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Perspective

Designed Multiple Ligands. An Emerging Drug Discovery Paradigm

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Introduction

For much of the past century, drug discovery relied largely on the use of animal models of disease as the first-line screens for testing the compounds produced by medicinal chemists. This in vivo pharmacology approach had the benefit of highlighting compounds that exhibited both desirable pharmacokinetic and pharmacodynamic profiles. A major disadvantage of this approach was that an animal model was essentially a "black box". When compounds were inactive, it was unclear whether this was because they no longer interacted with a molecular target or simply whether they had failed to reach the site of action. In many cases, the molecular target(s) driving the desired pharmacological effect had not been identified, and inevitably many older generation drugs cross-reacted with targets that caused detrimental side effects. Inexorably, the drug discovery paradigm shifted toward a reductionist "one-target, one-disease" approach that continues to dominate the pharmaceutical industry today. Many successful drugs have emerged from this strategy, and it will no doubt remain dominant for many years to come. However, despite the best efforts of drug discoverers, many diseases remain inadequately treated. There is an increasing readiness to challenge the current paradigm and to consider developing agents that modulate multiple targets simultaneously (polypharmacology), with the aim of enhancing efficacy or improving safety relative to drugs that address only a single target.[1−3]

There are three possible approaches to polypharmacology (Figure 1). Traditionally, clinicians have treated unresponsive patients by combining therapeutic mechanisms with cocktails of drugs. Most frequently, the cocktail is administered in the form of two or more individual tablets (scenario A).[4,5] However, the benefits of this approach are often compromised by poor patient compliance, particularly for treating asymptomatic diseases such as hypertension.[6] Recently, there has been a move toward multicomponent drugs whereby two or more agents are coformulated in a single tablet to make dosing regimes simpler and thereby to improve patient compliance (scenario B).[7,8] An alternative strategy is to develop a single chemical entity that is able to modulate multiple targets simultaneously (scenario C).[9]

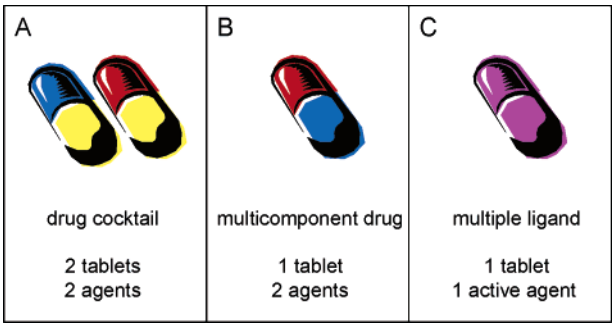

Figure 1. Three main clinical scenarios for multitarget therapy.

Across the pharmaceutical industry, scenario B is increasingly providing an attractive opportunity for enhancing R&D output. Several multicomponent drugs have recently been launched, such as Caduet[10] (amlodipine/atorvastatin) and Vytorin[11] (ezetimibe/simvastatin) that were approved in 2004 for the treatment of cardiovascular disease. However, there are significant risks involved in the development of multicomponent

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drugs. There is the commercial uncertainty arising from the risk that clinicians might still prefer prescribing combinations of existing monotherapies that may offer greater dose flexibility and lower cost treatment, particularly in the case of generic drugs. Differences in the relative rates of metabolism between patients can produce highly complex pharmacokinetic (PK)/pharmacodynamic (PD) relationships for multicomponent drugs, leading to unpredictable variability between patients and necessitating extensive and expensive clinical studies.

Compared to multicomponent drugs, the multiple-ligand approach (scenario C) has a profoundly different risk−benefit profile. A downside is that it is significantly more difficult to adjust the ratio of activities at the different targets. However, this increased complexity in the design and optimization of such ligands is shifted toward the earlier and therefore less expensive stages of the drug discovery process. The clinical development of multiple ligands, in terms of the risks and costs involved, is in principle no different from the development of any other single entity. Another advantage is a lower risk of drug−drug interactions compared to cocktails or multicomponent drugs.[12]

While many currently marketed drugs are in essence multiple ligands, very few were rationally designed to be so. Typically, the mechanism of action was elucidated retrospectively. Recently, there has been growing interest in the deliberate, rational design of ligands acting specifically on multiple targets, and this has been reflected by an increase in the number of relevant publications. Numerous terms are currently used to describe such ligands, dual ligand, heterodimer, promiscuous drug, pan-agonist, and triple blocker being just a few of many examples. The complexity and inconsistency of this nomenclature serve to obscure developments in this field. To improve communication and awareness, the authors propose using a common term, designed multiple ligands (DMLs), to describe compounds whose multiple biological profile is rationally designed to address a particular disease, with the overall goal of enhancing efficacy and/or improving safety. Ligands that possess significant activity at irrelevant targets should not be regarded as DMLs but rather as "nonselective" ligands, since undesirable cross-reactivity frequently leads to deleterious side effects.

An example of a nonselective ligand is the atypical antipsychotic drug clozapine, which displays an extremely complex in vitro pharmacology. To reduce side effects, a number of ligands that are selective for single receptors targeted by clozapine were developed, such as D_4 and 5-HT_{2a} antagonists, but these lacked sufficient efficacy in the clinic.[13] Research then shifted toward DMLs such as dual D_2/5-HT_{2a} antagonists.[14,15] This evolutionary process, from nonselective to selective to DML, has also been seen for other diseases. Nonselective tricyclic antidepressants such as amitryptyline were superseded by selective serotonin (5-HT) transporter inhibitors (SSRIs), which increased safety but had a slow onset of action and lacked efficacy in some patients. Dual serotonin and norepinephrine (NA) reuptake inhibitors (SNRIs) are now being developed clinically with the hope of addressing these deficiencies.[16] Likewise, the same trend is observed in the area of nonsteroidal anti-inflammatory drugs (NSAIDs), starting from nonselective agents such as aspirin to selective cyclooxygenase-2 (COX-2) inhibitors and then to dual COX-2/5-lipoxygenase (5-LOX) inhibitors.[17]

Strategies for Designing Multiple Ligands

Conceptually, there are two quite different methods of generating chemical matter with which to commence a DML project: *knowledge-based* approaches and *screening* approaches (Figure 2). Knowledge-based approaches rely on existing biological data from old drugs or other historical compounds, from either literature or proprietary company sources. Serendipitous approaches involve the screening of either diverse or focused compound libraries. Typically, diversity-based screening involves the high-throughput screening (HTS) of large, diverse compound collections at one target, and any actives are then triaged on the basis of activity at the second target. In focused screening, compound classes that are already known to provide robust activity at one of the targets of interest, A, are screened for signs of activity at a new target, B. Even if only weak activity is observed for target B, this can provide a useful baseline for increasing that activity by incorporating structural elements from more potent selective ligands for target B.

For both the screening or knowledge-based approaches, the identification of a lead compound with appropriate activity at both targets A and B is unlikely. In reality, a lead generation, or "hit-to-lead" phase, will be required. In one scenario, two compounds that bind with very high selectivity to their respective targets are used as the starting points. To incorporate activity at both targets into a single molecule ("designing in"), structural elements from the two selective ligands are combined. Incorporating a second activity into a compound that has no measurable affinity for that target, while retaining affinity for the original target, is not an easy task. However, many literature examples testify to the fact that it can often be achieved. Perhaps a more tractable scenario is to first identify a compound that has at least minimal activity at both targets. In this case, the activity at both targets must be modulated to achieve an optimal ratio. In a third scenario, a compound is identified that possesses activity at both targets A and B but also possesses undesirable activity at another target C. The optimization strategy must then focus on "*designing out*" this cross-reactivity. In some cases, a compound may possess more than one undesired activity, and this will inevitably increase the complexity of the task.

By far the most common trajectory for generating leads is to convert a ligand with a single activity into a dual ligand. The conversion of single ligands into triple ligands is more challenging and is much rarer. As the number of targets in a profile increases, the "designing in" philosophy will become less attractive compared to the "designing out" approach starting from a nonselective ligand.

The lead candidate will usually lack the optimal ratio of in vitro activities. In lead optimization, the ratio is adjusted so that both targets are modulated to an appropriate degree in vivo at similar plasma or brain concentrations. In most examples, the aim has been to

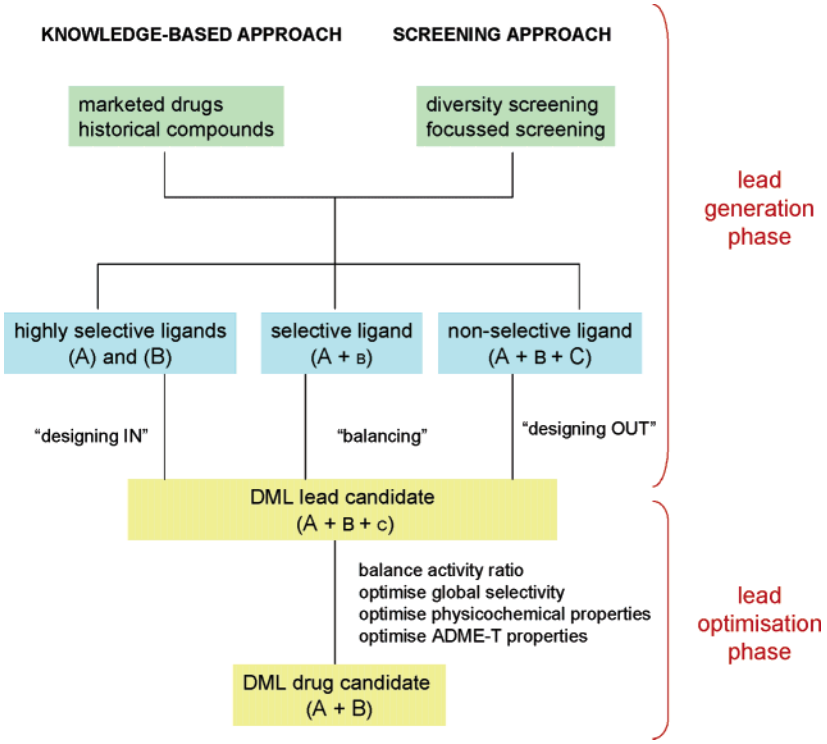


Figure 2. Different strategies for DML projects. In the lead generation phase, knowledge-based or screening approaches are used to provide starting compounds that may be highly selective (little or no activity at a second target), moderately selective, or nonselective (with undesired activity). The subsequent strategy involves "designing in", "balancing", or "designing out" activities, respectively. As well as balancing the activity ratio, lead optimization provides other major challenges, in particular adsorption, distribution, metabolism, excretion, and toxicity (ADME-T) optimization. In this schematic, activity at targets A and B is desired and activity at target C is undesired. The size of the target letter illustrates the affinity for that target.

obtain in vitro activities within an order of magnitude of each other, with the assumption that this will lead to similar levels of receptor occupancy in vivo. However, this may not necessarily be the case, and assuming a validated animal model is available, the testing of a lead candidate in vivo may help to clarify the required ratio of in vitro activities. Ultimately, feedback from clinical studies will be required to identify the optimal ratio that can be then be used to drive the design of "follow-up" compounds. In addition to adjusting the ratio of activities, optimizing wider selectivity against a broad panel of targets is often required. This will be particularly intricate for targets for which a large number of subtypes or isozymes exist. Many publications do not discuss the key issue of global selectivity, so it is frequently difficult to judge whether real selectivity for the disease-relevant targets has been achieved. Again, animal models and subsequent clinical studies will provide essential feedback on the level of cross-reactivity that can be tolerated. A particular challenge in lead optimization is to optimize the PK profile and to obtain physicochemical properties that are consistent with good oral absorption.

Classification of Designed Multiple Ligands

"Conjugates" are DMLs in which the molecular frameworks, which contain the underlying pharmacophore elements for each target, are well separated by a distinct linker group that is not found in either of the selective ligands (Figure 3). Most conjugates contain a metabolically stable linker. "Cleavable conjugates" employ a linker that is designed to be metabolized to release two ligands that interact independently with each target.

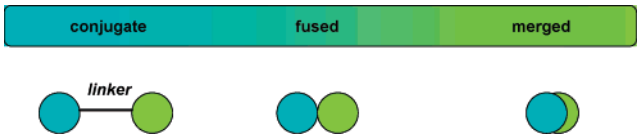


Figure 3. DML continuum. Ligands vary greatly in the degree of merger of the frameworks (and the underlying pharmacophores) of the selective ligands used as the starting points.

As the size of the linker decreases, a point is reached where the frameworks are essentially touching, and these DMLs can be regarded as "fused". In the most common type of DML, the frameworks are "merged" by taking advantage of commonalities in the structures of the starting compounds. In reality, the degree of merger of the frameworks forms a continuum, with high molecular weight conjugates with lengthy linker groups representing one extreme. At the other extreme are examples where the frameworks, and underlying pharmacophores, are highly merged, giving rise to smaller and simpler molecules.

