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Review

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Reviews

Comprehensive Survey of Combinatorial Library Synthesis: 2001

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This is the fifth review in an annual comprehensive survey series on combinatorial chemistry.[1] There were a total of 305 small-molecule libraries published in 2001 as delineated in Tables 1−10. The format remains the same as in previous reviews with libraries divided into two broad categories: libraries with disclosed biological activity (78 entries; Tables 1−5) and those without associated biological screening data (227 entries; Tables 6−10). Two new tables were added this year, recording solid-phase reagents and scavengers (Table 11) and solid-phase linkers (Table 12) reported in 2001.

The percentage of academic research groups (60%) publishing solid- and solution-phase research continued to outpace industrial groups by a moderate margin. Three years ago, the opposite was observed. Academic groups are the principal drivers for new solid-phase methodology and the synthesis of libraries based on natural-product templates.

Although the number of published libraries synthesized on solid-phase continues to dominate, solution-phase library synthesis, which includes the use of resin-bound reagents and scavengers, is clearly on the rise. Some 60% of the libraries found in Tables 1−5 were prepared using solution-phase chemistry, up over 150% from the previous year. Successful optimization programs in 2001 that relied on solution-phase chemistries include cathepsin K inhibitors,[228] raf kinase inhibitors,[274] Cdk4 inhibitors,[274] and CCR3 antagonists.[274] In contrast to libraries published with screening results, only 22% of the methodology-type libraries (Tables 6−10) were solution-phase.

The average size of the libraries in Tables 1−5, i.e., the number of compounds per library, decreased in 2001 (50% contain <100 members; 86% contain <1000 members). Several years ago, it was common to see the synthesis and screening of large libraries containing thousands of members. The current trend is to apply combinatorics in the iterative process of lead optimization by quickly creating small sets of libraries to address specific SAR and pharmacokinetic queries. Pharmaceutical companies appear to be outsourcing to an increasingly greater extent the synthesis of general discovery libraries. For example, Merck, Pfizer, Roche, and Pharmacia signed multiyear collaboration agreements in 2001 with companies such as Discovery Partners International and Evotec OAI to synthesize small-molecule chemical libraries. Some major pharmaceutical firms have reportedly scaled back their dedicated combinatorial chemistry departments, redirecting resources to medicinal chemistry optimization. Academic institutions, on the other hand, are creating new departments, schools, and centers of excellence for streamlined synthesis.

Selected library highlights for the year include an inspiring account of the discovery and optimization of selective Cdk4 inhibitors via an integrated strategy of computational lead generation, homology modeling, structure-based design, library synthesis, and traditional analogue synthesis.[109,110] The strength of combinatorial chemistry to simultaneously conduct "multiple-point modifications" was aptly demonstrated by Smith and co-workers[227] in a "hit-to-lead" raf kinase inhibitor campaign. Combinatorial chemistry allowed the Smith group to break free of a SAR paradigm defined by "sequential fragment-based" optimization, ultimately leading to a clinical candidate. The Lead Discovery group at Organon

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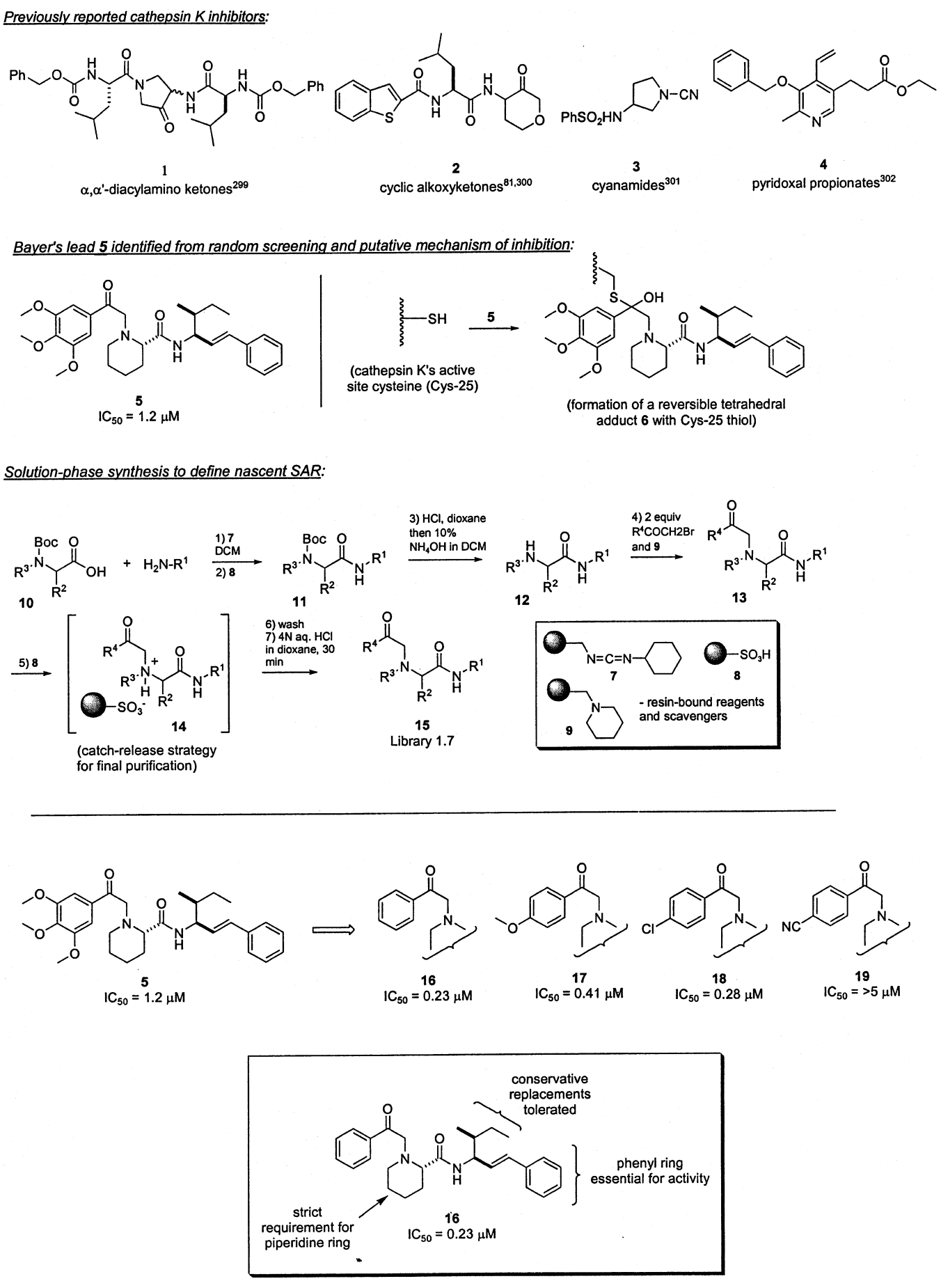


Figure 1. Aminomethyl ketones as cathepsin K inhibitors.[228]

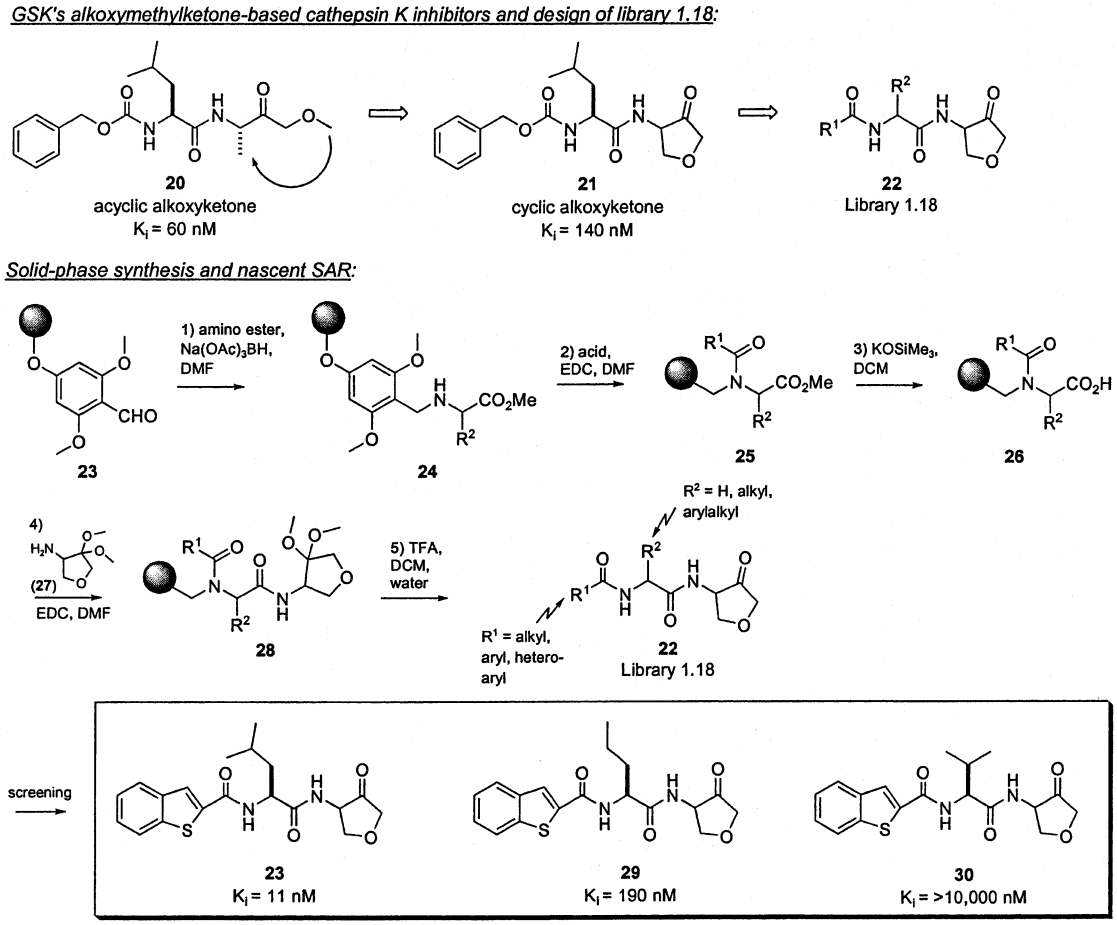


Figure 2. Cyclic alkoxyketones as cathepsin K inhibitors.[81]

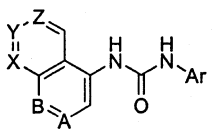
provided a detailed design of a general screening library biased toward central nervous system (CNS) bioavailability.[20,49] Finally, GlaxoSmithKline (GSK) described a thwarted account of optimizing a structurally complex oxytocin antagonist that was obtained as a screening hit from a combinatorial library.[80,274] Their work highlights the difficulty in simplifying complex, high molecular weight leads to optimize potency, selectivity, and pharmacokinetic parameters. The GSK report supports the contentions of Teague,[315] Hann,[316] and Oprea[317] who argue for library designs that yield simpler, low molecular weight structures as starting points for optimization. Detailed descriptions of these and other highlights are given below.

