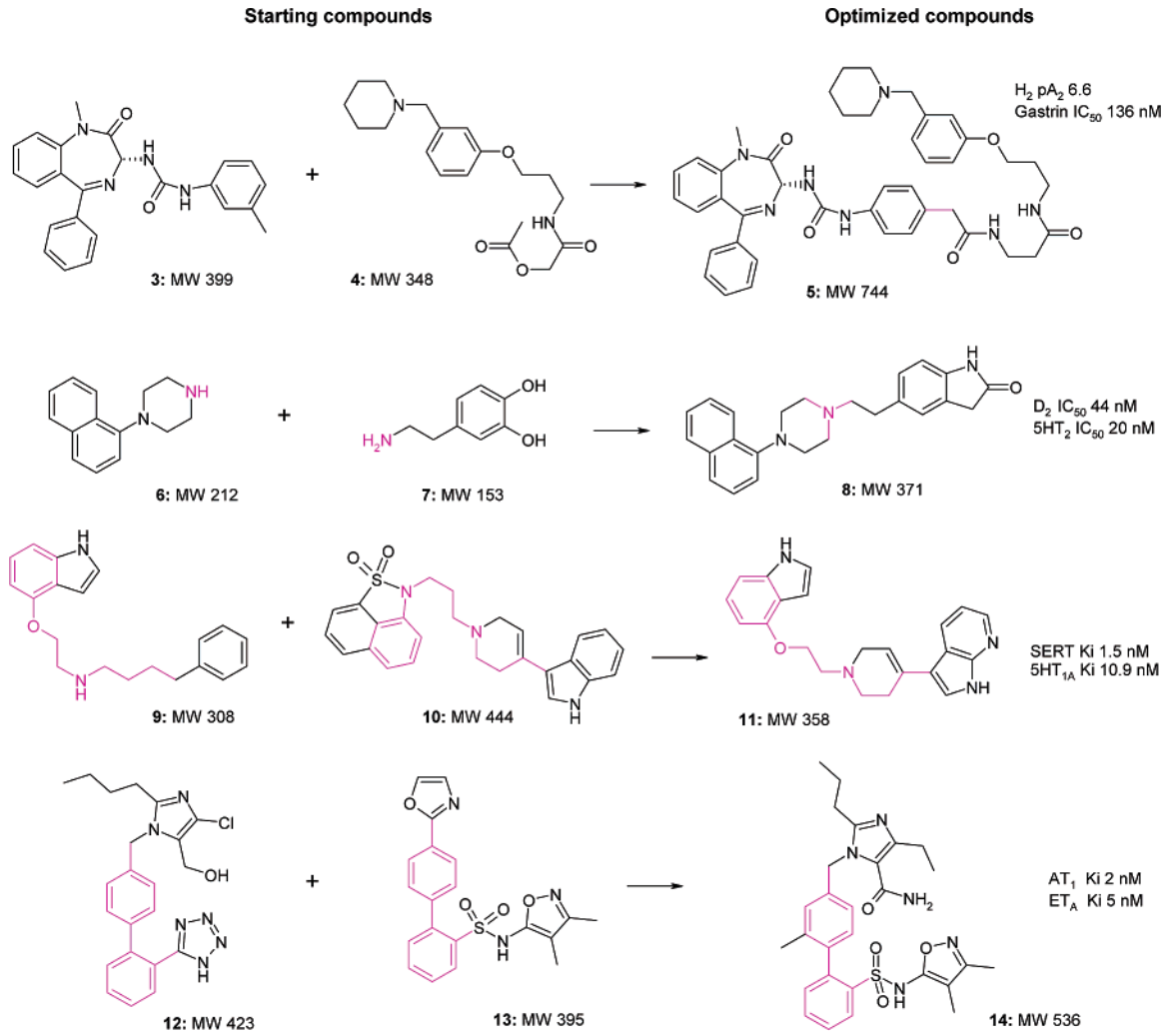

Figure 5. Structures and molecular weights of four optimized DMLs derived via a "framework combination" approach and the starting compounds from which they were derived. Conserved atoms are shown in magenta. The size of the optimized compound is determined by the size of the starting compounds, the degree of merger of the frameworks that can be achieved, and the potential to delete nonessential peripheral groups.

for a DML relative to the sum of the property values for the starting compounds, this can best be achieved by using a combination of deletions and framework combination. Since the SAR may not transfer directly from the selective ligands to the DML, it pays to keep an open mind during optimization and explore afresh the effect of deleting groups that were previously found to be essential in the selective ligands.