Knowledge-Based "Designing In" Approaches

Conjugates. Van Boeckel et al. designed conjugate **1** (Figure 4), a high-efficacy antithrombotic that inhibited both thrombin (via NAPAP) and ATIII-mediated factor Xa (via a heparin-derived pentasaccharide fragment).[18] A poly(ethylene glycol) linker conferred good aqueous solubility, thus making the compound suitable for parenteral administration. The crystal structure of NAPAP in thrombin was used to identify a tolerant position for attachment of the linker without affecting potency. Since the pentasaccharide demonstrated a

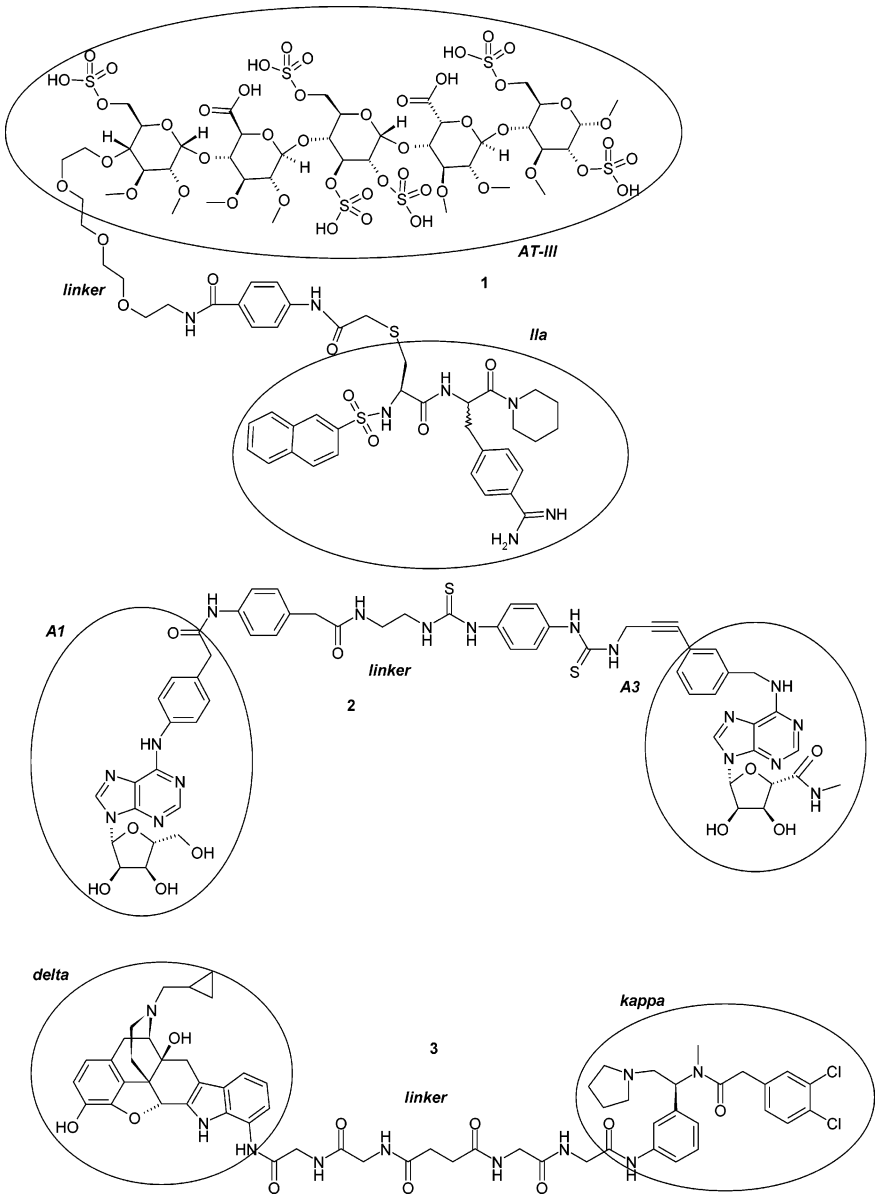


Figure 4. Structures of high molecular weight DML conjugates.

much longer half-life (13−15 h in man) than NAPAP (18 min), the authors postulated that a conjugate with NAPAP might possess improved pharmacokinetic properties. Indeed, this was confirmed, and in vivo studies revealed that **1** provided a stronger and longer-lasting antithrombotic effect compared to a cocktail of free pentasaccharide and NAPAP.

The covalent linking of selective adenosine A_1 and A_3 agonists by Jacobson et al. using a rigid ethynyl-based spacer led to conjugates with the desired dual activity **2**.[19] Evaluation of these conjugates in models of myocardial ischemia confirmed that activation of both A_1 and A_3 receptor subtypes resulted in a cardioprotective effect that is significantly greater than that induced by activation of either receptor individually.

Portoghese et al. reported a range of homo- and heterodimeric conjugates with varying linker length designed to investigate pharmacodynamic and organizational features of opioid receptors.[20] For example, recently reported heterodimeric conjugates containing δ-antagonist (naltrindole) and κ_1-agonist (ICI-199,441) pharmacophores tethered by variable-length oligoglycyl-based linkers **3** were demonstrated to possess significantly greater potency and selectivity compared to their monomer congeners, providing further evidence for the opioid receptor heterooligomerization phenomenon.[21]

Most of the cleavable conjugates reported in the literature contain an ester-based linker, which is designed to be cleaved by plasma esterases to release two individual drugs that then act independently. For example, several cleavable conjugates contain a nitrous oxide releasing functionality linked via an ester group to a known drug such as NO-aspirin **4** (NCX-4016) and the ibuprofen derivative **5** (Figure 5).[22,23]

Fused DMLs. When the hydrophobic gastrin receptor pharmacophore was combined with the hydrophilic histamine H_2 pharmacophore, "tolerant regions" were identified by superimposing non-peptide gastrin antagonist **6** (L-365,260) onto the peptide *N*-acetyl-CCK-7 (Figure 6).[24] It was predicted that the region around the C3′ tolyl group would be sufficiently open to accommodate functionality from the H_2 antagonist **7**. Indeed, **8** was found to possess balanced activity at H_2 and gastrin receptors, albeit with some cross-reactivity at

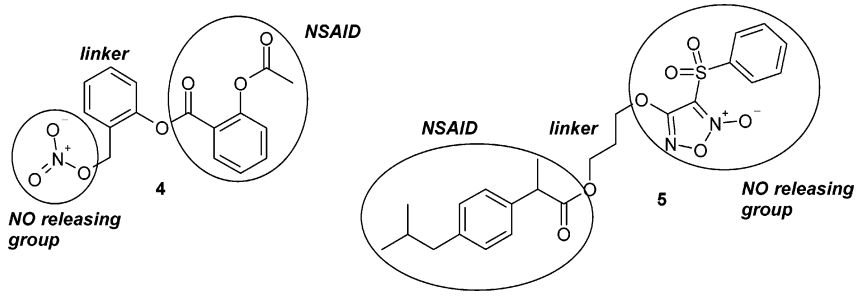


Figure 5. Structures of low molecular weight nitric oxide releasing conjugates.

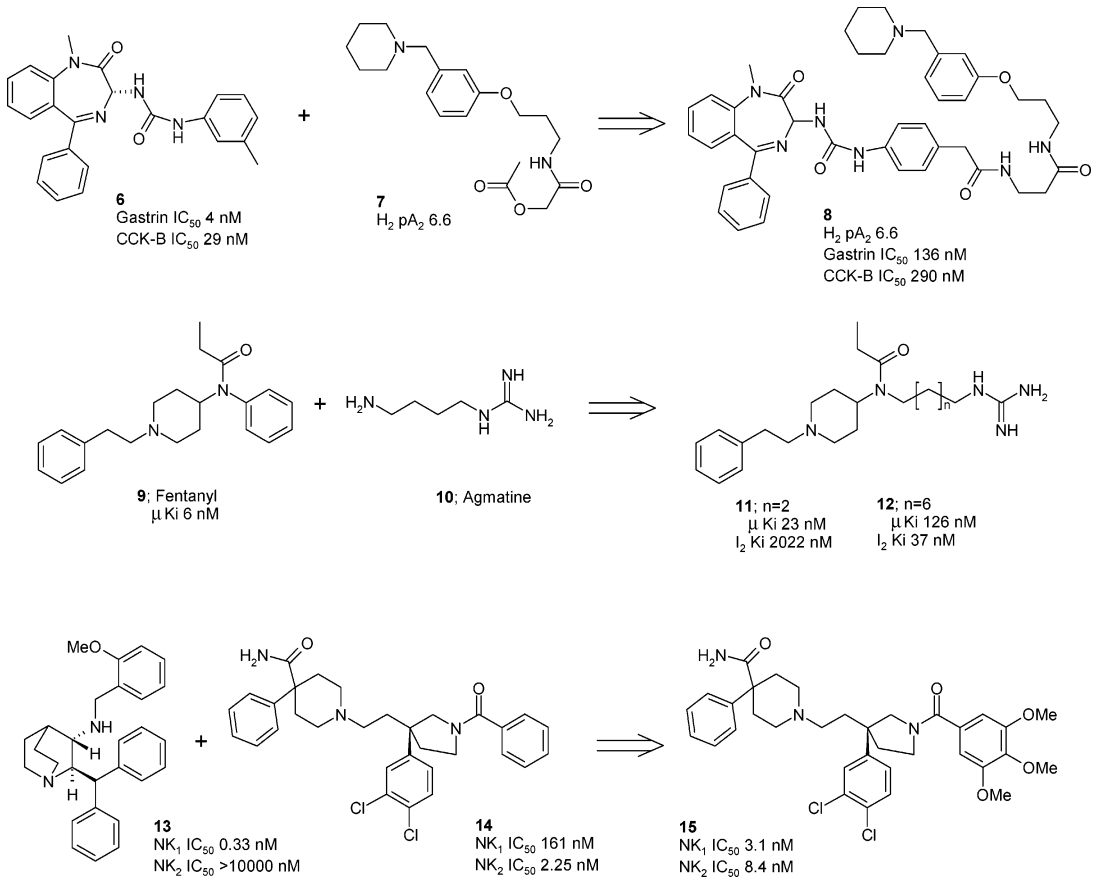


Figure 6. Structures of fused and merged DMLs (**8**, **12**, **15**) that bind to two GPCRs.

CCK-B receptors. For highly dissimilar targets, achieving multiple activities in a compact molecule in which the pharmacophores are merged may prove to be impossible. The only realistic option may be fusion of the frameworks by exploiting tolerant positions in each component, but oral absorption may then be compromised.

Merged DMLs. In their quest for an opioid analgesic with reduced side effects, Montero et al. combined agonism at two G-protein-coupled receptors (GPCRs): the μ-opioid and I_2-imidazoline receptors (Figure 6).[25,26] A guanidinium group from the I_2 ligand, agmatine **9**, was incorporated into the opioid, fentanyl **10**. The lead compound, **11**, possessed activity at both receptors, but the activity was unbalanced, having significantly higher affinity for the opioid receptor. In this example, the frameworks of the starting compounds are slightly merged with the agmatine-derived alkyl chain replacing the aniline system in fentanyl. The identification of such a "tolerant region" for both receptors is a key first step in any DML program. The compound with an eight-carbon spacer, **12**, possessed the best balance of activities.

Buckholder et al. desired a dual NK_1/NK_2 ligand because it was postulated that both SP and NK-A participated in the etiology of asthma. They started from a selective NK_2 ligand **14** that had weak NK_1 activity and then attempted to achieve balanced activity (Figure 6).[27] An overlay of **14** with the potent NK_1 ligand, **13**, showed a good overlap of the aromatic ring of the benzamide and the aromatic ring of the benzylamine, suggesting that a methoxy group on the benzamide of **14** might enhance NK_1 binding. Whereas the directly analogous 2-methoxy derivative was only 4-fold more active, the 3,4,5-trimethoxy derivative had much improved NK_1 affinity. So while the strategy was successful, the SAR around this ring in **15** was significantly different from that for **13**. Often the SAR does not transfer directly from the starting compounds to the DML possibly because of a slight shift in the mode of

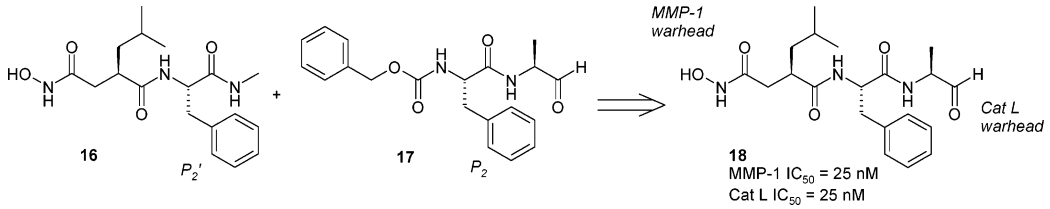


Figure 7. Design of a DML **18** that binds to two proteases.