1. Biologically Active Libraries (Tables 1−5)

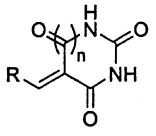
Cathepsin K Inhibitors.[81,228] Cathepsin K is a cysteine protease selectively expressed in osteoclasts and has been implicated in bone resorption. Inhibitors of the enzyme have been shown to reduce bone loss in vivo, supporting the hypothesis that such agents may be clinically useful therapeutics for the treatment of diseases characterized by excessive bone loss, e.g., osteoporosis. Several structurally distinct classes of compounds have been identified as cathepsin K inhibitors including α,α′-diacylamino ketones **1**, acyclic[300] and cyclic alkoxyketones **2**,[81] cyanamides **3**,[301] and pyridoxal propionate derivatives **4**[302] (Figure 1). During a high-throughput screening campaign, Smith and co-workers at Bayer Research discovered α-amino aryl ketones as a new class of cathepsin K inhibitors.[228] Screening hit **5**, IC_{50} = 1.2 μM, was thought to be a reversible inhibitor by virtue of its potential to form covalent tetrahedral adduct **6** with the active-site Cys-25. To explore the SAR of the aryl ketone fragment in **5**, an expedient solution-phase synthesis of library 1.7 (**15**) was developed, facilitated by polymer-supported reagents and scavengers. The synthesis began with coupling *N*-Boc-protected amino acids **10** to both custom and commercially available amines using resin-bound carbodiimide **7** as the activating reagent. Excess amines were scavenged with resin-bound sulfonic acid **8**. After removal of the *N*-Boc protecting group with HCl/dioxane, the resulting amine HCl salts were free-based with 10% NH_4OH/DCM to furnish amines **12**. Alkylation of **12** was carried out by treatment with 2 equiv of an α-halomethyl ketone in the presence of resin-bound piperidine **9**. Final purification of library members was achieved by a "catch-and-release" strategy in which products were first captured as their resin-bound sulfonic acid salts **14**, followed by thorough resin washing, and then liberated from resin upon exposure to 4 N aqueous HCl in dioxane. Evaluation of compound arrays against cathepsin K revealed a range of inhibitory activities in which less bulky but electron-rich or lipophilic aryl groups yielded more potent inhibitors, e.g., **16**, IC_{50} = 0.23 μM. Additional analogues were subsequently prepared to explore other regions of **5** to define the nascent SAR.

Structure-based approach:

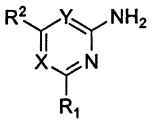
- Created homology model of Cdk4 from X-ray structure of Cdk2
- *de novo* design program LEGEND generated novel templates from homology model
- In-house SEEDS program then sifted through substructures of LEGEND outputs to identify commercially available or synthetic feasible derivatives
- Computational exercise led to four structural templates **31-34** possessing 15-500 μM affinity for Cdk4



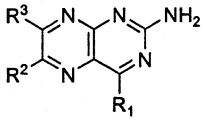
31
diarylureas



32
cyclic urea
and thiourea

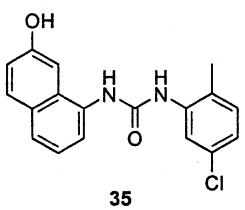


33
aminopyridine
and triazine

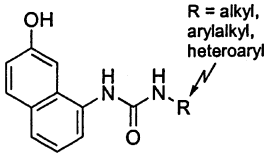


34
pteridine

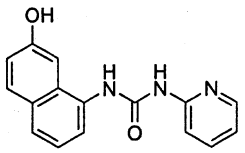
*After selecting diraryl ureas (e.g., **35**) as most tractable class, "informer" libraries 2.2 and 2.3 were synthesized:*



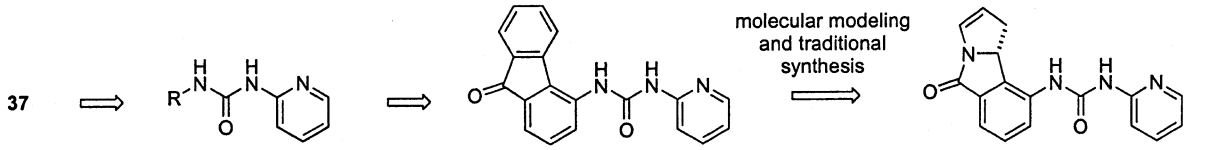
35
IC_{50} = 44,000 nM



36
Library 2.2
(55 members)



37
IC_{50} = 7600 nM

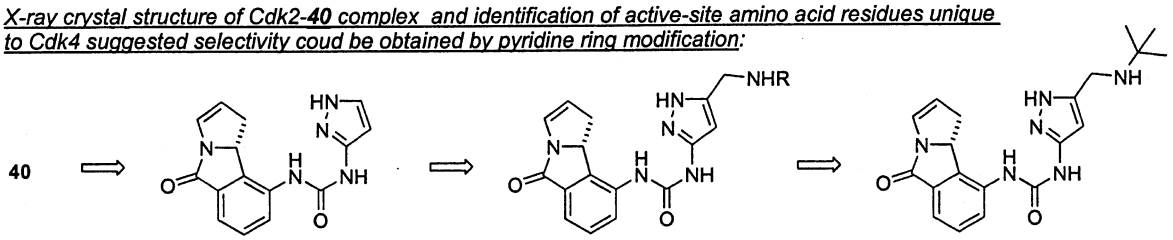


38
Library 2.3
(410 members)

39
IC_{50} = 100 nM
(poor selectivity against Cdk2)

40
IC_{50} = 42 nM
(poor selectivity against Cdk2)

*X-ray crystal structure of Cdk2-**40** complex and identification of active-site amino acid residues unique to Cdk4 suggested selectivity coud be obtained by pyridine ring modification:*

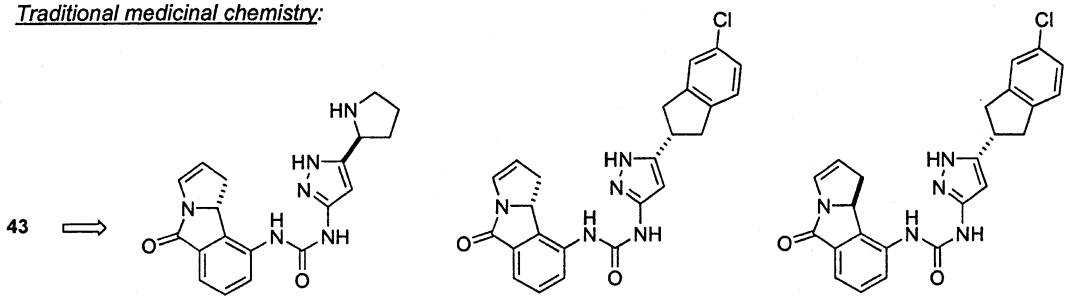


41
IC_{50} = 29 nM
(poor selectivity against Cdk2)

42
Library 2.4
(64 members)

43
IC_{50} = 56 nM
(180-fold selective over Cdk2)

Traditional medicinal chemistry:



44
IC_{50} = 220 nM
(*ca.*100-fold selective over
Cdk2 and Cdk1)

45a
IC_{50} = 1.6 nM
(>100-fold selective over Cdk2
and 400-fold over Cdk1)

45b
IC_{50} = 2.3 nM
(>200-fold selective over
Cdk2 and Cdk1)

Figure 3. Development of selective Cdk4 kinase inhibitors.[109,110]

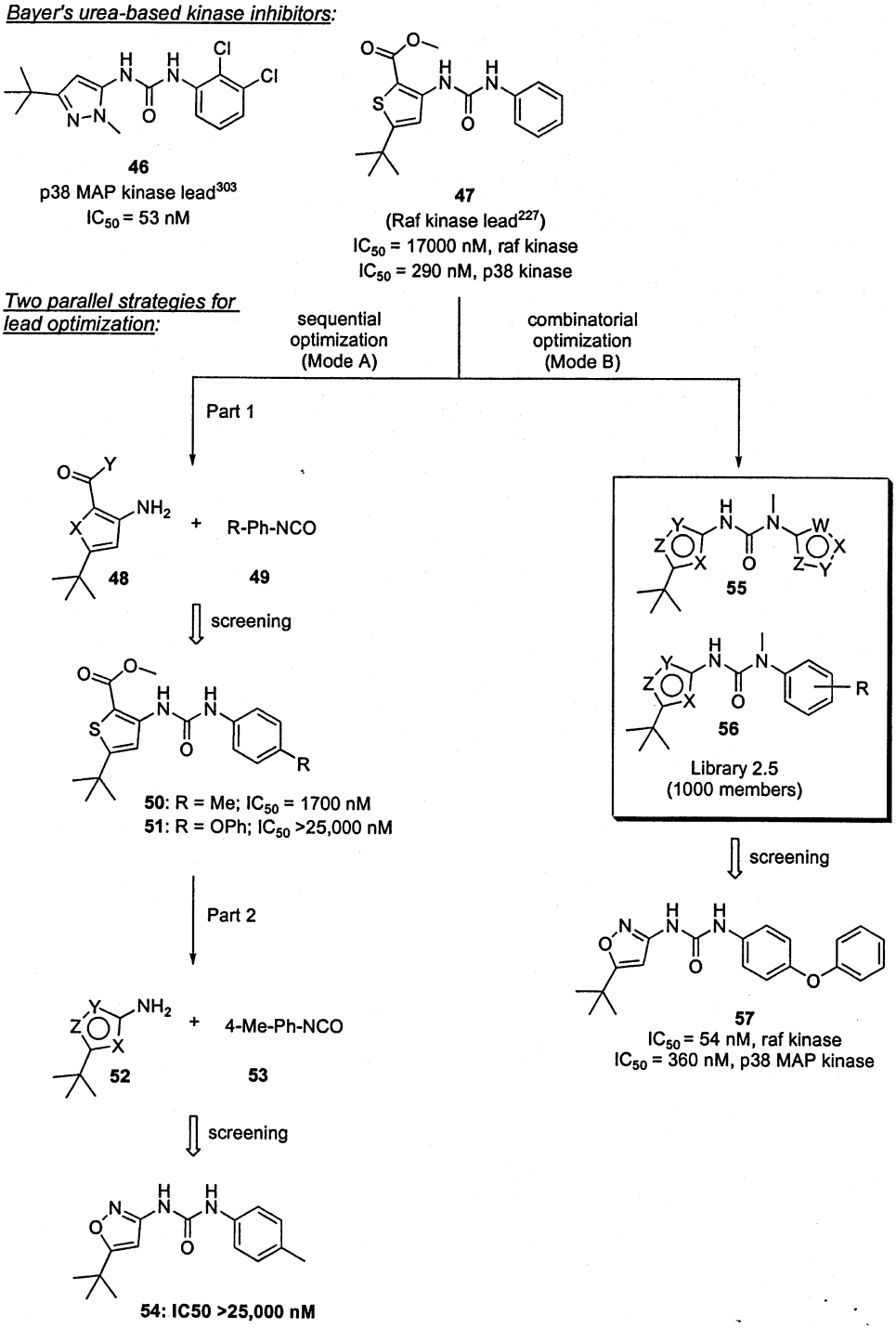


Figure 4. Library 2.5 yielding second-generation urea-based Raf kinase inhibitor lead.[81]

As part of an ongoing cathepsin K inhibitor program, researchers at GlaxoSmithKline described the solid-phase preparation of library 1.18 (**22**) based on cyclic alkoxymethyl ketone template **22** (Figure 2).[81] This library was designed to explore the SAR of initial lead **21** (K_i = 140 nM, cathepsin K), an inhibitor that was some 2-fold less active than its acyclic counterpart **20**. The synthesis commenced with the reductive amination of amino esters (10 equiv of each amine and $Na(OAc)_3BH$, DMF) and aldehyde resin **23**. The resin-bound secondary amines **24** were then acylated with a variety of carboxylic acids (3 equiv) employing standard coupling conditions. Hydrolysis of the ester with aqueous base led to racemization at R^2 in **26**. This problem was circumvented by treatment with potassium trimethylsilanoate (10 equiv) in DCM to furnish chiral acid **26**, which in turn was coupled to the protected keto amine **27** yielding **28**. Library 1.18 was obtained upon acid treatment (TFA/DCM/H_2O (7:2:1)) of resin **28**, simultaneously liberating the salient ketone functionality. The synthesis was semiautomated via application of the ACT496 robotics or encoding with IRORI radiofrequency tags. The most potent compound identified from the library was cyclic ketone **23** (K_i = 11 nM), some 10-fold more potent than lead **21**. On the basis of the poor affinity observed for analogues **29** and **30**, the leucyl side chain in **23** appeared to be optimal.