Since the physicochemical properties of DMLs are controlled by the dual influences of the target family and the lead discovery strategy, it is not surprising that the highest property values of all were found for DMLs for peptide GPCRs that were derived via a 2SC framework combination strategy. In this case, the median MW and PSA values were exceptionally high, 651 and 97, respectively. The 2SC framework combination strategy will be exceptionally difficult to execute for peptide GPCRs, and it is telling that there are no examples in our database of optimized compounds with MWs below 500. In one example, the framework of an AT_1 selective ligand **12** was combined with that of a ET_A ligand **13** with a good degree of overlap of the biaryl core being achieved in **14**.[19] Even when this high degree of integration of the frameworks was possible by cleverly exploiting a privileged substructure, the MW remains stubbornly above 500 because of the typically high MWs of the starting compounds. This series went on to deliver ligands with good oral bioavailability, indicating that with perseverance and skill even difficult families such as peptide GPCRs can sometimes be addressed with a 2SC approach. Nonetheless, given the lower median MW for the 1SC subset, a screening-based approach that attempts to directly deliver a hit with multiple activity, even if the initial activity is weak, might prove to be more fruitful for peptide GPCRs than the 2SC framework combination strategy. At the other end of the spectrum, the ligands for transporters, monoamine GPCRs, and oxidases generally possess favorable physicochemical properties and the feasibility of such targets for DML projects using a variety of lead discovery strategies will be relatively high.

The 2SC strategy can readily be applied to the discovery of pharmacological tools for validating novel target combinations and for the production of injectable drugs. For discovering ligands that bind more than two targets, screening is currently the only viable lead generation strategy.

Looking to the future, more sophisticated knowledge-driven design strategies and computational tools are clearly needed for tackling the difficult families. Whereas classical framework combination can lead to the presence of unnecessary "tolerated regions" and low binding efficiency, combination carried out at the level of the underlying pharmacophores has the potential to produce druglike DMLs with structures significantly different from those of any of the known selective ligands (scaffold hopping). Knowledge of the relationships between the underlying pharmacophores for the different targets will help maximize

ligand efficiency in terms of binding energy per unit of molecular weight or lipophilicity.

Conclusion

Many factors contribute to the chance of success for medicinal chemists when confronted with the challenge of designing ligands that seek to address more than one target.[1] Particularly important among these factors are physicochemical properties that relate to molecular size and complexity, given the critical relationship of such properties to the developability of orally administered drugs.

In this paper, we have found that the influence of the target family on the physicochemical properties of DMLs is broadly similar to that reported previously for preclinical compounds in general, with peptide GPCR ligands having unusually high values and transporter ligands unusually low values.[11] However, DMLs are typically larger and more complex than preclinical ligands, and one explanation for this is the popularity of a lead discovery strategy (2SC) whereby the molecular frameworks from two selective ligands are combined. Given that the selective ligands were already druglike and the extent of the overlap of the frameworks that could be achieved was often low, this process resulted in large property increases that often compromised oral bioavailability. Nonetheless, the 2SC approach is a conceptually elegant knowledge-driven strategy that effectively uses SAR knowledge derived from selective ligand projects. Furthermore, there are successful examples of oral drugs having been discovered by this strategy reaching the market, such as ziprasidone.[17] To achieve an orally active DML, it is important that the degree of framework overlap is maximized and the size and complexity of the selective ligands are minimized. These goals will typically be more feasible for targets with simple endogenous ligands and conserved binding sites, such as monoamine GPCRs and transporters.

Given the fact that DML projects usually demand a larger investment of resources than single target projects, an early assessment of the risk versus the potential benefit of a DML approach is essential. Where the targets in a combination are highly dissimilar, even if it is possible to achieve the desired profile, there is a higher risk that the resulting ligands will contain large "tolerated regions" and possess low binding efficiency. Since the median MW for the 1SC strategy was lower than for the 2SC strategy, focused or diversity-based screening approach may provide a route to smaller and less complex leads for difficult target combinations. New lead discovery strategies will certainly be required in the years ahead if this area of designing multiple ligands is to fulfill its full therapeutic potential.

Methods

The database of 281 multiple ligands was compiled by keyword searches of four medicinal chemistry journals (*Bioorg. Med. Chem.*, *Bioorg. Med. Chem. Lett.*, *Eur. J. Med. Chem.*, and *J. Med. Chem.*) published during the period 1990−2005. Of the 281 ligands, 257 were designed to be active at 2 targets, 23 ligands were designed for 3 targets, and 1 involved 4 targets. Of the 264 optimizations recorded in the database, 179 started from a single starting compound and 85 started from 2 starting compounds. The abstraction policy for the database was to select as the optimized compound the compound that was subjected to the most rigorous testing regime, and it was not necessarily the most potent compound in the primary in vitro assays.

Definitions of the methods used for calculating the numbers of hydrogen bonding groups (HBA and HBD) and rotatable bonds (RB) are provided in Supporting Information. Polar surface area (PSA) was calculated according to a published method.[20]

For some of the target family subsets, the property distributions for the compounds were not normally distributed. For that reason, more emphasis in the analysis and interpretation is placed upon the median values rather than the mean value, and the data sets were analyzed using nonparametric rank statistical methods. The Wilcoxon signed rank test was used to examine the significance of the changes in the properties during optimization, and the Mann−Whitney rank test was used to explore the significance of the differences in properties between the target family subsets and between the discovery strategy subsets. Statistical significance was defined as $p < 0.05$ for all cross-comparisons in this paper except in the case of the target family clustering (Figure 3) where $p < 0.1$ was used.[9]

Supporting Information Available: Tables of differences in the median property values and related *p* values for the target families; definition of hydrogen bond donors and acceptor and rotatable bonds. This material is available free of charge via the Internet at http://pubs.acs.org.

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