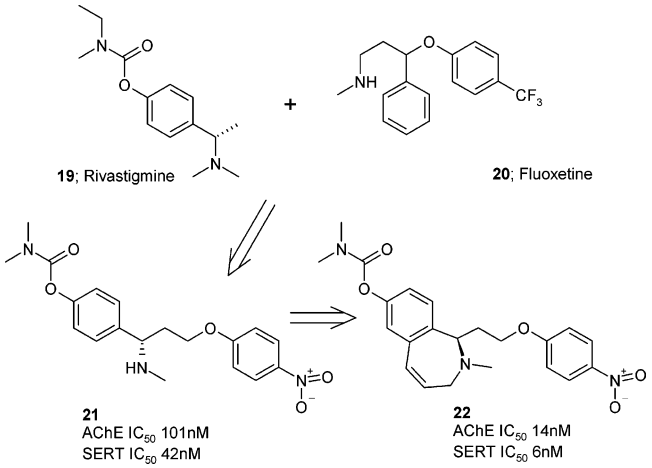


Figure 8. Design of a DML **22** that binds to an enzyme, acetylcholine esterase (AChE), and the serotonin transporter (SERT).

binding. Consequently, it is important to maintain an open mind with respect to the SARs when balancing the activities of DMLs.

The commonality between the P_2' and P_2 requirements for matrix metalloprotease-1 (MMP-1) (**16**) and cathepsin L (Cat L) inhibitors (**17**), and the use of two warheads positioned at either end, enabled the barrier between the metalloprotease and cysteine protease families to be overcome in **18** (Figure 7).[28]

It might be expected that rationally "designing in" activity for targets from fundamentally different superfamilies might be particularly difficult. However, a large number of recent examples show that spanning phylogenetically diverse targets, while still accommodating multiple pharmacophores within a single molecule, is possible. Kogen et al. describe efforts to combine acetylcholinesterase (AChE) and 5-HT transporter (SERT) inhibition for treating Alzheimer's disease. A pharmacophoric model of the active site of AChE showed that a marketed inhibitor, rivastigmine **19**, possessed three elements of the proposed AChE pharmacophore but lacked a fourth hydrophobic binding site (Figure 8).[29] It was hypothesized that a phenoxyethyl motif from the SERT blocker, **20** fluoxetine, might provide this hydrophobic interaction, thereby improving potency relative to rivastigmine. Hybridization of the two inhibitors, followed by optimization of the carbamate and phenoxy substituents, provided a reasonably balanced inhibitor, **21**. Conformational constraint using a seven-membered ring enhanced potency, **22**. This compound facilitated both cholinergic and serotonergic transmission in the brain following oral administration. In addition to producing a potent and balanced inhibition at two diverse targets, **22** possessed high selectivity over the targets most closely related to AChE and SERT, butyrylcholinesterase and norepinephrine/dopamine transporters (NET/DAT), respectively, as well as over monoamine GPCRs. This work also represents one of the rare examples so far published that uses biostructural information to guide the hybridization of the starting compounds.

DMLs from Screening Approaches

While screening relies largely on serendipity to generate a hit compound with multiple activity, the subsequent process to optimize the overall profile is carried out as rationally as for compounds derived from knowledge-based approaches. Thus, the optimized compounds, despite their screening lineage, can be regarded as DMLs. Screening can add particular value if there is a lack of selective ligands for the targets of interest and little knowledge of the individual SARs required for a more rational approach. Moreover, screening can deliver novel and unexpected chemotypes, as well as sometimes providing hits for unusual target combinations that span unrelated receptor families. For example, a diversity-based screen at UCB Pharma provided a multiple ligand with a surprising combination of activities at a peptide GPCR, the neurokinin NK_1 receptor, and a monoamine transporter, SERT.[30] Although the hit **23** had only modest activity, optimization of each aromatic moiety in turn provided a more potent compound with a balanced activity at both targets **24** (Figure 9). An aryl ether moiety was introduced to reduce lipophilicity, providing physicochemical properties predictive of central nervous system (CNS) penetration following oral administration. The similarity between the initial and optimized structures illustrates the value of a methodical stepwise approach in order to satisfy two sets of stringent receptor requirements.

In their quest for a dual 5-HT_{1A}/SERT blocker, van Niel et al. designed a focused library based on the 3-aryloxy-2-propanolamine scaffold found in the 5-HT_{1A} antagonist pinadol **25** (Figure 9).[31] The variations at the amine and phenol positions included privileged structures, as well as fragments reported to have affinity for either 5-HT_{1A} or SERT. The SAR around the indole region was reasonably tolerant for both targets, but the only amine group that provided reasonable SERT inhibition was a spiropiperidine **26**. This compound provided balanced inhibition and good oral exposure (F = 65%) and brain penetration in the rat.

The potential of using "old drugs" as a starting point for a DML project has also been demonstrated. For example, the 5-HT_3 antagonist tropisetron **27** was found to bind with nanomolar potency to the α_7 nicotinic acetylcholine receptor (nAChR) by Macor et al.,[32] and the COX-2 inhibitor celecoxib **28** was recently reported to potently inhibit carbonic anhydrases hCA II and IX but not hCA I (Figure 9).[33]

While there are many literature examples of the "designing in" approach for GPCRs, transporters,

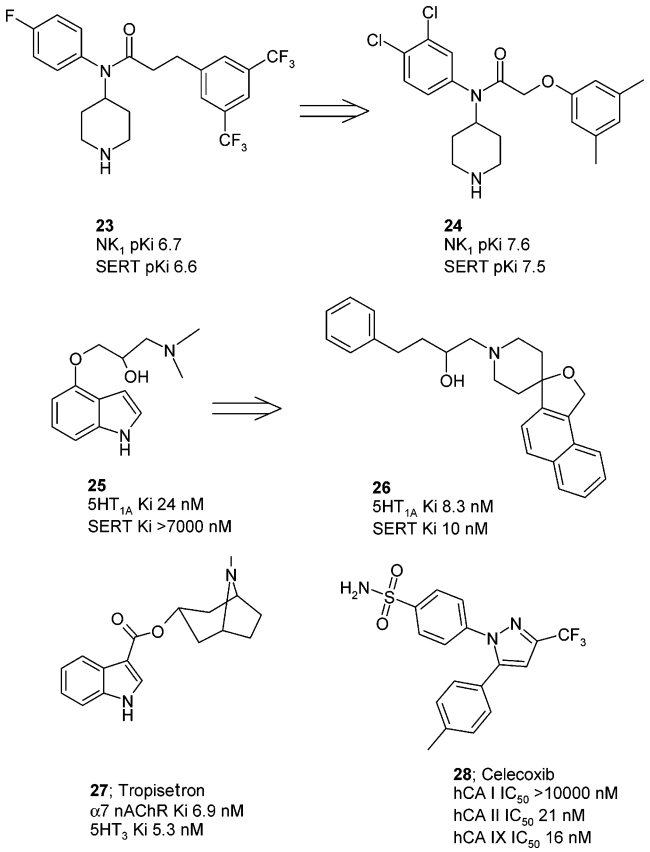


Figure 9. Structures of DMLs that were discovered via diversity or focused screening approaches.

nuclear receptors, proteases, and oxidases, we have so far identified no such examples for kinases or ion channels. Almost certainly, this is due to the fact that obtaining single target ligands for these superfamilies is still a major challenge, and this step has to precede the rational "designing in" of multiple activities, driven by a knowledge of the selective ligand SARs. Kinase DMLs are usually discovered serendipitously through cross-screening ligands from selective kinase programs against a wide panel of other kinases. At the present time, the most feasible strategy for designing multiple kinase inhibitors, acting via the ATP-binding site, appears to be starting from a nonselective inhibitor and attempting to "design out" undesired kinase activities.

The clinical effectiveness of imatinib **29** for the treatment of chronic myelogenous leukemia (CML) first validated the use of kinase inhibitors for the treatment of human disease (Figure 10). Currently there is growing interest in systematically targeting multiple kinases in order to increase efficacy in fighting diseases such as cancer.[34] In addition to its well-known activity as an Abl kinase inhibitor, imatinib has also been found to inhibit two other kinases, PDGFR and c-KIT, that might be involved in producing clinical efficacy. Imatinib was derived from a nonselective inhibitor **30** with activity at PDGF, PKCα, and Src.[35] The observation of Abl activity for this series was made later.[36] During subsequent optimization, the PKCα and Src activities were "designed out" via the introduction of a "flag methyl" group on the phenylaminopyrimidine scaffold **31**. Finally a piperidine ring was added to confer good solubility to imatinib **29**.

Compounds from Src kinase inhibitor programs are commonly found to possess activity at Abl, and dual Src/Abl inhibitors are currently of interest for the treatment of CML in patients who are resistant to imatinib because of mutations in the Abl gene. Boschelli et al. found a very close correlation between the Src and Abl SARs, reflecting the close homology of these kinases, and identified a high-affinity DML, **32** (Figure 10).[37]

The "designing out" strategy has also been applied successfully to other targets with conserved binding sites such as monoamine GPCRs, where broad-spectrum activity is commonly observed. For example, Bonnert et al. successfully "designed out" adrenergic α_1 activity from a dual dopamine D_2/adrenergic β_2 agonist.[38] Atkinson et al. removed adrenergic β_2 activity from a 5-HT_{1A}/SERT ligand.[39] In the peptide GPCR area, Reichard et al. "designed out" NK_3 affinity from a broad-spectrum neurokinin antagonist to give a dual NK_1/NK_2 antagonist.[40]

Main Areas of Focus in DML Discovery (1990−2004)

We have identified more than 300 references published in the primary medicinal chemistry journals since

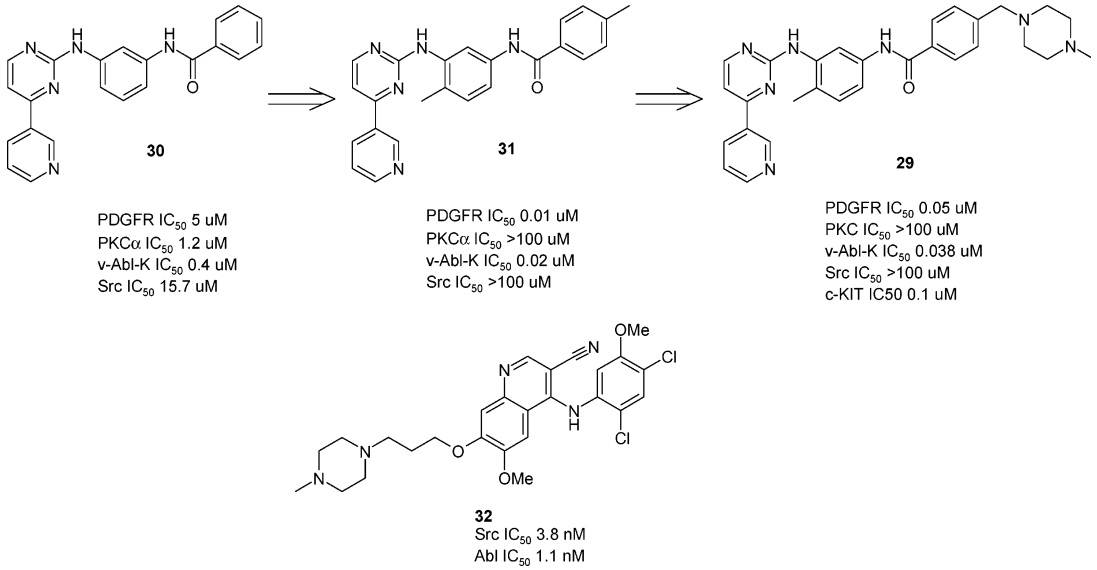


Figure 10. Structures of DMLs, **29** and **32**, that inhibit multiple kinases.

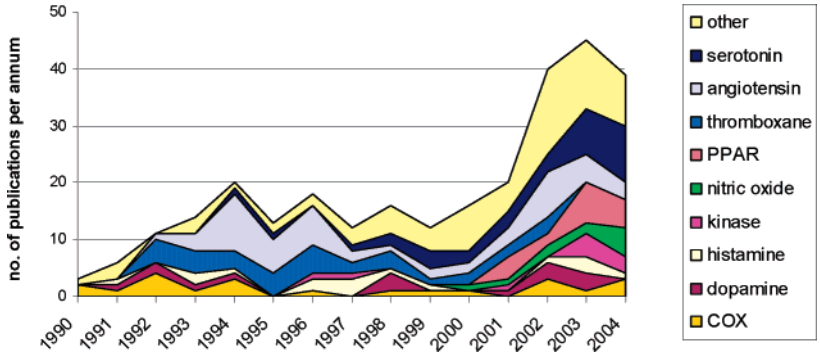


Figure 11. DML examples published in the primary medicinal chemistry literature between 1990 and 2004, classified according to the main areas of focus.[41]

1990 (Figure 11).[41] While our literature survey is inevitably incomplete because of the difficulties of tracking relevant articles, we believe that it is illustrative of the activity in the field. Moreover, the primary goal of this review is to focus on state-of-the-art design strategies rather than to provide a comprehensive compendium of multiple ligands. Compounds that were described only in patents or pharmacological journals were excluded, and indeed, many of the pioneering examples of multiple ligands from the pre-1990 period were also not included because the manner of their discovery either was serendipitous or has never been reported in depth. A relatively small number of target combinations have predominated in terms of their percentage share of the total number of publications. During the 1990s, activity was dominated by the angiotensin, thromboxane A_2, cyclooxygenase, and histamine target areas. More recently, new areas of focus have emerged, such as serotonin receptors, peroxisome proliferator activated receptors (PPARs), kinases, and nitric oxide releasing conjugates.