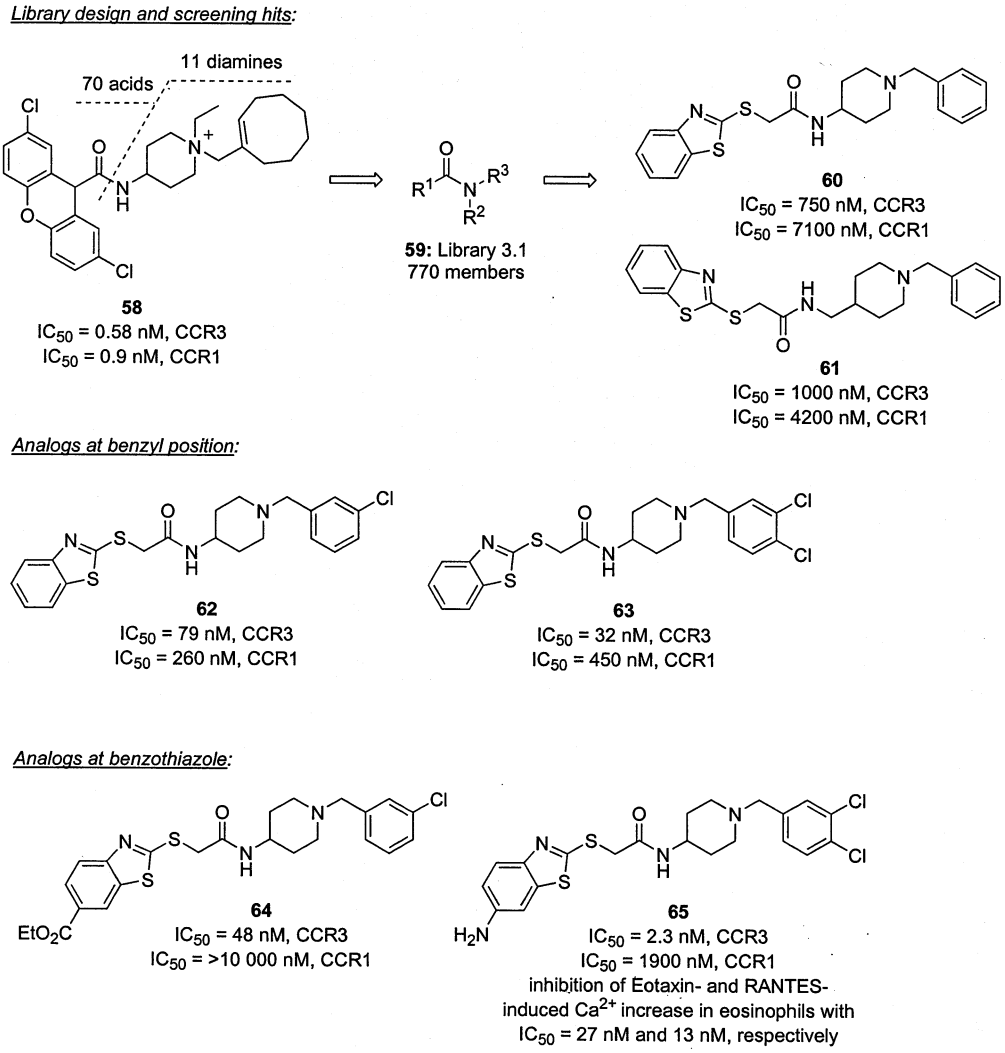


Figure 5. Selective CCR3 chemokine antagonists.[175]

Cyclin-Dependent Kinase 4 (Cdk4) Inhibitors.[109,110] A new class of highly selective Cdk4 inhibitors was identified by Honma and co-workers using an integrated drug discovery strategy of structure-based design, library synthesis, and traditional analogue synthesis (Figure 3).[109,110] The first step was the construction of a Cdk4 homology model derived from the crystal structure of Cdk2.[109] This was accomplished using the de novo design program LEGEND, which sequentially generated some 1000 structures inside the deep, narrow cavity of Cdk4's ATP binding site. Typical of outputs from de novo design programs, many of the putative inhibitors produced by LEGEND were neither commercially available nor synthetically feasible. To overcome this issue, a second in-house computational program "SEEDS" was used to dissect the structures to afford pharmacophore queries. The queries in turn were used to survey compound databases. For instance, on searching the Available Chemicals Directory (ACD), some 4884 compounds (MW < 350) were culled, from which ca. 380 compounds were purchased. When screened in a cyclin-Cdk4 assay, 18 hits were obtained with IC_{50} values of 15−500 μM. The hits were classified into four structural types **31**−**34**. Urea **35** (IC_{50} = 44 μM), belonging to the class of diarylureas **31**, was designated as the lead for SAR development. Two complementary "informer" libraries 2.2 (**36**) and 2.3 (**38**) based on **35** were sequentially synthesized using solution-phase methods (465 compounds total). Urea **39** (IC_{50} = 100 nM) emerged, possessing a 440-fold improvement in binding affinity over lead **35**. Molecular modeling and traditional synthesis led to urea **40** (IC_{50} = 42 nM). An X-ray analysis of the Cdk2−**40** complex was obtained, confirming the predicted binding mode in the ATP binding site.

Although urea **42** was reasonably potent against Cdk4, it lacked selectivity against Cdk2 and related kinases. Examination of the Cdk2−**40** crystal structure and identification of active-site residues unique to Cdk4 suggested that modification of the pyridine ring in **40** might lead to more selective inhibitors.[110] Exchange of the pyridine for a pyrazole ring afforded inhibitor **41** (IC_{50} = 29 nM). On the basis of X-ray crystallographic studies and homology modeling, it was thought that introducing a C(5) substituent into the pyrazole heterocycle would lead to further enhancement in potency and selectivity. Hence, library 2.4 (**42**; 64 members) was prepared, yielding **43** as a potent inhibitor of Cdk4 with 180-fold selectivity over Cdk2. Further analogue synthesis furnished ureas **45a** and **45b**, IC_{50} = 1.6 and 2.3 nM against Cdk4, respectively, both possessing high selectivity across a panel of kinases. Cell-based assays demon-

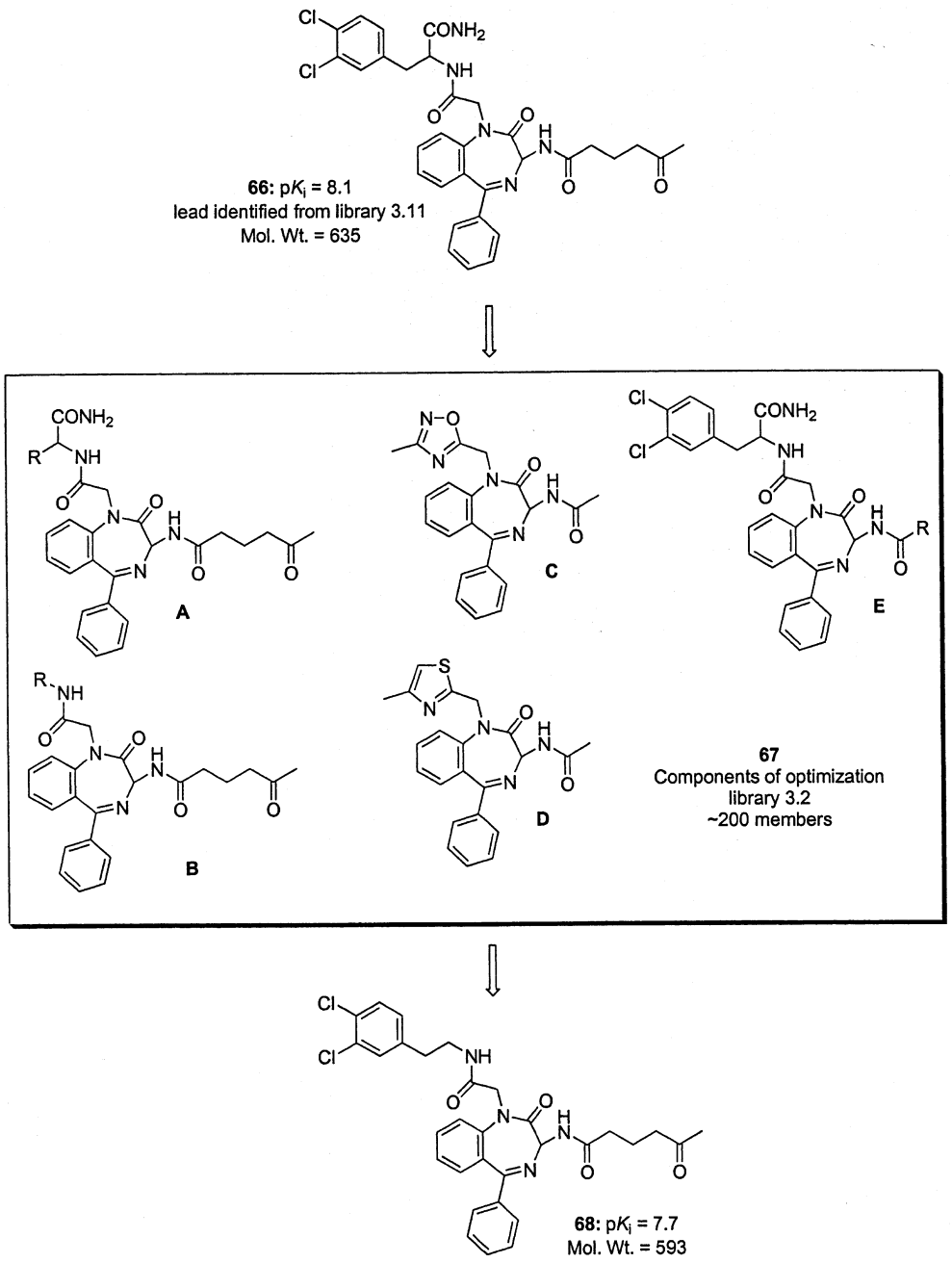


Figure 6. Attempted optimization of oxytocin antagonist 66.[80,274]

strated that **45b** caused G_1 arrest in Rb(+) cancer cell line (Molt-4).