5HT Transporter-Based DMLs for Depression

There has been a long-standing hypothesis that depression is associated with reduced levels of 5-HT in the brain. First-generation tricyclic antidepressants, such as amitriptyline, were efficacious in many patients but suffered from a delayed onset of action as well as exhibiting cardiovascular side effects and toxicity in overdose. Second-generation agents, namely, the SSRIs, were considerably safer but were no better in terms of efficacy or time of onset. In an attempt to address these deficiencies, SERT inhibition has been combined with activity at a secondary monoamine target such as the GPCRs, $5HT_{1A}$, $5HT_{1D}$, α_2, and NK_1 receptors, or the transporters, NET and DAT.

The time delay for first- and second-generation drugs has been attributed to the need for the desensitization of 5-HT_{1A} autoreceptors by sustained SERT blockade, so mimicking this desensitization by antagonizing 5-HT_{1A} autoreceptors might accelerate the onset time. This theory is supported by clinical trials in which 5-HT_{1A} antagonists, such as (±)-pindolol, were found to accelerate the antidepressant effect of SSRIs.[42]

In one of the earliest papers in this area, Perez et al. described hybrids of the 5-HT_{1A} antagonist, pindolol **33**, and SERT ligands such as milnacipran **34** (Figure 12).[43] SERT motifs were attached to the 3-aryloxy-2-propanol framework of pindolol via a common nitrogen to give a

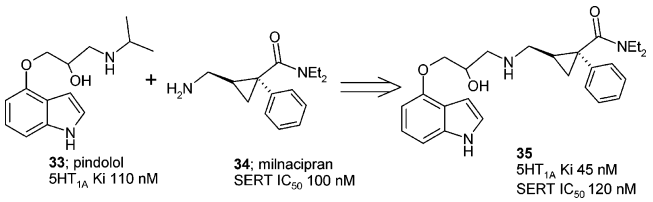


Figure 12. Design of a SERT/$5HT_{1A}$ ligand **35**.

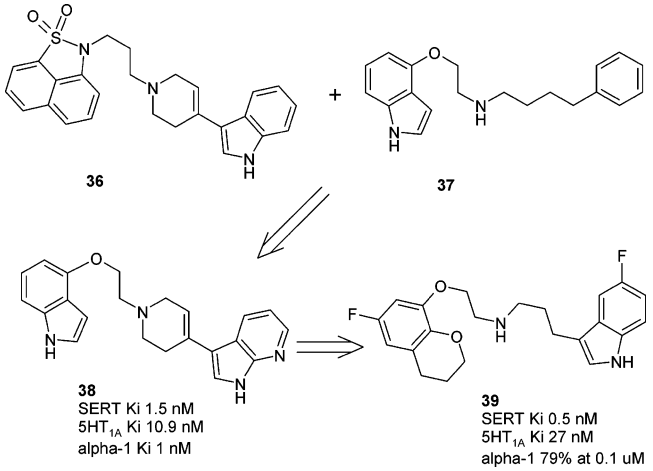


Figure 13. Design of a SERT/$5HT_{1A}$ ligand **39**.

reasonably well balanced DML **35**. However, compound **35** is not very potent, reflecting the relatively low activity of the two starting compounds.

In contrast, Mewshaw et al. started from a template known to possess robust SERT activity **36** and added 5-HT_{1A} features in the form of the aryloxyethyl group found in **37** (Figure 13).[44] The justification for this approach was that the 5-HT_{1A} pharmacophore was particularly well understood, and so this facilitated the incorporation of 5-HT_{1A}-conferring functionality. This illustrates an important general point in DML design; namely, that it is often wise to start with a compound for which the most difficult to optimize, or least understood, activity is closest to its required value and then to try to incorporate structural elements that seek to address the more tractable target. Once again, a basic nitrogen was the common feature that allowed the two frameworks to be merged to give **38**. In this case, it was observed that changes in the SERT derived area of the molecule influenced SERT activity more and that changes in the 5-HT_{1A} derived area of the molecule influenced 5-HT_{1A} activity more. However, this is by no means always the case, and often all regions of a DML are

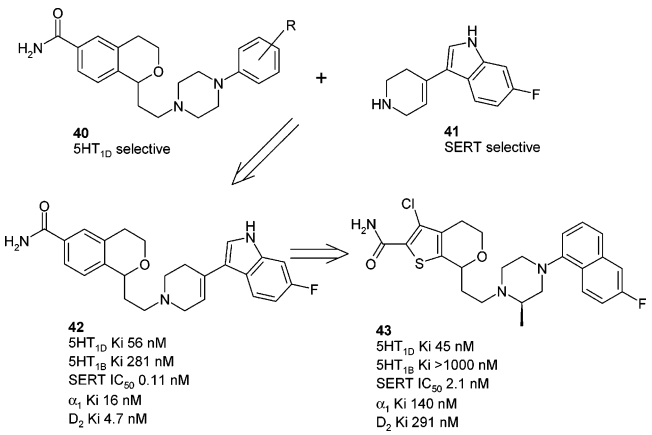


Figure 14. Design of a SERT/5HT$_{1D}$ ligand **43**.

found to affect all activities to a similar extent. The initial piperidine lead **38** had lower 5-HT$_{1A}$ activity than SERT activity and suffered from high adrenergic α_1 activity.[45] By introduction of a secondary amine, there was some improvement obtained in the selectivity over α_1 for **39**, but cross-reactivity still remained an issue for this series.

The slow onset of SSRIs has also been ascribed to a need for the desensitization of terminal 5-HT$_{1D}$ receptors, so some researchers aimed for dual SERT/5-HT$_{1D}$ blockers, such as Timms et al. at Eli Lilly.[46] Again, the basic nitrogen in both components, **40** and **41**, was used to merge the frameworks (Figure 14). Not only was the bulky biaryltetrahydropyridine group tolerated by 5-HT$_{1D}$, but its incorporation gave a serendipitous shift from 5-HT$_{1D}$ agonism for **40** to the desired antagonism for **42**. However, **42** suffered from a lack of balance of the two activities as well as cross-reactivity at α_1 and D_2 receptors. In a follow-on paper, Torrado et al. described modifications that significantly reduced α_1 and D_2 affinity, namely, the replacement of the indole by a naphthyl group and the introduction of a methyl group adjacent to the piperazine nitrogen.[47] Finally the introduction of a chloride substituent at C3 gave the best overall profile, **43**. In this example, both activities were similarly influenced by changes in the thienopyran and naphthylpiperazine regions of the molecule.

Most of the 5-HT examples employ knowledge-based "designing in" strategies. However, successful implementation of an HTS-based strategy was recently reported.[39] HTS was performed using a 5-HT$_{1A}$-expressing cell line, and actives were then triaged by testing for SERT blockade. The high potency of the hit **44** at 5-HT$_{1A}$ might be expected because of the pindolol **33**-like substructure, so in this case HTS did not produce a novel chemotype (Figure 15). High affinity at β_2 receptors was also observed. It was postulated that this cross-reactivity was due to the presence of an aryloxypropanolamine moiety. The simplified analogue **45**, lacking the hydroxy and methyl groups, retained 5-HT$_{1A}$ and SERT activity and had much reduced β_2 activity. Significantly, this is one of the few examples to date of rationally "designing out" an activity using knowledge of the pharmacophore for the undesired target. To increase potency, conformational constraint was introduced in the region of the basic amine and the indole was replaced by a 5-quinolinyloxy group. Compound **46** had a good profile together with low clearance in the rat and an oral bioavailability of 45%. The 2-methyl group on the quinoline ring served to protect that position from oxidation by aldehyde oxidase. Compound **46** was profiled against a panel of other receptors and transporters, and significant activity was only observed at 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors.

Adaptive changes in adrenergic α_2 heteroreceptors have also been implicated in the slow onset time for SSRIs. SERT inhibition may, by increasing 5-HT concentrations, activate not only 5-HT$_1$ autoreceptors but also α_2 heteroreceptors indirectly by enhancing NE release.[48] Thus, an agent that blocks both SERT and α_2 receptors might increase synaptic 5-HT levels above those achievable with a SSRI and produce a more rapid onset.

Meyer et al. identified through screening a hit compound **47** that had high affinity for the α_2 receptor and modest potency at SERT (Figure 16).[49,50] Potency at

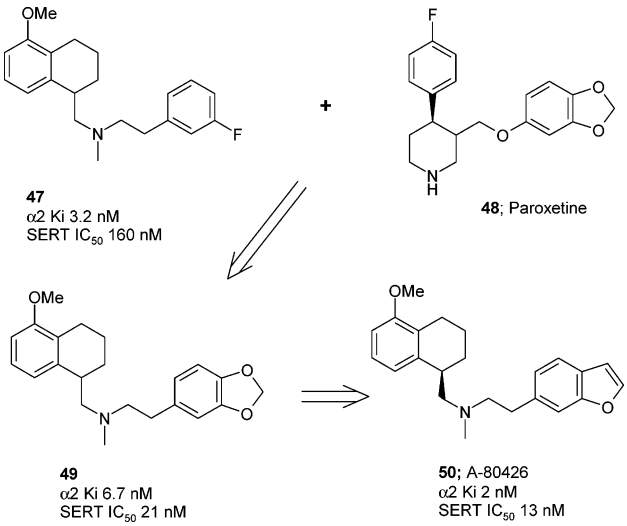


Figure 16. Design of a SERT/α_2 ligand **50**.

SERT was increased 8-fold by incorporating the methylenedioxyphenyl group from the potent SERT blocker, paroxetine **48**. Replacement of the methylenedioxy group in **49** by a benzofuran gave a slightly more potent compound, **50**. Crucially, both activities resided in the *R*-enantiomer. In the DML field, it is strongly preferred

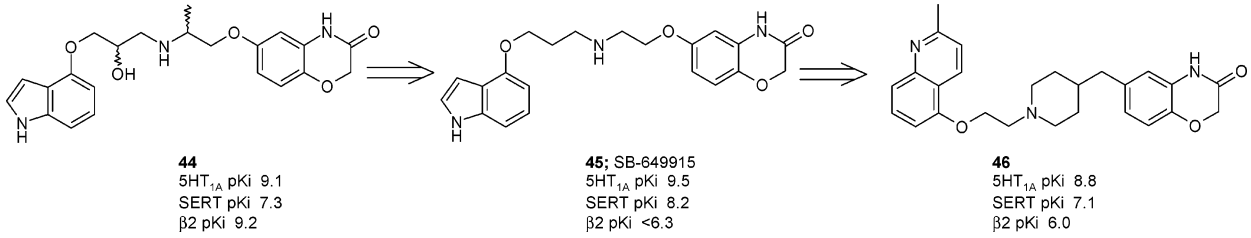


Figure 15. Design of a SERT/5HT$_{1A}$ ligand **46**.

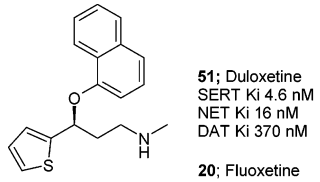


Figure 17. Structure of the SNRI ligand, duloxetine **51**.

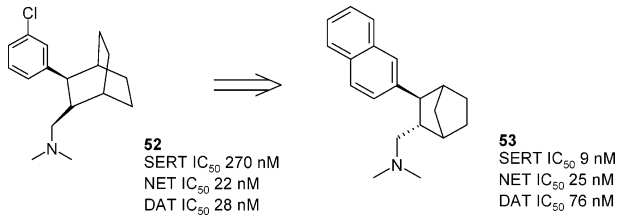


Figure 18. Design of the SMUB ligand **53**.

that all activities reside in a single enantiomer because if a racemate is used, differences in metabolism between the two enantiomers may over time change the desired ratio of activities. The SAR in the region of the pendant arylethyl group was flat for both the α_2 receptor and the 5-HT transporter. The presence of a tolerant region that is common to both targets allows physicochemical properties, such as solubility, to be manipulated more easily. Changes to the 5-methoxy substituent on the tetralin ring affected SERT activity more than α_2 activity. Compound **50** is clean at a wider panel of monoamine GPCRs and transporters, except D_2 (K_i = 52 nM) and 5-HT_2 (K_i = 144 nM), and demonstrated activity in the olfactory bulbectomized rat model of depression.