Raf Kinase Inhibitors.[227] One clinically promising strategy for the treatment of cancer is the inhibition of raf kinase. This kinase is a downstream effector of ras, a signal transduction pathway involved in the regulation of cell differentiation and division. Activating mutations of ras are found in nearly one-third of all human cancers. Several years ago, Smith and co-workers at Bayer discovered heteroaryl ureas, e.g., **46**, as potent inhibitors of p38 MAP kinase (Figure 4).[302] This group found that this compound class also inhibits raf kinase, suggesting that heterocylic ureas may represent a privileged kinase inhibitor motif.[227] Lead **47** emerged from a high-throughput screening campaign. It has an $IC_{50} = 17\ \mu M$ against raf kinase, although it is a much more potent inhibitor of p38 MAP kinase, $IC_{50} = 0.29\ \mu M$. Two parallel approaches were taken to improve the potency and selectivity of **47** for raf kinase. These included a "sequential" optimization strategy (mode A) in which the thienylamine was held constant while the aniline unit was varied (**48** + **49**) and vice versa (**52** + **53**) and a "combinatorial library" optimization strategy (mode B) in which broad combinations of heterocycles and anilines (library 2.5; **55** and **56**) were synthesized. Despite extensive analoguing

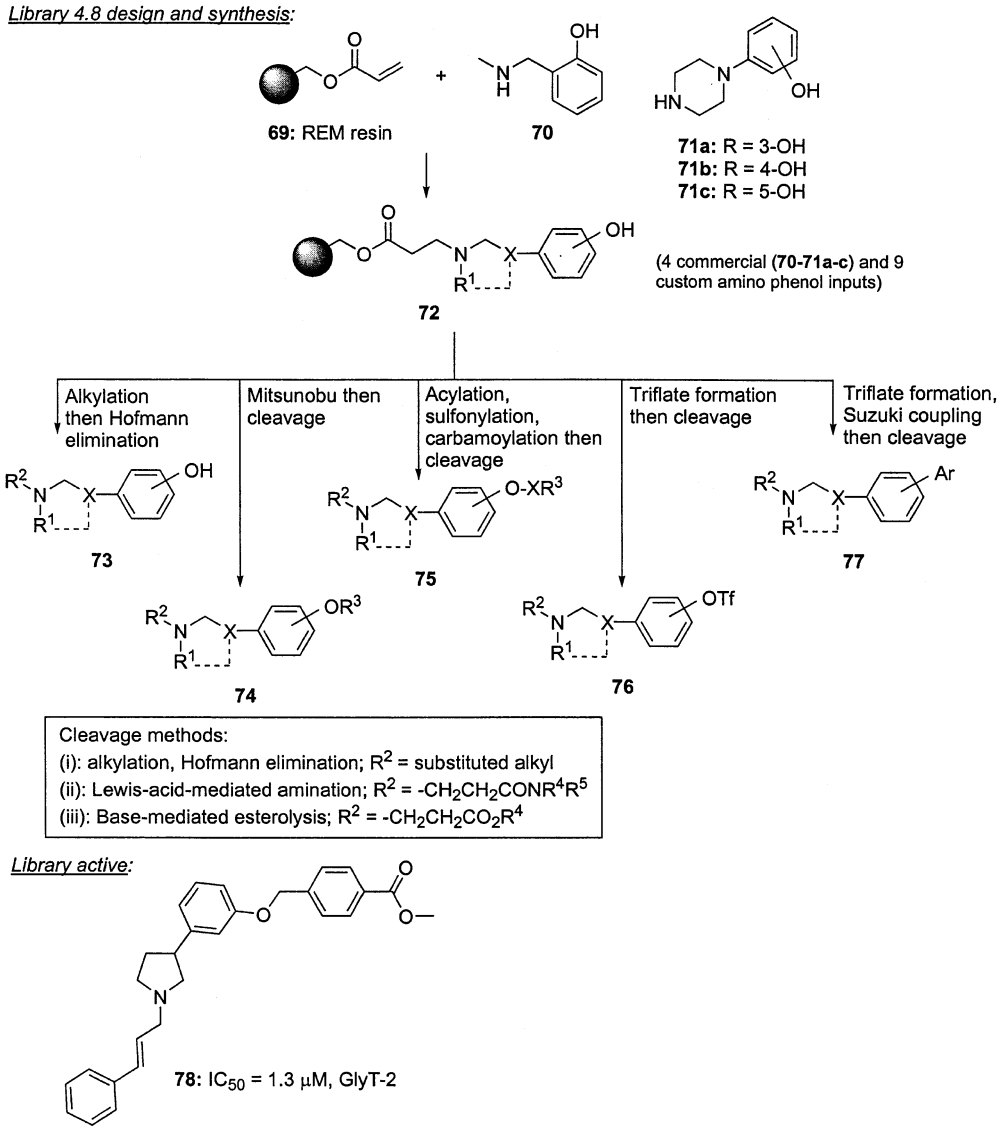


Figure 7. Library 4.8 synthesized using REM resin methodolgy.[20]

Table 13. Molecular Property Analysis

molecular property	66% of CNS-active drugs (displayed property range)	library 4.8 (% members with property)	GlyT-2 inhibitor **78**
molecular weight	125−425	98% ≤ 450	427
CLogP	1.5−6.5	80% ≤ 6	6.24
no. of H-bond donors	0−2	99% ≤ 1	0
no. of H-bond acceptors	1−2	40% ≤ 2 (75% ≤ 3)	4
no. of rotatable bonds	0−7	55% ≤ 7 (80% ≤ 9)	9
cLogBB[20b]	−0.74 to 0.77	75% ≤ 0.75 (98% ≤ 1)	0.5

via the sequential mode A, raf kinase potency could not be improved beyond the 1 μM level. For example, introducing a *p*-methyl group in the phenyl ring of **47** gave urea **50** (IC_{50} = 1.7 μM; a 10-fold increase in binding), while many other analogues including **51** and **54** were inactive (>25 μM). In contrast, compound **57**, with a raf kinase IC_{50} = 54 nM and showing 7-fold selectivity versus p38 MAP kinase, was identified from the combinatorial library mode B. Urea **57** clearly lies outside the SAR established by sequential optimization. On the basis of the inhibitory activities of **51** and **54**, compound **57** would have been dismissed as an "inactive analogue" and therefore would not have been prepared in mode A optimization. This exercise demonstrates the power of combinatorial chemistry to conduct simultaneous "multiple-point modifications" to identify novel biologically active agents. Further studies on this class of compounds led to the identification of a clinical candidate.[227]

Chemokine Receptor CCR3 Antagonists.[175] Activation of the CCR3 receptor is an important determinant in the recruitment and accumulation of eosinophils to inflammatory sites characteristic of allergic diseases such as asthma. Thus, antagonists of CCR3, expected to suppress eosinophil infiltration, may have clinical potential to ameliorate allergic diseases. Banyu Tsukuba Research Institute reported amide **58** as a subnanomolar dual antagonist of CCR1 and CCR3

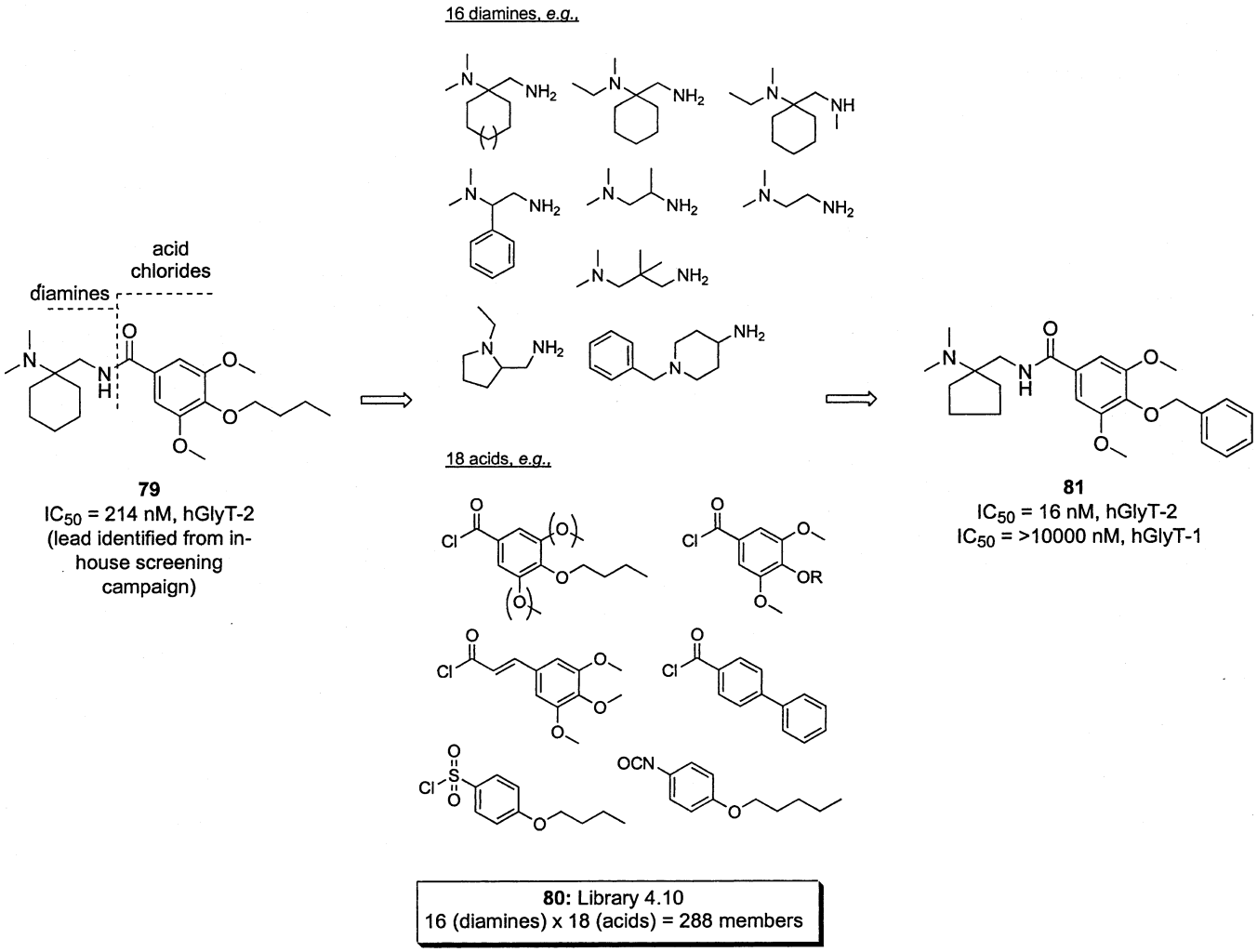


Figure 8. Glycine transporter type-2 inhibitors.[49]

(Figure 5). Preliminary SAR studies of **58** demonstrated the importance of the carbonyl group as a hydrogen bond acceptor, a basic amine for electrostatic interaction to CCR3, and hydrophobic groups flanking the amide carbonyl and basic amine. It was also recognized that the quaternary ammonium group in **58** was a barrier to oral absorption and hence must be removed. Using this information, amide library 3.1 (**59**) was designed and synthesized using 70 carboxylic acid and 11 amine inputs, generating 770 total compounds. Inputs were culled from commercial and in-house collections after clustering based on the binary Tanimoto coefficient and calculated by the MDL keys as a structural descriptor. Screening of the library furnished only two active compounds **60** and **61** possessing micromolar affinity for CCR3 and 4- to 10-fold selectivity over CCR1. Although the 1000-fold loss in receptor potency relative to **58** was disappointing, **60** and **61** represented second-generation leads that no longer contained the quaternary nitrogen. Amide **61** proved to be most amenable to SAR development. Sequential optimization, first at the benzyl moiety and then at the benzothiazole ring, gave rise to substantial improvements in affinity and potency. In particular, introducing chlorine atoms onto the benzyl ring increased CCR3 receptor affinity 50- to 100-fold, with IC_{50} values of 79 and 32 nM for **62** and **63**, respectively. Incorporation of an amino group in the benzothiazole ring furnished **65**, a highly potent and selective antagonist: IC_{50} = 2.3 nM versus CCR3; IC_{50} = 1900 nM versus CCR1. Amide **65** inhibited Eotaxin- and RANTES-induced Ca^{2+} increase in eosinophils. It is interesting to note that if the benzothiazolylacetic acid had not been one of the 70 carboxylic acid library inputs, neither amides **60** and **61** would have been discovered nor subsequent SAR studies carried out leading to **65**.