Another 5-HT-based approach for the treatment of depression was to combine SERT inhibition with activity at other monoamine transporters.[51] For example, the dual SERT/NET blocker (SNRI), duloxetine **51**, is being clinically evaluated as an antidepressant (Figure 17). Duloxetine belongs to the same aryl benzyl ether series as fluoxetine **20**. A key difference is the presence of a naphthyl group, which is important for imparting dual activity.

Supermixed uptake blockers (SMUBs), which concurrently block the reuptake of 5-HT, NE, and DA, may possess mood-elevating properties and, provided the three potencies are appropriately balanced, may deliver better control of depression than either SSRIs or SNRIs. Axford et al. started from a mixed NE and DA reuptake inhibitor **52** and attempted to enhance SERT activity (Figure 18).[52] Pharmacophore models predicted that a bicycloaryl group could be tolerated by all three binding sites, and by introduction of a 2-naphthyl group, SERT activity was increased and NET and DAT activity was retained, **53**. The 2-(*S*),3-(*S*) isomer was active in in vivo models of 5-HT, NE, and DA function.

Dopamine D_2-Receptor Based DMLs for Schizophrenia

The pharmacological treatment of schizophrenia has traditionally been dominated by D_2 antagonists such as haloperidol. While demonstrating efficacy against the positive symptoms of the disease (hallucinations, delusions), haloperidol does not address the negative symptoms (such as social withdrawal) and caused extrapyramidal side effects (EPS) such as Parkinsonism. The "atypical" antipsychotic drug clozapine addresses both positive and negative symptoms without producing EPS but in a few cases causes potentially fatal agranulocytosis. One of a number of possible explanations for this atypical profile is that clozapine has higher antagonist affinity for the 5-HT_2 receptor than it does for the D_2 receptor. This observation led to the so-called "D_2/5-HT_2 ratio" hypothesis whereby agents with >10-fold selectivity for 5-HT_2 over D_2 were sought. Several atypical antipsychotics with low D_2/5-HT_2 binding ratios have now been introduced onto the market, such as risperidone,[53] quetiapine,[54] and olanzapine.[55]

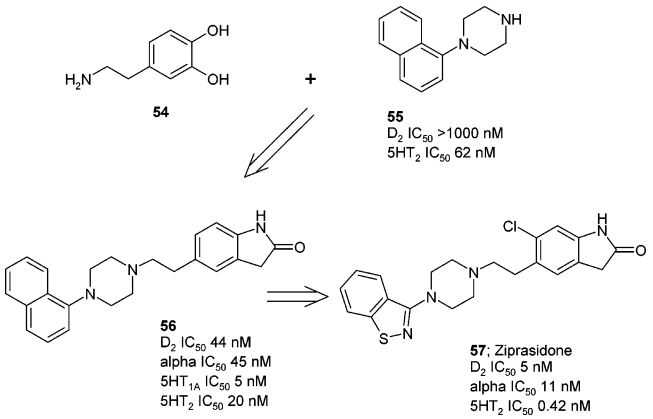


Figure 19. Design of the D_2/$5HT_{2A}$ ligand ziprasidone **57**.

A strategy employed by Lowe et al. at Pfizer was based on ideas first espoused by Ariens in the 1970s. The structure of the endogenous agonist for the D_2 receptor, dopamine **54**, was modified with a large lipophilic group from the 5-HT ligand **55**, which transformed the D_2-agonist activity of the endogenous ligand into an antagonist (Figure 19).[56] Various heterocyclic groups were selected containing hydrogen-bonding groups that might mimic the phenolic interaction, such as the oxindole found in **56**. Further optimization involved replacing the naphthyl group by a 1,2-benzisothiazole group (**57**), which provided D_2 blockade comparable in potency to the typical antipsychotic haloperidol, together with a desirable D_2/5-HT_2 ratio of 11, comparable to the atypical agent clozapine.[57] The D_2/α_1 ratio of 0.44 for **57** is substantially lower than that for clozapine, suggesting that the former should have less propensity to cause orthostatic hypotension. The ratio hypothesis was validated by clinical studies, and **57** (ziprasidone) was launched in 2001 by Pfizer for the treatment of schizophrenia.

D_4 selective antagonists were found to be ineffective in a phase 2 trial in schizophrenics.[13] Thereafter, it was postulated that the unique profile of clozapine in treating psychosis may be due to a precise ratio of affinities between D_2 and D_4 receptors, with higher affinity required at D_4 than at D_2. Zhao et al. tried to reproduce this exact ratio with the goal of obtaining D_4 affinity of less than 10 nM, D_2 affinity of less than 200 nM, and to minimize cardiovascular side effects, α_1 affinity above 1000 nM.[58] They started from a nonselective $D_2/D_4/\alpha_1$ compound **58** discovered via a screening approach (Figure 20). Introduction of a methyl group in the 2-position of the indoline ring gave a dramatic reduction

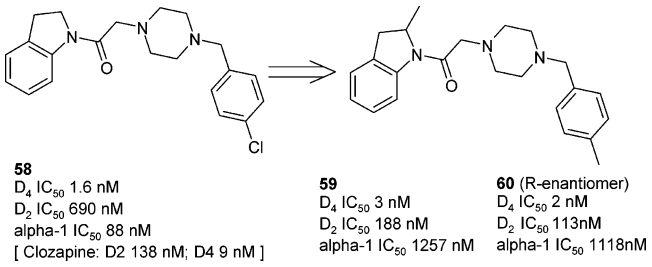


Figure 20. Design of the D_2/D_4 ligand **60**.

in α_1 activity as well as a slight improvement in D_2 activity, **59**. The *R* enantiomer **60** displayed a slightly better profile than the racemate and also had good selectivity against a diverse range of other targets, with limited activity at SERT ($IC_{50} = 500$ nM).[59] It displayed activity in an in vivo test of psychosis, the inhibition of amphetamine-induced locomotor activity, and showed low activity in a catalepsy test, suggesting a low propensity to cause EPS. The behavioral data for this dual antagonist provided support for the "D_2/D_4 ratio" hypothesis, although the approach still needs clinical validation.

Histamine H_1 Receptor-Based DMLs for Allergies

Histamine is a primary mediator of the immediate allergic response in humans. H_1 receptor antagonists have found utility in the treatment of hay fever and other allergic reactions but have been largely ineffective for the treatment of asthma.[60] Interestingly, almost all the H_1 antagonists that show some efficacy against asthma are reported to possess additional activities, suggesting that other chemical mediators are also involved in its pathogenesis. As a result, various groups aimed to produce DMLs combining H_1 antagonism with platelet activating factor receptor (PAF), thromboxane-A_2 receptor (TxA_2R), leukotriene D4 (LTD_4), or 5-LOX activity.

Clinical data had demonstrated that patients treated with a combination of an H_1 antagonist and an LTD_4 antagonist responded better than those treated with a single agent.[61] Zhang et al. screened 22 structurally diverse H_1 antagonists against LTD_4 and found that cyproheptadine **61** exhibited weak activity against LTD_4-induced contraction of guinea pig ileum (50% inhibition at 10 μM) (Figure 21).[62] It was reasoned that the potency could be increased by incorporating structural features from the endogenous agonist LTD_4 **62**, since many LTD_4 analogues showed antagonist activity. Incorporation of an amino acid like group from LTD_4 at the nitrogen of cyproheptadine, a tolerant region, gave **63**, which had well balanced affinity for both GPCRs. Compound **63** was tested for inhibitory activity against the antigen-induced contraction of guinea pig trachea and was found to be more efficacious than selective H_1 or LTD_4 antagonists.

Since leukotriene biosynthesis is mediated via 5-LOX, an alternative approach was to combine H_1 antagonism with 5-LOX inhibition. The starting points for framework combination were the selective H_1 antagonist **64** and the 5-LOX inhibitor **65** (Figure 22).[63] Once again, the strategy took advantage of the flat SAR around the basic nitrogen of the antihistamine to introduce a butynylhydroxyurea group required for 5-LOX inhibition, **66**.

Ohshima et al. aimed to combine H_1 and TxA_2R pharmacophores in a single molecule for the treatment of allergies.[64] This endeavor was facilitated by the observation that both the selective H_1 antagonist **67** and the TxA_2R antagonist **68** contained a common benz[*b*,*e*]-oxepin scaffold (Figure 23). This example illustrates that it might still be possible to obtain DMLs even for target combinations where the endogenous ligands are highly dissimilar. The tertiary amine group in **69** successfully mimicked the benzimidazole moiety that was known to be crucial for the TxA_2 activity of **68**. Compound **69** was active at both GPCRs, albeit with rather different binding affinities, and was selective over related GPCRs.

Aslanian et al. aimed for a dual H_1/H_3 antagonist for the treatment of allergic diseases such as nasal congestion.[65] The approach was based on the combination of structural features from the H_1 antagonist **70** and the alkylamine class of H_3 antagonists **71**, using a common nitrogen as an anchor group, **72** (Figure 24).

The most advanced area of "H_1 plus" research from a clinical perspective has been dual H_1/PAF receptor antagonism. PAF appears to act alongside HA in the pathogenesis of the allergic response.

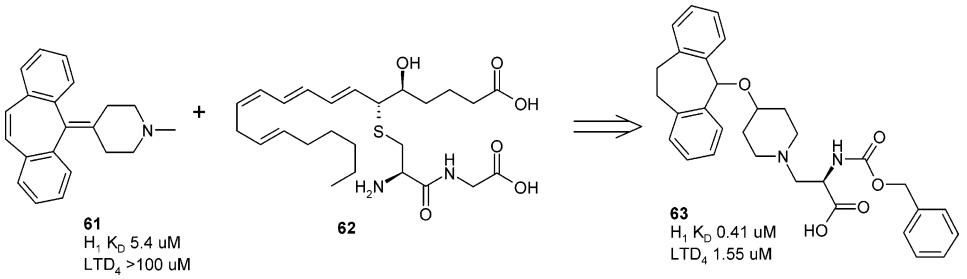


Figure 21. Design of the H_1/LTD_4 ligand **63**.

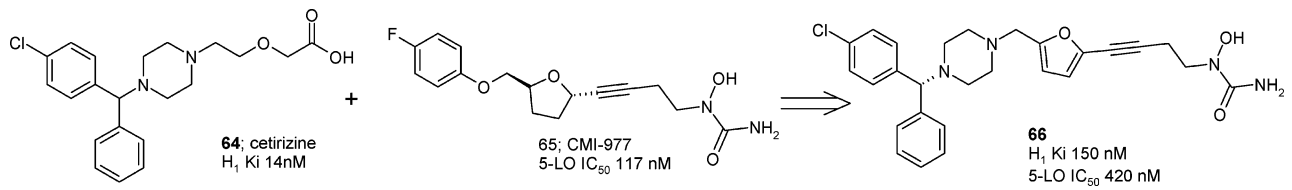


Figure 22. Design of the H_1/5-LO ligand **66**.

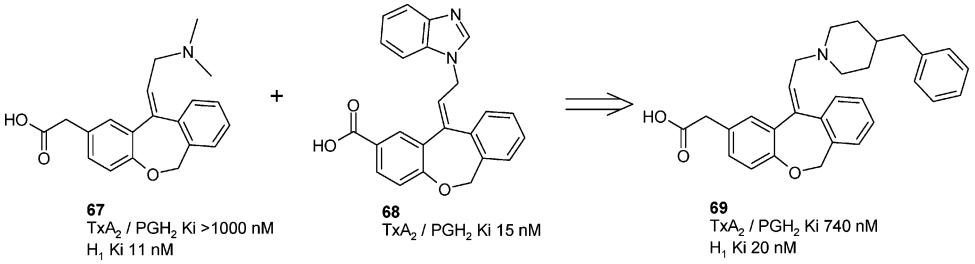


Figure 23. Design of the H_1/TxA_2 ligand **69**.

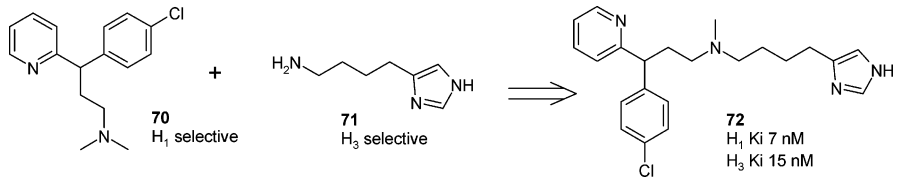


Figure 24. Design of the H_1/H_3 ligand **72**.