Oxytocin Antagonists.[80,274] The potent oxytocin antagonist **66** was identified at GlaxoSmithKline directly from a fully encoded differential release library (Figure 6).[80] Compound **66** (pK_i = 8.1) displayed a poor pharmacokinetic profile, and an optimization program was undertaken to enhance both oxytocin antagonism and pharmacokinetic parameters. Given the high molecular weight and number of sites for metabolism, library design and SAR investigations centered on reducing the molecular weight and structural complexity of **66**. Compound arrays of more than 200 new analogues were prepared using a combination of solid- and solution-phase synthesis (library 3.2). The first library members were modifications to the 3,4-dichlorobenzyl substituent (**67A**). Replacement of the phenyl ring with alkyl or cycloalkyl groups and removal of the chlorine atoms or their replacement with fluorine all resulted in loss of binding affinity.

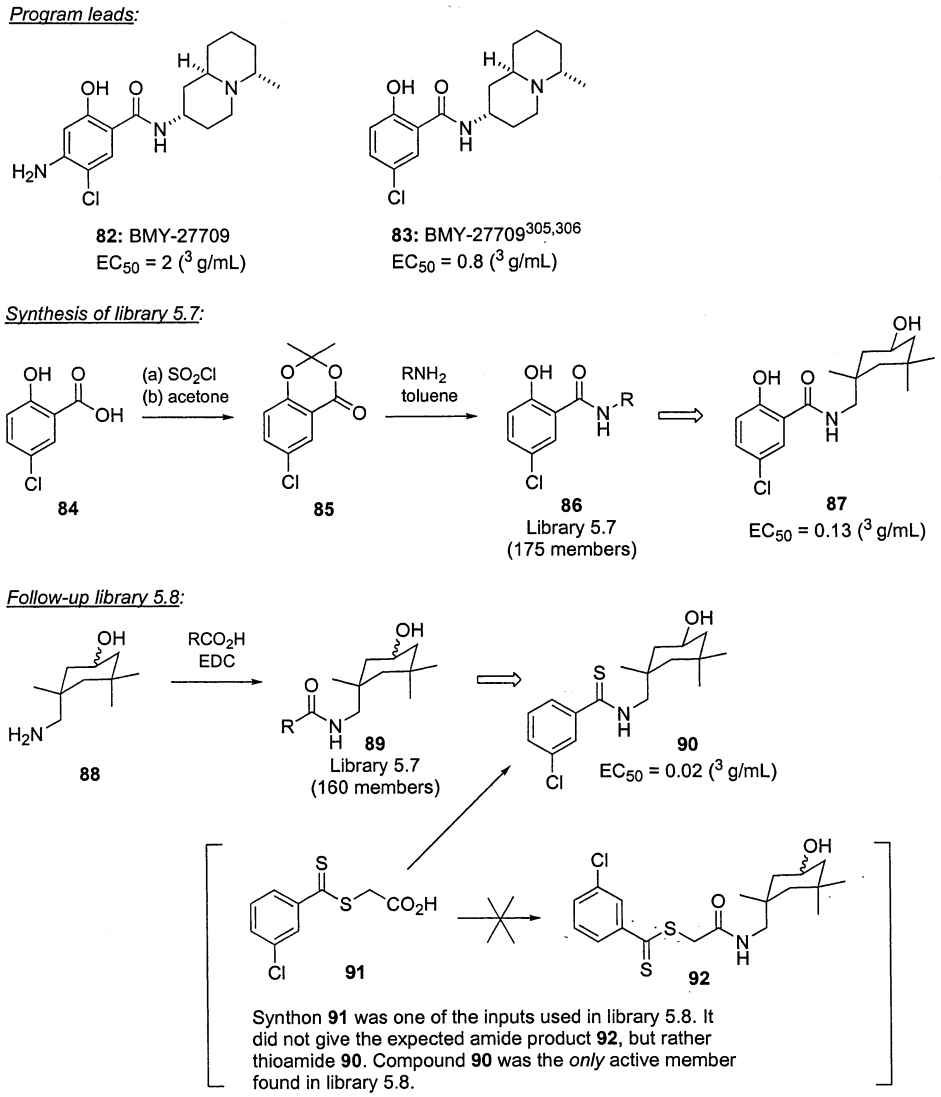


Figure 9. Inhibitors of influenza virus fusion.[68]

The primary amide was next examined (**67B**), and it was established that this functionality could be removed, yielding **68** ($pK_i = 7.7$). This compound displayed a modest loss in antagonist activity and a substantial decrease of plasma clearance, doubling the intravenous half-life. Further modifications to this region of the molecule via **67C**,**D** and shortening the length of the 3-(5-oxohexanoamide) substituent **67E** gave at best modest reductions in potency without any improvement in pharmacokinetic parameters. Attempted optimization of **66** highlights difficulties experienced in simplifying complex, high molecular weight leads and underscores preferred library designs that yield simpler low molecular structures as starting points for optimization.

CNS Library Design: Glycine Transporter-2 (GlyT2) Inhibitors.[20,49] The design and synthesis of a 3042-member library (library 4.8) on REM resin was carried out at Organon Laboratories (Figure 7).[20] Designated as a general-purpose library for screening against diverse molecular targets, its physiochemical properties were biased toward central nervous system (CNS) permeability. This was accomplished by incorporating functionality and molecular properties found in CNS-active drugs. An analysis of the frequency of structural fragments present in 373 orally bioavailable CNS agents revealed that aromatics and amines occur respectively in 83% and 63% of the drugs, followed by alcohols/phenols (21%), esters/aldehydes (~10%), and acids (4%). In addition, the molecular property distribution of these marketed CNS-active drugs are shown in Table 13. Considering these statistical data, library 4.8 was designed to contain a diverse collection of arylamines whose molecular property distribution fell within the above-stated property limits.

Approximately 20 g of 13 phenol amine scaffolds, 4 commercial amines (**70** and **71**), and 9 custom amines (structures not disclosed) were loaded onto REM resin to give ca. 12 g of each resin-bound scaffold **72**. The phenolamine cores served to ensure that each library member contained at least one aryl ring and one basic nitrogen atom and provided an avenue for bidirectional derivatization. Chemistry was carried out in either IRORI MicroKans or in Syro II reactors. To maximize chemical diversity within the library, five phenolic OH derivatization chemistries (Mitsunobu, Suzuki, acylation, sulfonylation, and carbamoylation) were employed in combination with three different cleavage strategies ((i) alkylation−Hofmann elimination, (ii) $AlCl_3$-

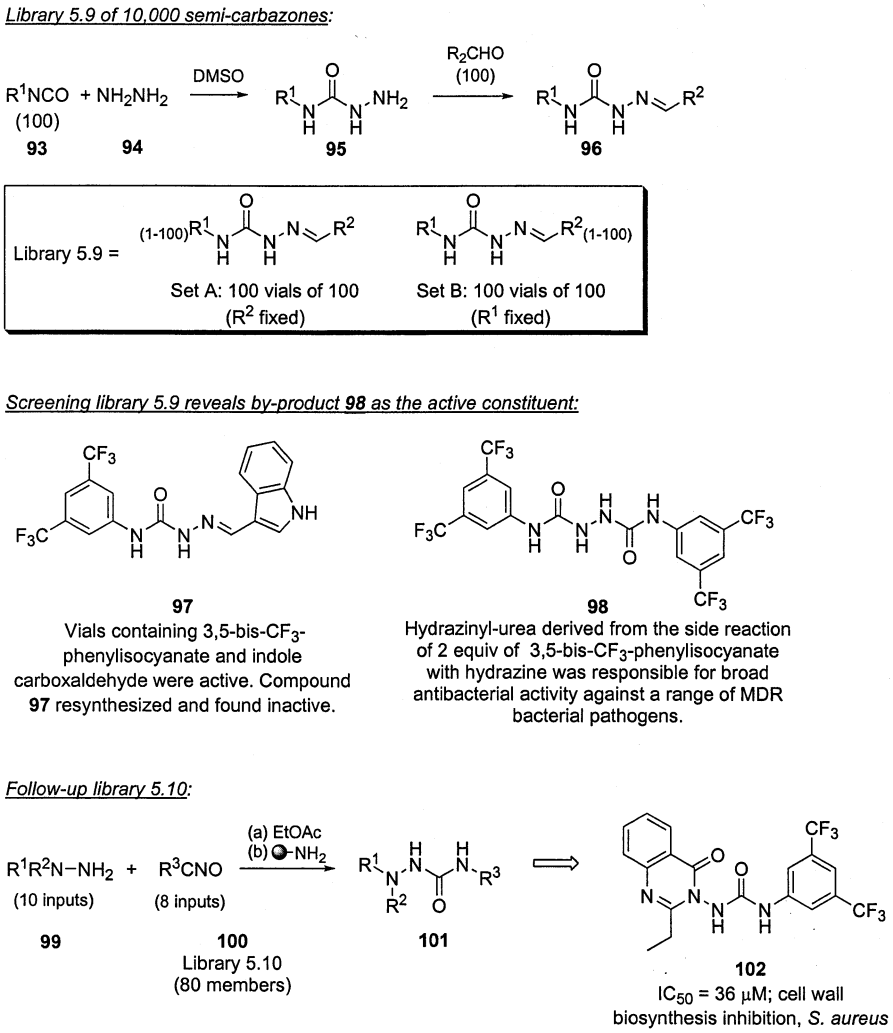


Figure 10. Hydrazinyl-urea byproduct identified as potent antibacterial agent.[268]

promoted aminolysis, and (iii) base-mediated esterolysis). The library chemistry is the most sophisticated reported to date on REM resin. This approach provided over 3000 tertiary amines containing phenol, aryl ether, aryl ester, aryl sulfonate, biaryl, and propionyl ester and amide functionality. The molecular property distribution of the final library (Table 13) indicated that the majority of compounds are predicted to penetrate into the CNS. Finally, screening library 4.8 against the human GlyT-2 afforded arylamine **78** (IC_{50} = 1.0 μM). The physiochemical properties of **78** are largely consistent with a CNS-drug-like profile, although they are at the upper end of the desired range and exceed the preferred number of H-bond acceptors and rotatable bonds. No CNS bioavailability data were reported for **78**.

In a separate screening effort, the Organon group discovered amide **79** (IC_{50} = 214 nM) to inhibit [^{3}H]-glycine uptake into CHO cells stably expressing the human GlyT-2 protein (GlyT-2 assay).[49] GlyT-2 is one of two major glycine transporters localized to the spinal cord and brain stem. Glycine is an inhibitory neurotransmitter producing muscle relaxation. Selective inhibition of the transporter is hypothesized to lead to an increase in synaptic levels of endogenous glycine and therefore represents an opportunity for developing a novel muscle relaxant, anesthetic, and/or analgesic. A "hit-to-lead" program was initiated to increase the potency of **79** while maintaining transporter/receptor selectivity and a CNS-like drug profile. Rapid SAR exploration was achieved by generating library 4.10 (**80**) via solution-phase methodology. A total of 16 commercially available and custom diamines were derivatized with 18 inputs including 16 carboxylic acid chlorides, 1 sulfonyl chloride, and 1 isocyanate. The two-dimensional array of inputs allowed simultaneous investigation of the structure−activity requirements for cyclic versus acyclic diamines, diamine ring size, α- and β-substitution in the ethylenediamine unit, amide versus another type of linkage, and aromatic ring substitution. Chemistry was performed in four 96-well plates, yielding 10−15 mg quantities of each library member (288 compounds) and purities in excess of 80% (LC/MS). One of the more interesting analogues obtained from screening the library in the GlyT-2 assay was amide **81**. It displayed an IC_{50} = 16 nM against GlyT-2, >1000-fold selectivity versus GlyT-1 and a panel of receptors, and physiochemical properties consistent with known CNS agents.