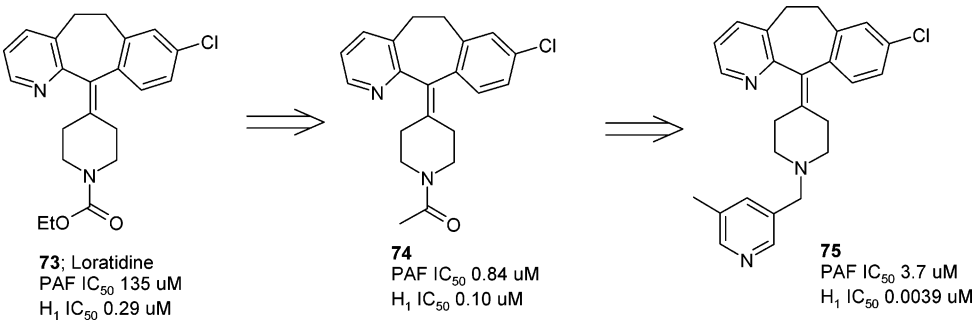


Figure 25. Design of the H_1/PAF ligand **75**.

Piwinski et al. observed that the H_1 antagonist **73** (loratidine) was a very weak PAF antagonist (Figure 25).[66] To increase the PAF activity, the ethoxycarbonyl group was replaced by a simple acetamide **74**. The SAR for PAF and H_1 receptors was fundamentally different, reflecting the difference in the lipophilicity of the endogenous ligands. The series was further optimized by replacing the acetamide by a 3-pyridylmethyl group **75**, which was 25-fold more active than **74** in the H_1 assay and marginally less active in the PAF assay.[67] Compound **75** (rupatidine, UR-12592) was more active than loratidine in an HA-dependent in vivo test of passive cutaneous anaphylactic shock after oral dosing and has been launched by Uriach for the treatment of allergic rhinitis.

The possibility that combined blockade of H_1 and NK_1 receptors might produce added therapeutic benefit led to the exploration of dual inhibitors by Maynard et al.[68] On the basis of an understanding of the SARs for H_1 and NK_1 antagonists such as **76** and **77**, it was predicted that hybrid structures such as **78** would retain NK_1 affinity (Figure 26). The compounds from this series were subjected to CoMFA analsis. This indicated that the benzamide end of the molecule **78** harbored the NK_1 activity without significantly affecting H_1 activity. Variations to the benzimidazole end affected H_1 activity much more than NK_1 activity. Supporting this observation, overlays of **78** with selective H_1 and NK_1 antagonists indicated little in common between them.

DMLs Targeting the Angiotensin System for Hypertension

Angiotensin converting enzyme (ACE) inhibitors, such as captopril **79**, gained wide acceptance for the treatment of hypertension and congestive heart failure (Figure 27). Neutral endopeptidase (NEP) is another metallopeptidase that is responsible for the degradation of atrial natriuretic peptide (ANP), a peptide hormone with opposing actions to those of angiotensin II (AT-II), which is released by the heart in response to atrial distension and causes vasodilatation. Consequently, it has been postulated that dual ACE/NEP inhibition may produce a beneficial synergistic effect in the management of hypertension and congestive heart failure.

One of the earliest dual ACE/NEP inhibitors, dipeptide **80**, was rationally designed using the knowledge of binding requirements for both enzymes. NEP favors a hydrophobic substituent at S1′, preferably a benzyl group such as that present in the NEP selective inhibitor **81** (SQ28603), whereas ACE is more tolerant in this region but strongly favors a proline residue at P_2'.[69] To further improve the in vitro and in vivo potency, a group at Bristol-Myers Squibb (BMS) focused their optimization efforts on conformationally restricted dipeptide mimetics. A range of diverse constrained analogues have been designed by drawing extensively from the SAR generated for selective ACE inhibitors. One of main challenges for optimization within this series proved to be a relatively tight SAR for NEP. Fortuitously, this was counterbalanced by a remarkably flexible SAR for ACE. One of the most successful biomimetics was a series of

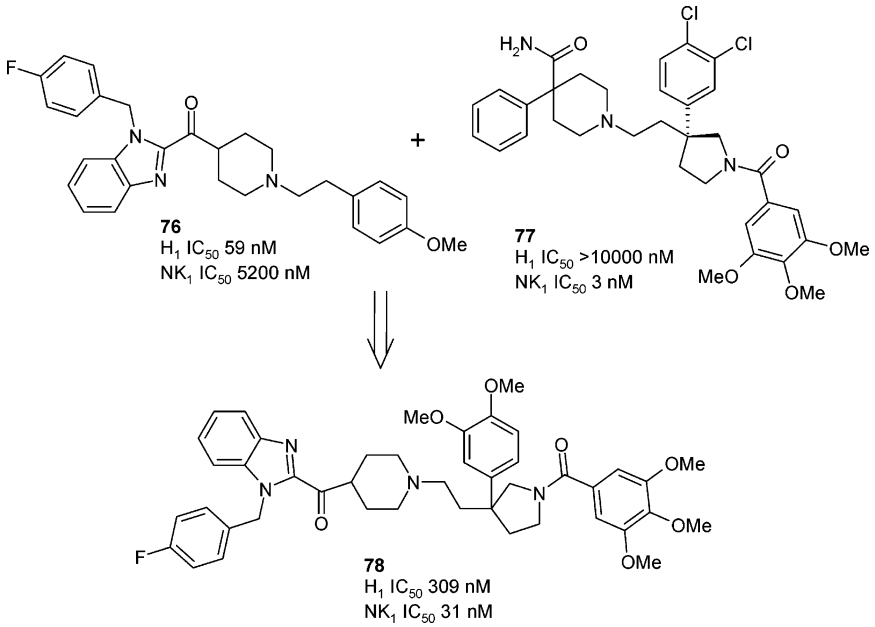


Figure 26. Design of the H_1/NK_1 ligand **78**.

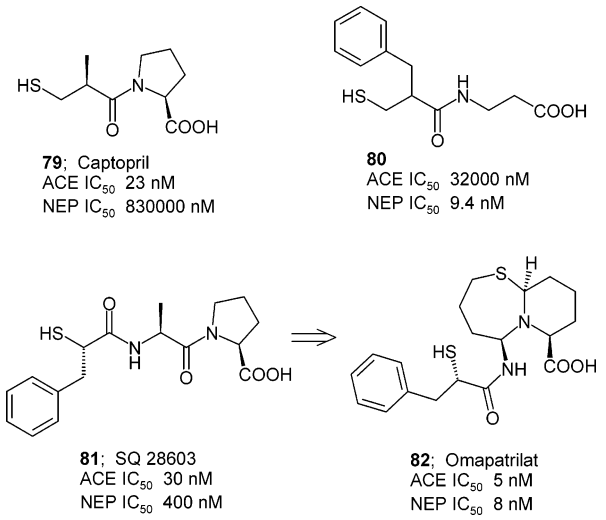


Figure 27. Design of the ACE/NEP ligand omapatrilat **82**.

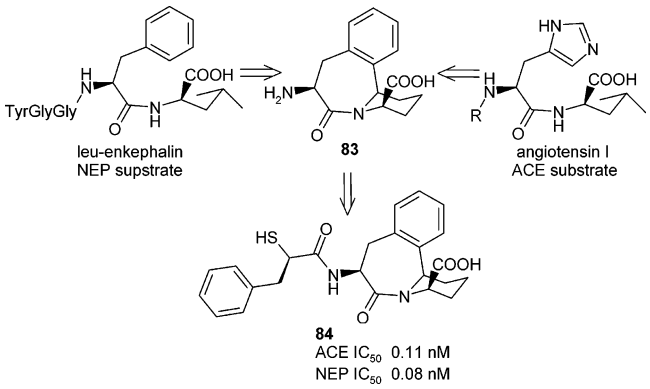


Figure 28. Design of the ACE/NEP ligand **84**.

7,6- and 7,5-fused bicyclic thiazepinones and oxazepinones. Omapatrilat **82** displayed high ACE/NEP potency and the best pharmacokinetic profile in this series, so it was advanced into clinical development for treatment of hypertension.[70]

Scientists at Marion Merrell Dow also employed a constrained dipeptide mimetic strategy for the design of dual ACE/NEP inhibitors except that instead of starting from a known inhibitor like the BMS group, they adopted a substrate-based approach. This strategy is based on the fact that the two proteases cleave similar dipeptide fragments from their natural substrates, indicating topological similarity within the prime sides of their active sites, the region to which inhibitors such as captopril and SQ 28603 bind. Therefore, a highly constrained anti phenylalanine containing dipeptide mimetic **83** was designed to mimic a postulated low-energy conformation of the His-Leu portion of angiotensin I bound to ACE and the Phe-Leu portion of Leu-enkephalin bound to NEP (Figure 28). Indeed, the corresponding mercaptoacetyl derivative **84** was found to be a highly potent inhibitor of both ACE and NEP.[71]

One of potential limitations of the ACE/NEP dual inhibition approach is an increase in plasma levels of endothelin I (ET-1), a vasoconstricting peptide similar to angiotensin II that is degraded by NEP. This might be overcome by additionally inhibiting endothelin converting enzyme (ECE-1), a closely related zinc metallopeptidase involved in ET-1 formation that has a 51% homology to NEP in the active site region. To tackle the challenge of designing a triple inhibitor, Roques et al. synthesized noncyclic constrained compounds that interact with the S1′ and S2′ subsites of the three enzymes and bear a thiol group as the zinc ligand, with the general formula $HSCH_2CH(P1')CO$-Trp-OH. It was reasoned that a noncyclic constraint should still lead to increased affinity by reducing the entropy loss upon binding, but unlike cyclic constraints, there would be some residual structural flexibility that would allow for adaptation at each of the three active sites. Owing to the importance of the P2′ tryptophan residue for interacting with the S2′ subsite of ECE-1, this group was held constant. One of the best compounds derived from this approach was the indanyl analogue **85** displaying potent triple inhibition (Figure 29).[72]

Like ACE inhibitors, AT-II receptor antagonists are clinically efficacious agents for controlling hypertension. The first agents introduced to the market, such as

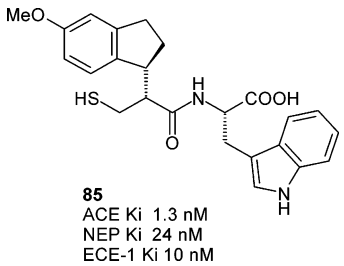


Figure 29. Structure of the ACE/NEP/ECE-1 ligand **85**.

losartan, were selective for the AT_1 receptor over the AT_2 receptor. Antagonism of the AT_1 receptor was found to result in an elevation of circulating angiotensin II levels, which has the potential to lead to an overstimulation of AT_2 receptors. Therefore, it was thought that a dual AT_1/AT_2 ligand might have clinical advantages.

Screening of a number of AT_1 selective quinazolinones at the AT_2 receptor revealed compounds with weak activity, such as **86** (Figure 30).[73] The introduction of a propyl group in the 2-position, together with increasing the size of the 6 substituent, led to a well balanced antagonist, **87**, that was active orally in inhibiting the pressor response in normotensive rats to exogenously administered AT-II. An ex vivo binding assay using plasma samples from the dosing of normotensive rats with **87** was used to confirm that balanced AT_1/AT_2 inhibition was maintained in vivo. Clearly, when working with DMLs, it is important to confirm that balanced activity in a simple in vitro assay translates into an appropriate balance in a whole animal.

A combination of the AT_1 selective antagonist losartan and the ET_A/ET_B selective antagonist SB-290670 produced an additive reduction in blood pressure compared to either drug alone, prompting groups at Merck and BMS to develop simultaneous blockers of AT_1 and ET_A receptors.[74] Fortunately, these two peptide-binding GPCRs share a number of structural and functional similarities. The aromatic-containing amino acids at positions 13 and 14 of the endothelins, as well as the C-terminal acid, are crucial for ET_A binding. Conveniently, such groups are appropriately positioned in some non-peptide AT_1 antagonists, and this prompted Merck to conduct a focused screen of AT_1 ligands for ET_A affinity.[75] Compounds with weak ET_A activity were identified, such as **88** (Figure 31). Incorporation of a benzodihydrofuran and an acylsulfonamide acid isostere gave ligand **89**, which exhibited balanced activity at all four receptors.