Influenza Virus Fusion Inhibitors.[68] Salicylic amide **82** (EC_{50} = 2 ^{3} g/mL) was a recently identified as an inhibitor of the H1 and H2 subtypes of influenza A virus strains in cell culture (Figure 9).[305,306] The biological activity is thought

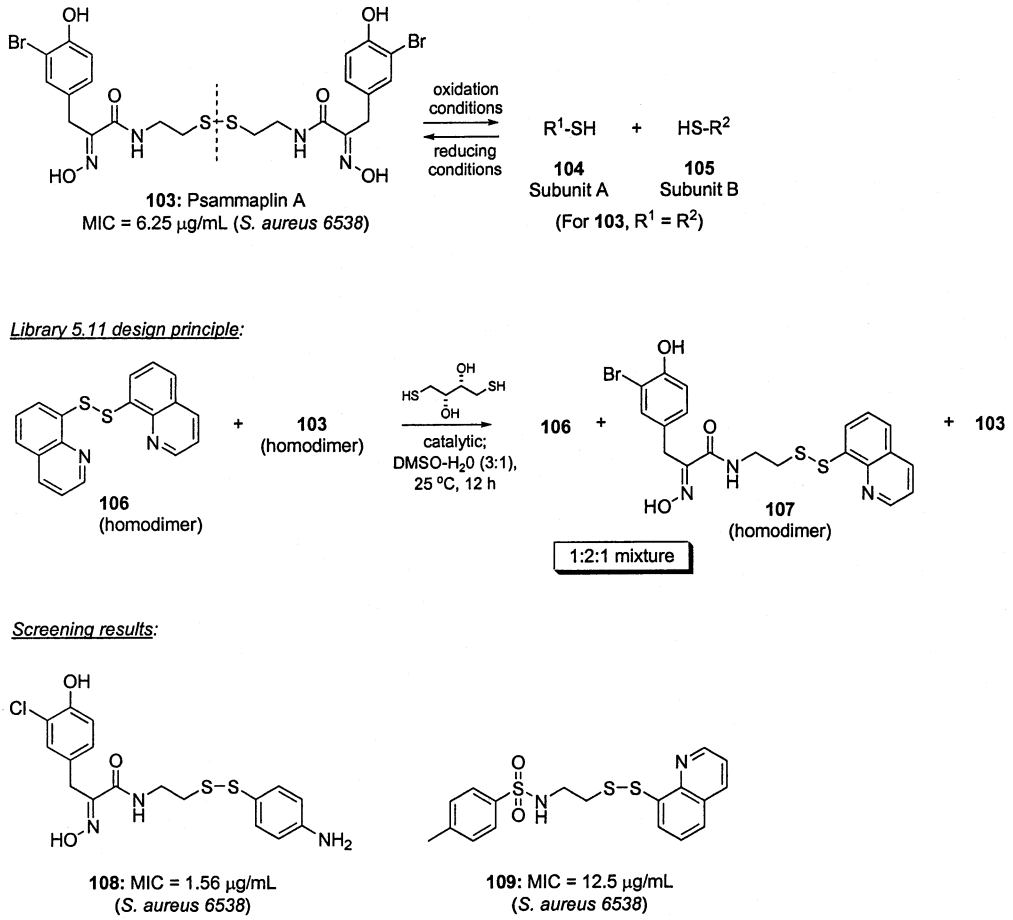


Figure 11. Disulfide library 5.11 based on psammaplin A.[180,181]

to interfere with virus infectivity by preventing the low-pH-induced conformational rearrangement of hemagglutinin into its fusogenic state and hence blocking obligate virus and host cell fusion. Early SAR work established the importance of the salicylic hydroxyl group, the nonessential anilino group, and stereochemistry of the quinolizidine ring as embodied in analogue **83** ($EC_{50} = 0.8^{3}$ g/mL). In an effort to increase the potency of the series, to broaden the activity to include H3 influenza subtypes, and to simplify the structure, a two-part sequential optimization program was undertaken. First, surrogates for the quinolizidine ring were sought. Library 5.7 (**86**; 175 members) was prepared in solution by reacting isopropylidine **85** with a range of primary amines (3-fold excess). This led to amide **87** ($EC_{50} = 0.13^{3}$ g/mL), a substituted cyclohexylmethylamine no longer containing a basic nitrogen. Second, library 5.8 (**89**), designed to explore the SAR of the salicylic acid, was constructed using the optimized cyclohexylmethylamine synthon from **86**. Some 160 amides were synthesized, meeting an 80% purity cutoff for screening. This second library produced *only a single active member* derived from carboxylic acid **91**. The expected product from the reaction was amide **92**. However, NMR and MS analysis confirmed the formation of thioamide **90**, its formation occurring via an alternative coupling mode between the amine and dithioester carbonyl. Thioamide **90** was a potent inhibitor of influenza viral fusion ($EC_{50} = 0.02^{3}$ g/mL), and its unanticipated formation opened up a new window for future SAR development.

Urea-Based Antibacterials.[268] A second example of the isolation and identification of a biologically active byproduct from a library was reported by Wilson (Figure 10).[268] A 10 000 member mixture-library of semicarbazones (**96**; library 5.9) was synthesized in solution as shown in Figure 10. Hydrazine **94** was acylated with isocyanates **93** to form semicarbazides **95**, which were then condensed with aldehydes to yield semicarbazones **96**. Indexed library 5.9 was prepared in two sets of 100 vials each. The first set (A) contained 100 isocyanate inputs per vial and the second set (B) 100 aldehyde inputs. The vials were diluted with DMSO to a compound concentration range of 100−500 mg/mL. Library 5.9 was screened in cell wall biosynthesis and bacterial growth inhibition assays. Two particular vial sets demonstrated dual activity: set A defined by 3,5-bis-(trifluoromethyl)phenyl isocyanate; set B defined by indole-3-carboxaldehyde. This suggested that the activity was due to the cross-product, semicarbazone **97**. However, upon resynthesis, its activity did not confirm it. Careful analysis of the active vial from set A revealed two minor byproducts corresponding to the 3,5-bis(trifluoromethyl)phenyl semicarbide (**95**) and urea **98**, where hydrazine had reacted with 2 equiv of isocyanate. Synthesis of these two compounds confirmed biological activity exclusively due to **98**. A follow-up library 5.10 was synthesized to develop its SAR. Urea **102** was one of the more potent compounds obtained from this library.

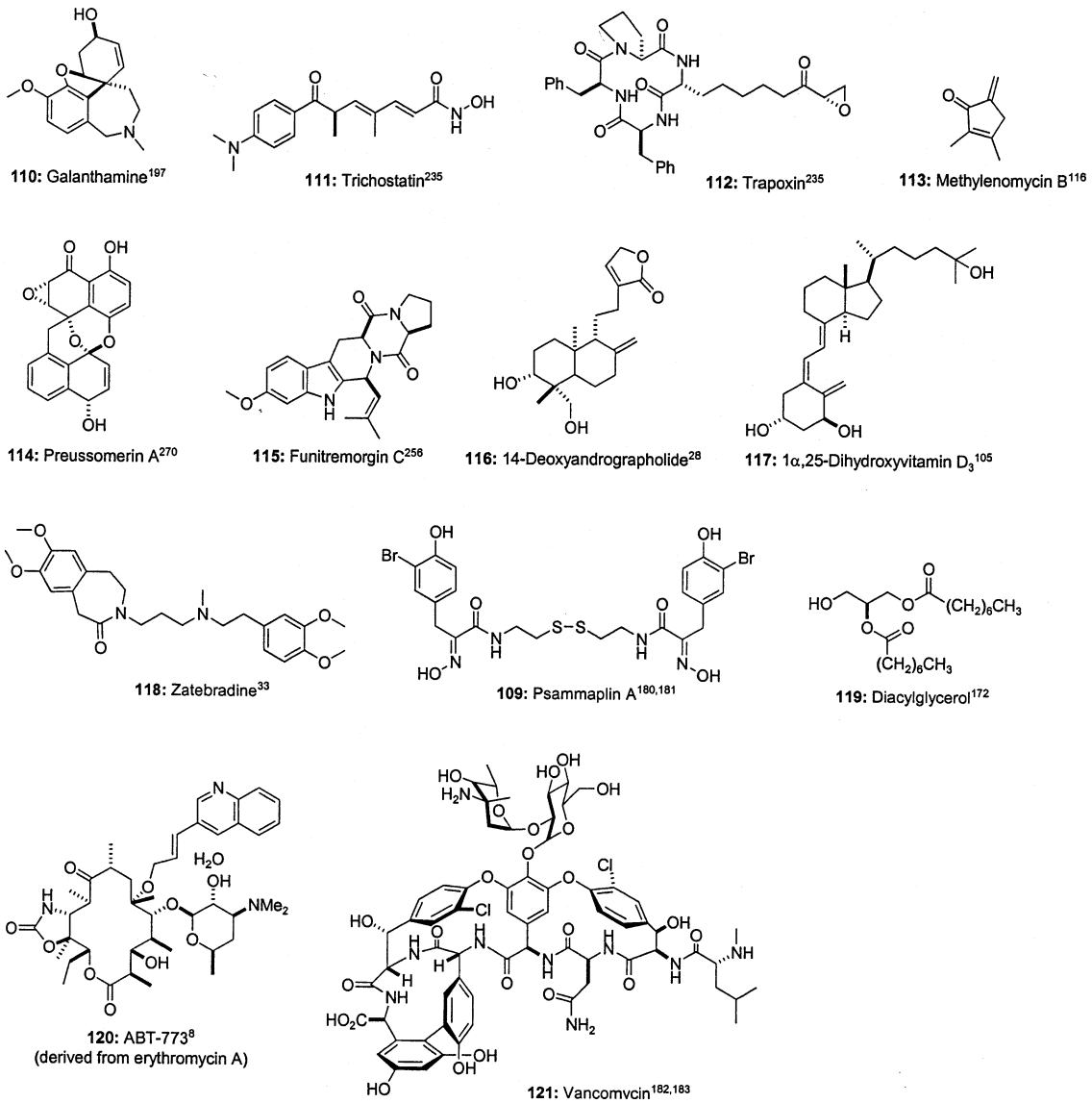


Figure 12. Natural products as library templates in 2001.