The design strategy followed by Murugesan et al. was based on the observation that both the selective AT_1 and ET_A antagonists, **90** and **91**, respectively, contain a biaryl core (Figure 32).[76] Fortuitously the heterocycle

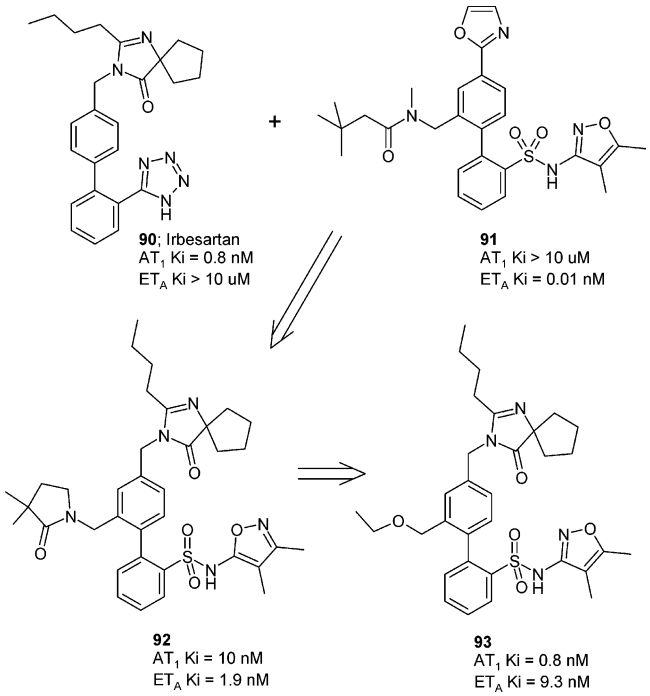


Figure 32. Design of the AT_1/ET_A receptor ligand **93**.

in the 4′-position of the biaryl, required for AT_1 activity, was tolerated by ET_A, albeit with reduced affinity. The

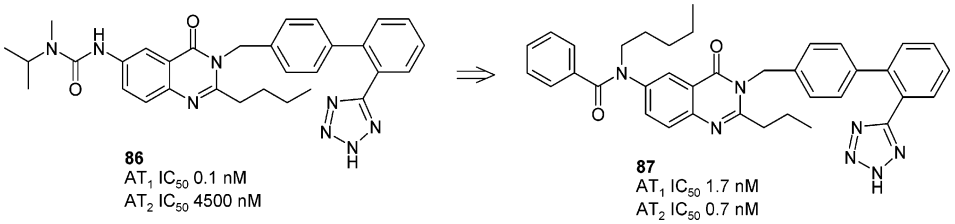


Figure 30. Design of the AT_1/AT_2 ligand **87**.

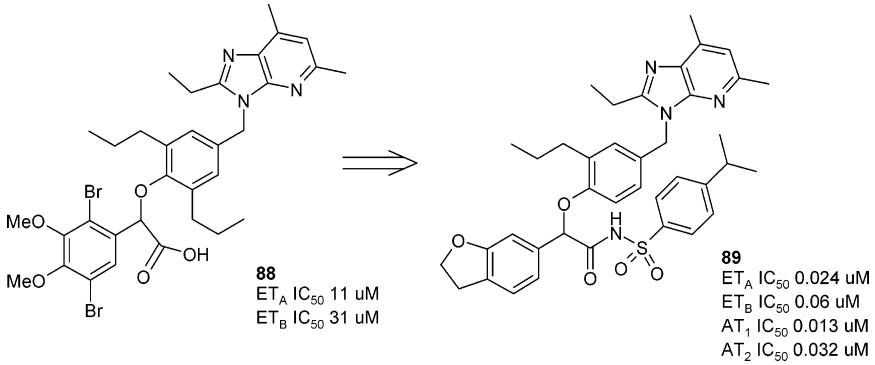
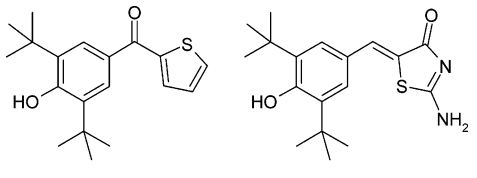


Figure 31. Design of the angiotensin/endothelin receptor ligand **89**.



94; R-830
COX IC_{50} 0.5 μM
5-LOX IC_{50} 20 μM

95; PD 136095
COX IC_{50} 0.39 μM
5-LOX IC_{50} 0.77 μM

Figure 33. Structures of the COX/5-LOX ligands **94** and **95**.

acylsulfonamide moiety was found to be a carboxylic acid bioisostere that was suitable for both receptors. By introduction of a new substituent in the C2′ position of the biaryl, a balanced dual activity at AT_1 and ET_A receptors was obtained, **92**. Interestingly, unlike **89**, this compound was selective over AT_2 and ET_B receptors.

Good oral bioavailability was observed in rats (F = 38%), but this compound was found to have lower oral bioavailability in dogs and monkeys (<10%). Further optimization focused on reducing the molecular weight and the number of hydrogen-bonding groups and addressing a site of metabolism on the 5-aminoisoxazole ring.[77] Incorporation of a 3-isoxazole solved this metabolism problem, and the use of a 2′-ethoxymethyl substituent helped to lower the molecular weight. Compound **93** showed good oral bioavailability in rats, dogs, and monkeys (40%, 86%, and 21% respectively) and was superior to irbesartan in the spontaneously hypertensive rat model, demonstrating the synergy of AT_1 and ET_A blockade.

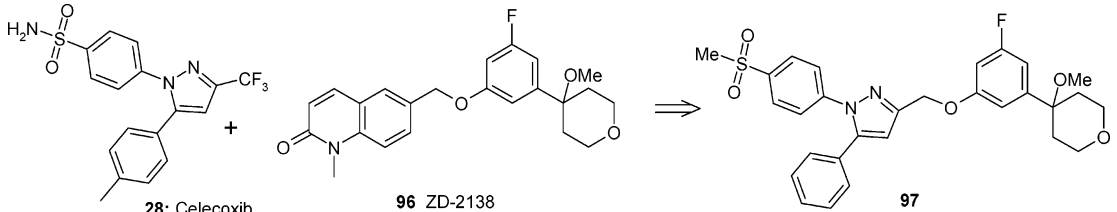
Nonsteroidal Anti-Inflammatory Drugs

NSAIDs exert their anti-inflammatory effect by inhibiting COX-1 and COX-2, key enzymes in prostaglandin (PG) biosynthesis from arachidonic acid.[78] Side effects often limit their use, in particular gastrointestinal ulcerogenic activity and renal toxicity.[79] In contrast to the "single target" strategy adopted for COX-2 inhibitors like celecoxib **28**, a number of DML approaches targeting various key proteins involved in arachidonic acid biosynthesis have been reported. These include combinations of COX/5-LOX, 5-LOX/TxA_2S, and TxA_2R/TxA_2S.

NSAID-induced gastric toxicity may involve the shunting of arachidonic acid metabolism from the COX to the 5-LOX pathway, thereby producing proinflammatory and gastrotoxic leukotrienes such as LTB_4.[80] Thus, combined inhibition of COX and 5-LOX may provide safer and more effective NSAIDs.[17,81]

A hypothesis suggesting important roles for free radicals in the inflammatory process led to the serendipitous discovery of the "redox-based" class of COX/5-LOX dual inhibitors. One of the earliest such compounds was R-830, **94**, and its anti-inflammatory efficacy was attributed to antioxidant and radical scavenging properties of the phenol group (Figure 33).[82] The 2,6-di-*tert*-butyl-1-hydroxy substitution pattern was shown to be optimal for dual inhibition and in vivo activity. Reducing the size of one of the *tert*-butyl groups had no detrimental effect on the in vitro profile, but the resulting derivatives lacked in vivo efficacy, possibly because of rapid phase II metabolism.[83] Optimization activities therefore focused almost entirely on the 4-position, which proved to be more tolerant of change. Researchers at Parke-Davis aimed to improve the generally poor aqueous solubility of this class of compounds, with a range of ionizable groups in the 4-position. This work led to the discovery of a potent DML PD-136095, **95**, which possessed favorable physicochemical and pharmacokinetic properties.[84]

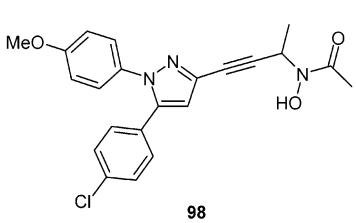
Henichart et al. designed a dual COX-2/5-LOX inhibitor by fusing the tricyclic moiety present in celecoxib **28** with a aryltetrahydropyran moiety from the 5-LOX inhibitor, **96** (ZD-23138) (Figure 34).[85] Both starting compounds were completely inactive at the second target, but the resulting DML **97** possessed nanomolar potencies for both enzymes, as well as surprising selectivity for COX-2 over COX-1. Modeling studies revealed that the aryltetrahydropyran group actually enhanced affinity for COX-2 by interacting positively with several amino acids in its active site.



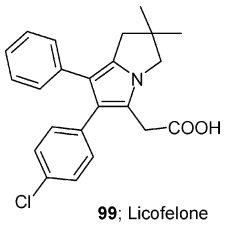
28; Celecoxib

96 ZD-2138

97
COX-2 IC_{50} 50 nM
5-LOX IC_{50} 3 nM
COX-1 IC_{50} > 10 uM



98
COX IC_{50} 0.03 μM
5-LOX IC_{50} 0.11 μM



99; Licofelone
COX-1 IC_{50} 0.16 μM
COX-2 IC_{50} 0.37 μM
5-LOX IC_{50} 0.21 μM

Figure 34. Structures of the COX/5-LOX ligands **97**−**99**.

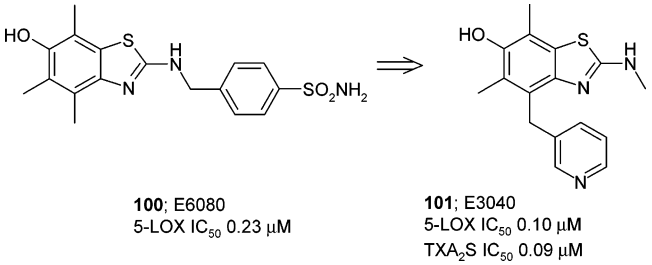


Figure 35. Design of the TxA_2/5-LOX ligand **101**.

An observation that arachidonoyl hydroxamate is a potent inhibitor of 5-LOX,[86] presumably because of chelation of the iron in the enzyme catalytic site, led to the development of a range of hydroxamic acid and *N*-hydroxyurea-based 5-LOX selective inhibitors.[87] This finding has also been successfully used in the rational design of dual inhibitors such as **98**, which is a result of the combination of the tricyclic core characteristic of selective COX-2 inhibitors such as celecoxib **28** and the iron-chelating hydroxamic acid of 5-LOX inhibitors.[88]

Licofelone **99**, first reported in 1994 by scientists at Merckle GmbH, is currently in phase III clinical studies for the potential treatment of osteoarthritis (Figure 34). Lacking an iron-chelating functionality and antioxidant properties, the compound is considered a substrate-based inhibitor. A good alignment of licofelone with a hypothetical conformation of arachidonic acid bound to COX and LOX has been achieved. The carboxylic acids overlap, and the two aromatic groups in **99** match the double bonds of arachidonic acid.[89]

Arachidonic acid is converted by COX enzymes into prostaglandin H_2 (PGH_2), which in turn is converted by TxA_2 synthase (TxA_2S) into TxA_2. Increased levels of LTB_4 and TxB_2, the stable metabolite of TxA_2, have been associated with inflammatory bowel disease, stimulating an interest in developing dual inhibitors of 5-LOX and TxA_2S. Hibi et al. started from a selective 5-LOX inhibitor, E6080 **100**, into which they incorporated a pyridine moiety known for its potential to coordinate the iron atom in the enzyme catalytic site (Figure 35).[90] Whereas the replacement of the phenylsulfonamide group in **100** with a methylene-3-pyridinyl moiety was unsuccessful, attachment of the pyridinyl substitution to the phenol portion of the molecule led to a series of compounds displaying a well balanced dual profile, of which compound **101** was most potent.

TxA_2R activation triggers platelet aggregation, vasoconstriction, and bronchoconstriction, so targeting the TxA_2 pathway is of interest for the treatment of cardiovascular, renal, and pulmonary diseases. Selective TxA_2R antagonists and TxA_2S inhibitors were developed as antiplatelet agents, but clinical results were disappointing. The lack of efficacy was attributed to the accumulation of PGH_2, which itself is a potent agonist of TxA_2R.[91] It was therefore hypothesized that dual blockers of TxA_2R and TxA_2S may show improved efficacy by simultaneously blocking the actions of both TxA_2 and PGH_2 while conveniently shunting PGH_2 metabolism toward beneficial PGI_2 with its vasodilating and platelet aggregation inhibitory effects.[92,93]

The essential structural features of TxA_2S inhibitors such as isbogrel **102** are a pyridine nitrogen and a carboxylic group separated by a distance range between 8.5 and 10 Å (Figure 36).[94] Since TxA_2S is a cytochrome P-450 enzyme, it was postulated that the pyridine moiety forms a complex with the heme group of the enzyme catalytic site. A key feature of TxA_2R antagonists such as daltroban **103** is a carboxylic acid separated by a nonspecific spacer from a benzenesulfonamide group. Integration of the TxA_2S and TxA_2R features produced compounds such as samixogrel **104**, which showed low nanomolar activity at both targets.[95]

Adopting a similar approach, researchers at Pfizer combined structural features from the TxA_2R antagonists sulotroban **105** with an imidazole-containing TxA_2S inhibitor **106** to give **107** (Figure 37). Replacement of the imidazolyl group with a pyridinyl group resulted in increased potency at both targets, **108**.[96]

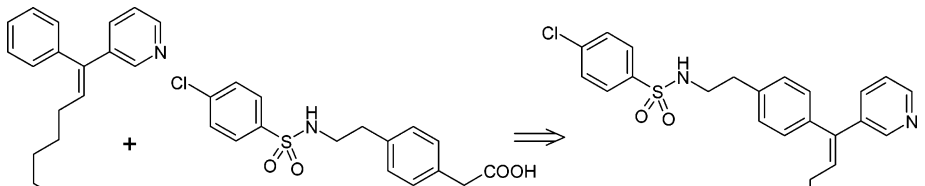


Figure 36. Design of the TxA_2R/TxA_2S ligand **104**.