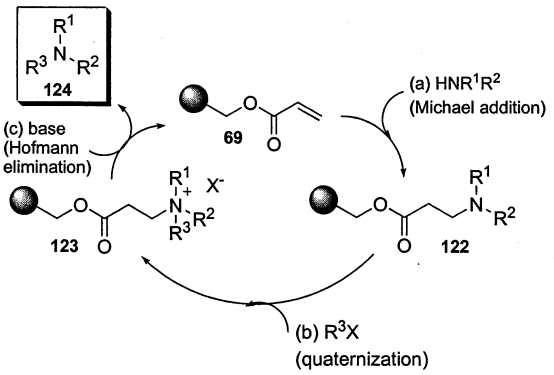
Psammaplin A Based Antibacterials (Natural Product Templates).[180,181] Psammaplin A **103** is a symmetrical bromotyrosine-derived disulfide natural product exhibiting in vitro antibacterial activity against methicillin-resistant *S. aureus* (MRSA). In an effort to gather SAR information and gain insight into its mechanism of action, the 3828-member library 5.11 of homodimeric and heterodimeric disulfides was prepared (Figure 11). A novel combinatorial disulfide exchange strategy was devised in which a 1:1 mixture of two homodimeric disulfides (e.g., **106** and **103**) was scrambled in the presence of a catalytic amount of dithiotreitol (0.15 equiv, DMSO/H_2O (3:1), 25 °C, 12 h). Under thermodynamic control, the heterodimeric disulfide (e.g., **107**) was generated as part of a 1:2:1 mixture of products (**106**/**107**/**103**). Eighty-eight custom and commercially available homodimeric disulfides were scrambled in a two-dimensional 96-well plate format. LC/MS analysis of ca. 100 wells showed the formation of expected mixtures of products in excellent purity. Screening the library directly without purification of products against various strains of MRSA afforded several active wells. Resynthesis of these screening hits confirmed a number of heterodimeric disulfides, in some instances with increased antibacterial potency over the natural product (e.g., **108** and **109**). Further optimization of the leads was reported in a subsequent report.[181] It was established that the mechanism of action of **103** and related analogues is not attributed to the inhibition of DNA gyrase as previously proposed. Circumstantial evidence was presented suggesting that **103** does interact with a specific, albeit presently unknown, molecular target(s) as opposed to acting through a nonspecific redox-type mechanism.

Other natural products serving as inspiration for library synthesis in 2001 are shown in Figure 12.

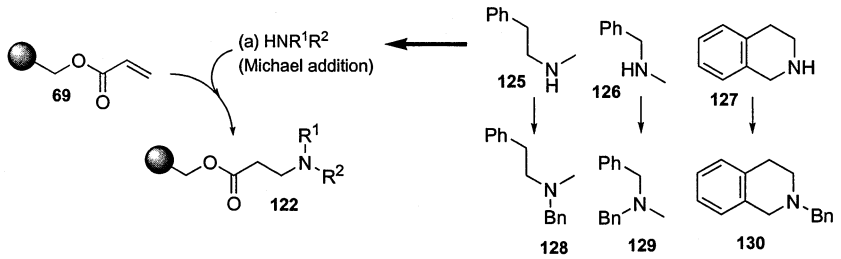
2. Solid- and Solution-Phase Transformations: Libraries without Disclosed Biological Activity (Tables 6−10)

Advances in REM Resin Methodology.[169] As exemplified in the preparation of the CNS-biased library 4.8, REM resin methodology is an efficient protocol for the solid-phase synthesis of tertiary amines (Figure 13A). REM chemistry was first introduced by Brown, Rees, Rankovic, and Morphy

A. Tertiary amine synthesis using REM resin:[307]



B. Fluorocarbon solvents facilitate Michael addition on REM resin:[169]



Solvent in step (a)	*Yield*		
DMF	<5%	<5%	<5%
Perfluorohexane + 3% DMF	94%	72%	80%

C. Two-resin method for cleavage of amines from REM resin:[10]

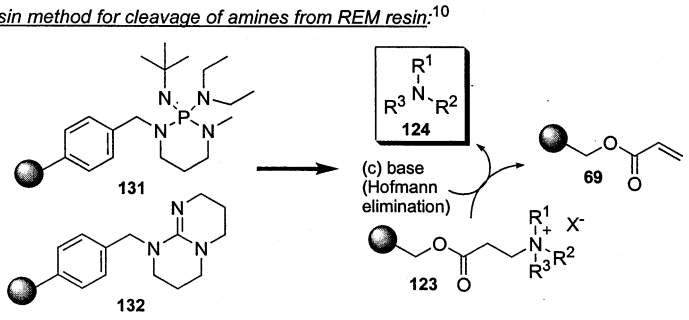


Figure 13. Advances in REM resin methodology.[10,169]

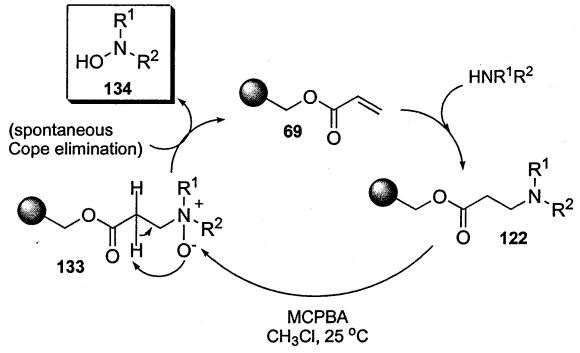


Figure 14. Substituted hydroxylamines from REM resin.[218]

at Organon in 1997.[307] It proceeds via the Michael addition of amines to resin-bound acrylate (**69**−**122**), formation of quaternary ammonium salt **123** with an alkyl halide, and then upon exposure to mild base, Hofmann elimination liberating tertiary amine **124** and regeneration of resin **69**. Continued research at Organon led to the observation that perfluorous organic solvents allow for a large reduction in both reaction time and the amounts of amine required for the Michael reaction (Figure 13B). Dramatic increases in product yields were also realized. Given the immiscibility of perfluorocarbons with common organic solvents, the observed rate and yield enhancements are presumably due to trapping amine reagents inside the bead, a so-called "reagent concentration effect". This concept of "fluorcarbon accelerated supported transformations" (FAST) may have broad application in solid-phase synthesis. In the present REM resin study, three amines **125**−**127** were reacted with **69** in a variety of solvents and combinations thereof: DMF, DMSO, neat amine, water, hydrocarbons, and perfluoroalkyls and perfloroaromatics. Perfluoroaromatic solvents did not give any product after resin quaternization with benzyl bromide and Hofmann elimination (**128**−**130**). Reaction of **69** with 4 equiv (versus 20 equiv) of amine for 2 h was sufficient to effect Michael

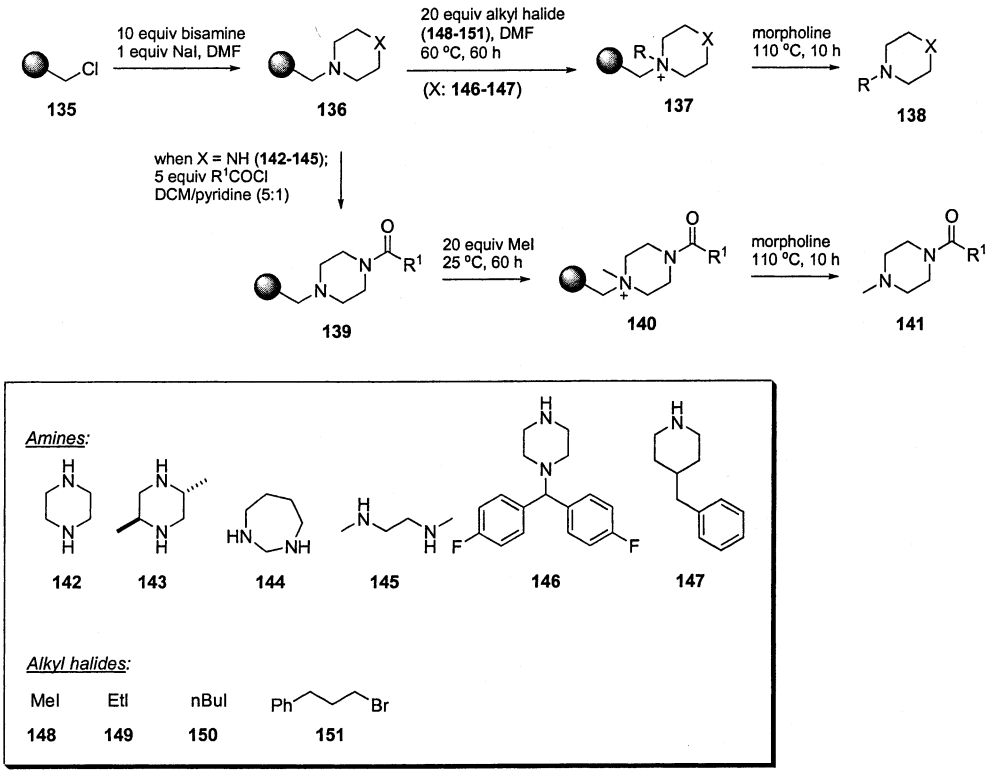


Figure 15. Traceless amine synthesis using Merrifield resin.[45]

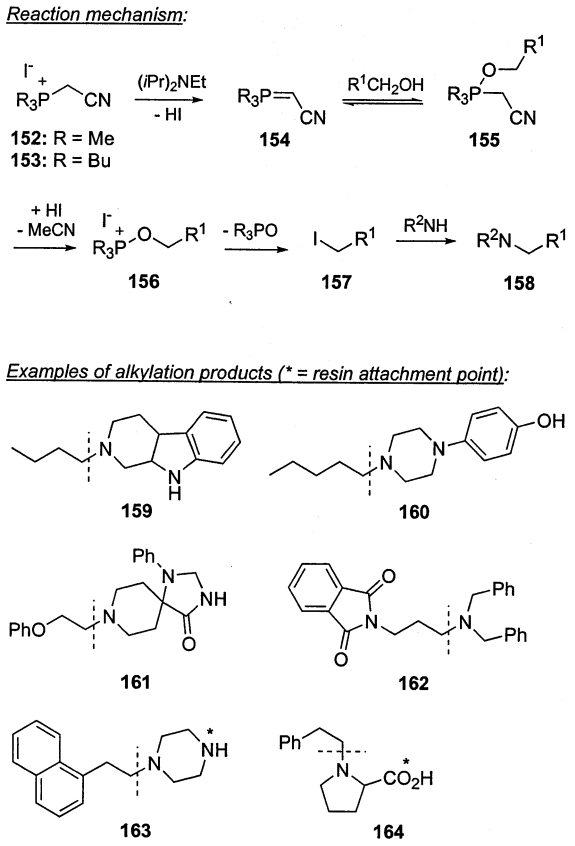


Figure 16. Alkylation of secondary amines with primary alcohols using (cyanomethyl)trialkylphosphonium iodides.[288]

addition. The perfluorohexane containing 3% DMF appeared to be the optimal solvent combination. Perflurous solvents also had a positive effect on the quaternization and Hofmann elimination steps; details are forthcoming.

Alhambra reported that resin-bound phosphazene **131** or quanidine **132** significantly improved the yield of the Hofmann elimination step (Figure 13C).[10] Under standard cleavage conditions with Et_3N or $(iPr)_2EtN$, the tertiary amine products may be contaminated with Et_3N or $(iPr)_2EtN$ hydrobromide or hydroiodide salts. Postcleavage extraction of SPE chromatography can be used to purify products, but this is labor-intensive with large sets of compounds. The advantage of a two-resin cleavage method is that it avoids salt formation and gives products of superior purity. Resin-bound base **131** and in particular **132** were reported to be superior to previously employed resin-bound diisopropylbenzylamine.

Substituted hydroxylamines **134** were prepared using REM resin (Figure 14).[218] After Michael addition, resin **122** is treated with *m*-chloroperbenzoic acid (MCPBA) at 25 °C to furnish the corresponding amine oxide **133**. Resin **133** undergoes spontaneous Cope elimination and release of hydroxylamine.