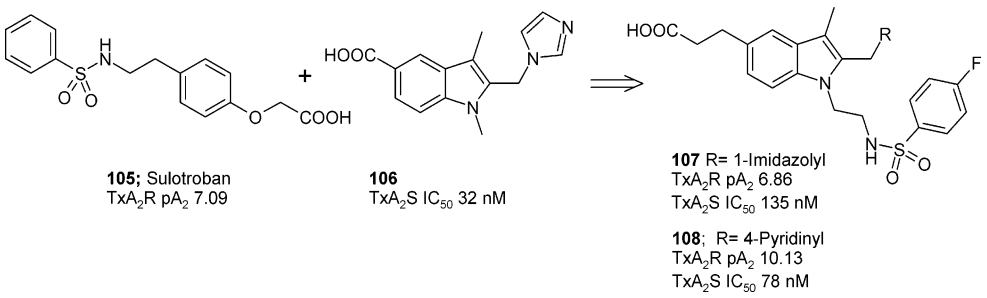


Figure 37. Design of the TxA_2R/TxA_2S ligand **108**.

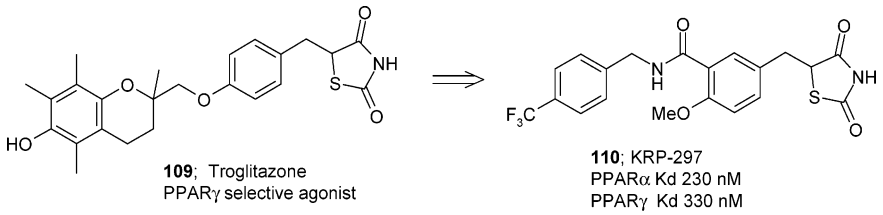


Figure 38. Design of the PPARα/γ dual agonist **110**.

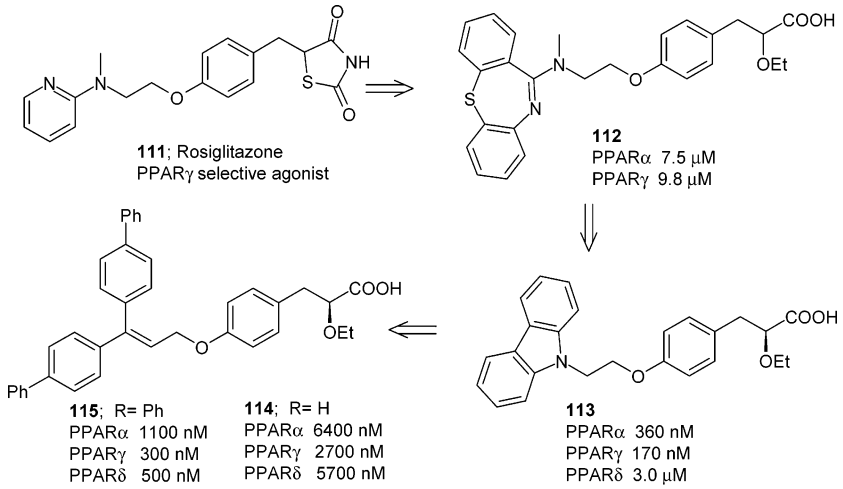


Figure 39. Design of the PPARα/γ/δ triple agonist **115**.

PPAR-Based DMLs for Metabolic Disease

The realization that the fibrate class of drugs used to treat dyslipidemia and the insulin-sensitizing thiazolidine-2,4-dione derivatives (glitazones) used in treatment of type 2 diabetes, exerting their effects through activation of PPARα and PPARγ, respectively, led to an explosion of research in this field and the development of selective ligands for each of the PPAR receptor subtypes. However, recent findings suggest that insulin resistance, dyslipidemia, and obesity can be seen as components of a complex mixture of abnormalities known as "metabolic syndrome". This has stimulated interest in developing dual PPARα and PPARγ agonists.[97] Dual agonists might be expected to show reduced PPARγ-mediated side effects, like weight gain and fluid retention.

The first reported "balanced" dual agonist, KRP-297 **110**, was identified through the testing of thiazolidine (TZD) derivatives of the PPARγ selective agonist troglitazone **109** in in vivo models of hyperglycemia and hyperlipidemia in genetically obese ob/ob mice (Figure 38).[98] The compound demonstrated superior efficacy compared to troglitazone. It was only later that the compound's dual in vitro profile was established, leading the authors to conclude that the superior in vivo pharmacological effects of KRP-297 could be attributed to its activation of both subtypes.

TZD derivatives were shown to completely racemize under physiological conditions. To avoid this problem, scientists at Novo Nordisk combined structural features of TZD-containing rosiglitazone **111**, a marketed PPARγ agonist, and the alkoxypropionic acid class of insulin sensitizers known for their reduced tendency for racemization (Figure 39).[99] This approach led to identification of the initial tricyclic lead **112** showing moderate but balanced dual activity. Molecular modeling studies based on the 3D structure of rosiglitazone cocrystallized with the PPARγ ligand binding domain (LBD) suggested a preference for planar tricyclic systems in the lipophilic "tail" region, which led to the discovery of the carbazole analogue **113**, a more potent PPARα/γ dual agonist showing around 10-fold selectivity over PPARδ.

Following reports that PPARδ selective agonists show increased levels of HDL cholesterol and decreased levels of triglycerides in obese monkeys, the same group further elaborated **113** with the aim of building in PPARδ activity and developing ligands with a pan-agonist PPARα/γ/δ profile.[100] They retained the acid component of the dual PPARα/γ agonist and focused on modifications to the lipophilic "tail". Opening the carbazole central ring and replacing the nitrogen with an sp^2 carbon led to the biphenyl analogue **114** with balanced activity across all three subtypes. The SAR exploration around phenyl rings of **114** showed that large and lipophilic groups are preferred in this region and ultimately led to identification of bis-biphenyl derivative **115** with more potent triple activity.

An interesting combination of screening and structure-based approaches, reported by a group at Eli Lilly,[101] resulted in the identification of carboxylic acid **116** containing a bulky lipophilic group in the α-position as a moderate dual PPARα/γ agonist (Figure 40). The fact that **116** exhibited activity for both targets despite lacking the lipophilic "tail" characteristic of PPAR ligands suggested that the α-benzyl group might improve the binding affinity of **117**, a well balanced dual agonist. The α-benzyl derivative **118** indeed showed improved activity at both PPARα and PPARγ. Shifting the oxygen adjacent to the quaternary stereogenic center in **118** to the alternative benzylic position provided a significantly more potent dual agonist **119**.

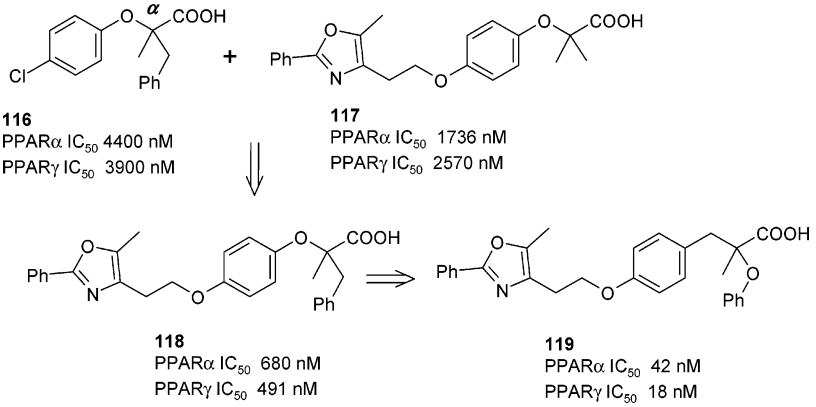


Figure 40. Design of the PPARα/γ dual agonist **119**.

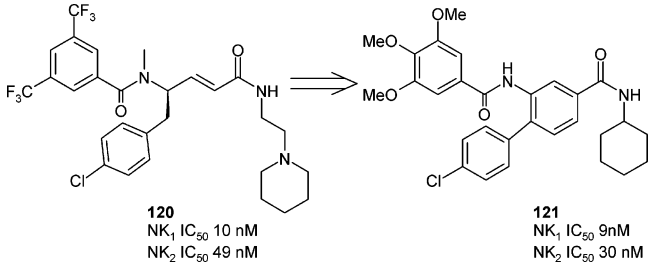


Figure 41. Simplification of a NK_1/NK_2 ligand, **120**, during lead optimization.

The Physicochemical Challenge

Given the need to satisfy two or more sets of stringent pharmacophoric requirements, it might be expected that sufficiently potent DMLs would be larger and more structurally complex than ligands that are selective for a single target. As we have previously reported, the average molecular weight for DMLs is considerably higher than that for marketed oral CNS or non-CNS drugs.[9] Larger, more lipophilic, and more flexible molecules are often associated with poorer oral absorption profiles, and yet this route of administration is required for most DMLs.[102,103] So optimizing the pharmacokinetics, in addition to attaining a balanced profile, is usually the most challenging aspect of working with DMLs. Many DML lead compounds have molecular weights well above 500 and clogP values greater than 5. To improve PK profiles, a strong emphasis has often been required during lead optimization on simplifying the structures by removing functionality and rotatable bonds. As described above, Murugesan et al. successfully improved the oral bioavailability of the AT_1/ET_A antagonist **92**. Mah et al. simplified the structure of the NK_1/NK_2 lead compound, **120**, to give a biaryl derivative **121** that possessed good oral bioavailability while maintaining the desired receptor profile (Figure 41).[104]

Where the pharmacophores are fundamentally different, it may not be possible to integrate the requirements of both binding sites into a small and compact molecule, and a higher molecular weight conjugate may be unavoidable. Inevitably, this will mean that some combinations of targets will be more difficult, if not impossible, to address with a "druglike" molecule. It is likely that rationally designing multiple ligands is most feasible where the targets are more similar, in terms of binding the same endogenous ligand or belonging to the same superfamily. While many DMLs reported in the literature thus far have the desired in vitro profile, they lack the in vivo activity and PK profile required for their further development as oral drugs. Nonetheless, such DMLs may represent useful pharmacological tools to validate particular target combinations, particularly if in vitro methods of target validation are available.

Conclusion

Compounds that act at multiple targets often deliver superior efficacy against complex diseases compared to compounds with high specificity for a single target. Consequently, there is increasing interest in the identification and validation of new target combinations that are attractive from both a disease-relevance and druggability perspective. Furthermore, combining existing targets, many of which are clinically validated and druggable, is one possible way of expanding the "biological space" that is available for drug discovery and improving the productivity of the pharmaceutical industry.

Our aim in this review has been to highlight the gradual emergence of an exciting new area for medicinal chemists, particularly for those working in disease areas where selective agents often lack clinical efficacy. Already, the literature contains many elegant and increasingly rational approaches to the discovery of DMLs. To address the "physicochemical challenge", more sophisticated design strategies and computational tools will certainly be needed. Rather than simply merging predefined molecular frameworks found in selective ligands, increasingly DMLs will be designed and optimized at the level of their underlying pharmacophores. Greater application of biostructural information and pharmacophore modeling will facilitate the "designing in" of desired activities and the "designing out" of undesired cross-reactivities. Computational tools that can rapidly search for commonalities in binding sites will help predict those targets that are phylogenetically distant but still have similar surface cavities.[105] By delineating cellular signaling networks, the emerging field of systems biology has the clear potential to identify the inherent redundancy within many biological systems that provides the opportunity for achieving higher efficacy with a DML.

Inevitably, medicinal chemists will face target combinations that are particularly compelling in terms of biological rationale but are problematical from the perspective of combining appropriately balanced in vitro and in vivo activities with acceptable oral bioavailabil-

ity, duration of action, and safety. In many cases, alternative formulations and routes of administration will need to be investigated. The systematic discovery of multiple ligands is a field that presents future drug discoverers with many challenges and opportunities in their quest for superior medicines.

Biographies

Richard Morphy completed his B.Sc. (1985) and Ph.D. at Durham University (U.K.) before becoming a medicinal chemist at Celltech in Slough (U.K.) in 1989. Since 1995, he has worked at Organon Laboratories in Scotland and is currently a Section Head in the Medicinal Chemistry Department. His work on a number of CNS-related projects has led to a keen interest in the area of designing multiple ligands.

Zoran Rankovic received his Ph.D. degree in organic chemistry from the University of Leeds (U.K.). In 1995 he joined Organon Laboratories in Scotland and is currently a Medicinal Chemistry Section Head with research interests in the CNS and CV fields, in particular in the design of multiple ligands.

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