New Methods for Tertiary Amine Synthesis.[45,96,288] Merrifield resin was utilized in a traceless synthesis of tertiary amines (Figure 15). Substitution of the benzylic chloride in **135** with secondary amines (X not equal to NH) using NaI as a catalyst afforded the corresponding resin-bound amine **136**. Quaternization employing MeI took place at 25 °C in DMF, while use of alkyl halides **149**−**151** required heating at 60 °C for up to 60 h. Dequaternization and release of the tertiary amine was effected by heating resin **137** with morpholine at 110 °C for 10 h. The selection of morpholine as the preferred cleavage reagent is due to its superior resin-swelling property. The utility of the chemistry was further demonstrated by constructing a library of 16 compounds in IRORI MacroKans in which secondary diamines (**142**−**145**)

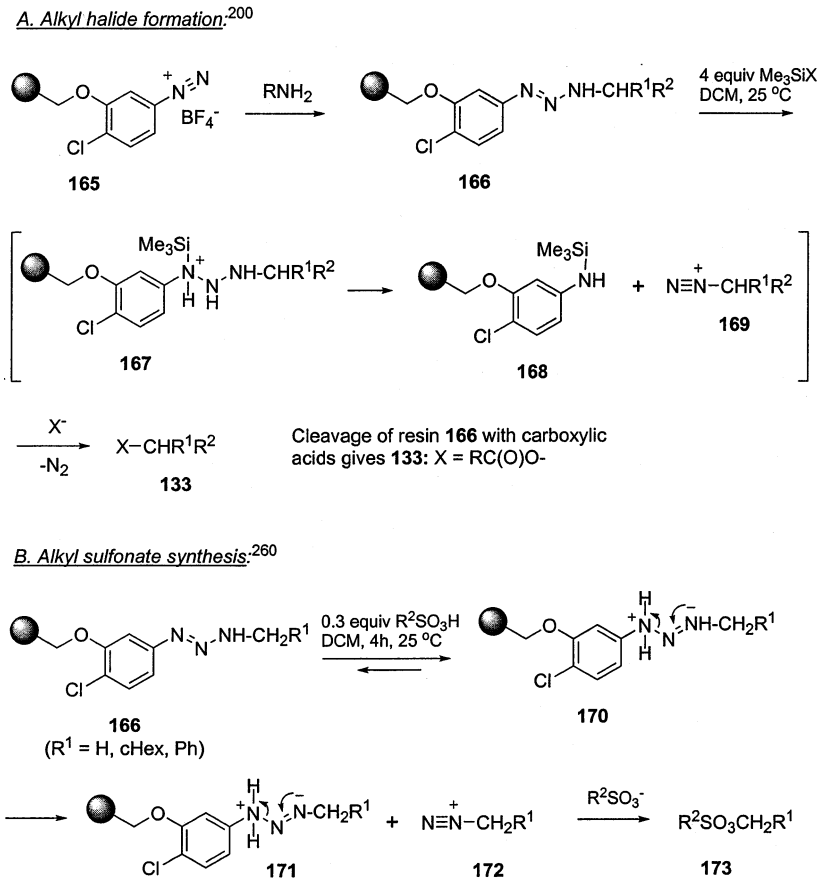


Figure 17. Application of resin-bound triazene in solid-phase synthesis.

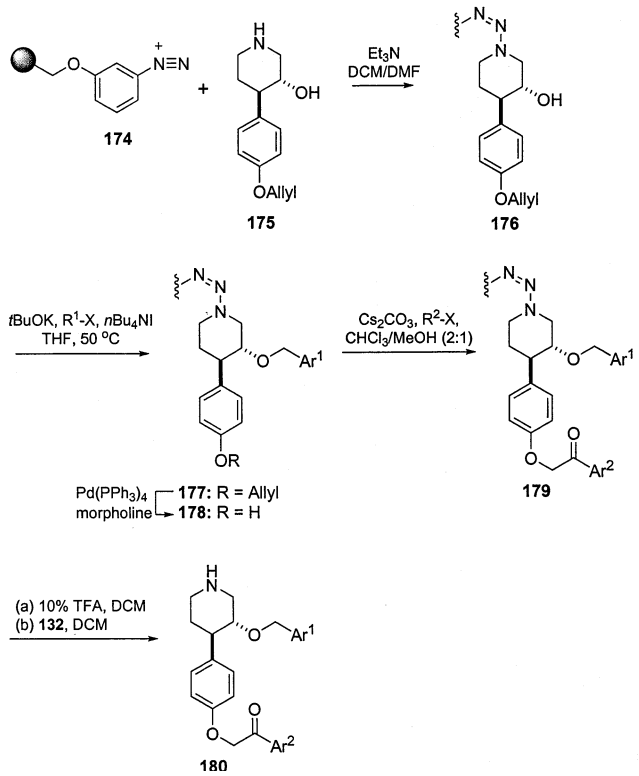


Figure 18. Synthesis of 3,4-disubstituted piperidines using triazene linker.[44]

attached to resin were N-acylated, converted to their methylammonium salts **140**, and cleaved with morpholine to give methyl tertiary amines **141**. Yields averaged ~75% with product purities in excess of 90%.

Zaragoza and Stephensen at Novo Nordisk succeeded in utilizing (cyanomethyl)trialkylphosphonium iodides as efficient reagents for alkylation of amines with alcohols in solution and on solid phase (Figure 16).[288] This operationally simple method is carried out by adding (cyanomethyl)-trimethylphosphonium iodide **152** (1.2 equiv) to a mixture of a primary alcohol (1.05 equiv), a secondary amine (1 equiv), and DIEA (1.3 equiv) in propionitrile. The reaction mixture was heated to 90 °C for 2 h. An aqueous solution of K_2CO_3 was then added to quench the reaction, and the tertiary amine **158** was extracted with a suitable solvent (EtOAc) and purified by standard techniques. The mechanism of the reaction involves deprotonation of the phosphonium salt **152** (**153**) and reaction with alcohol to yield species **155**. Thermolysis of **155** in the presence of DIEA hydroiodide leads to P−C bond cleavage, release of acetonitrile, and formation of alkoxyphosphonium salt **156**. Decomposition of **156** yields primary iodide **157**, the amine alkylating agent. In a solid-phase variant, resin-bound proline (Wang resin) was treated with phosphonium salt **153** (6 equiv) and a solution of alcohol (7 equiv) and DIEA (8 equiv) in acetonitrile. The reaction mixture was shaken at 80 °C for 24 h, filtered, extensively washed, and then cleaved with TFA/DCM to furnish the tertiary amine in good yield (~75%) and high purity. Examples of amines **159**−**164** produced using this protocol (in solution and on solid phase)

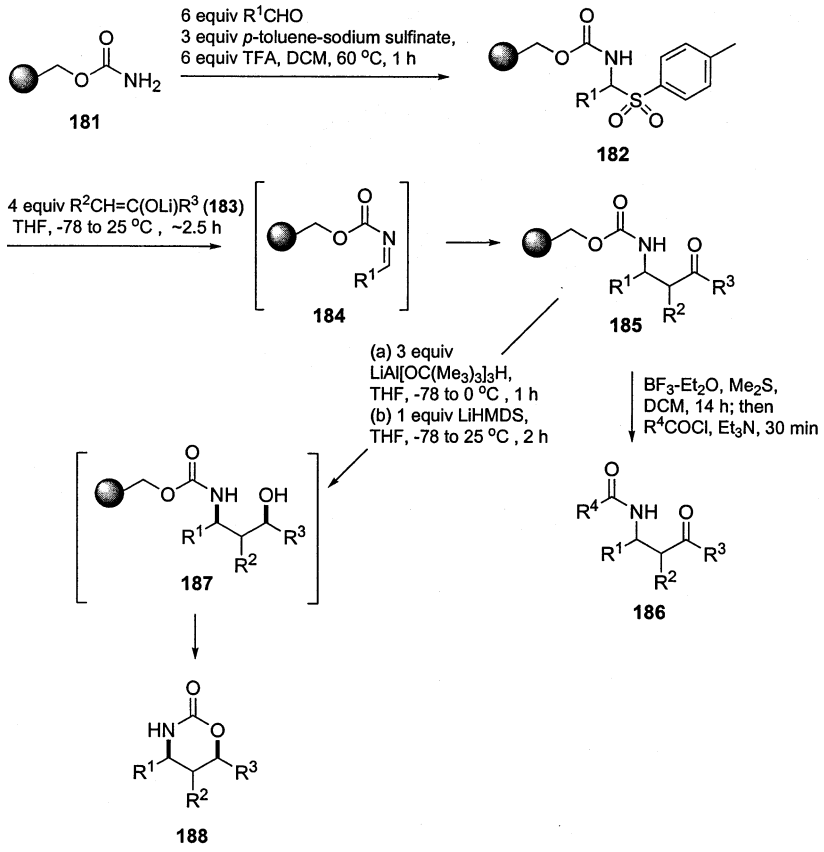
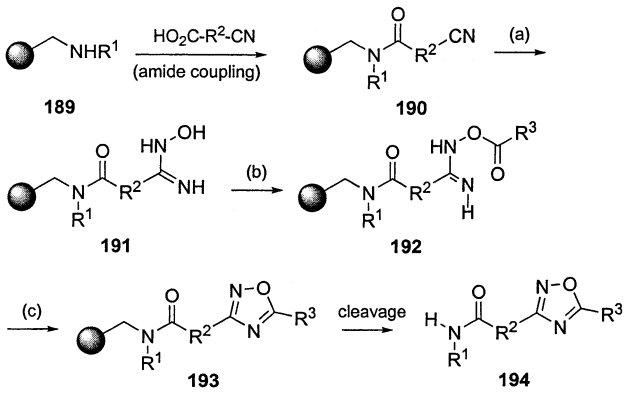


Figure 19. Resin-bound acylimines.[22]



Ref. No.	Reaction step (a)	(b)	(c)
[213]	50% aq NH_2OH, EtOH, reflux, 1 h	RCOCl, pyridine, DMF	TBAF, THF, 25 °C, 12 h
[311]	NH_2OH.HCl, DIEA, $MeOCH_2CH_2OH$, 85 °C, 16 h	RCOOH, DIC, 2-methoxyethyl ether	2-methoxyethyl ether, 85 °C, 6 h

Figure 20. 1,2,4-Oxadiazole synthesis on solid support (from resin-bound nitriles).

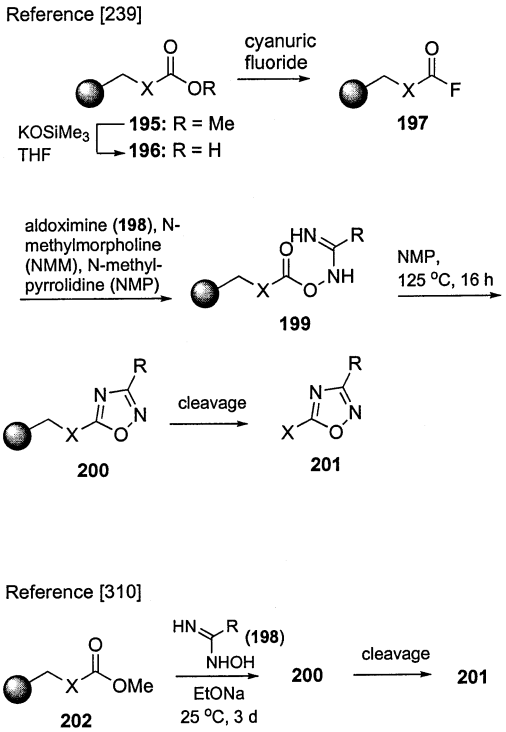


Figure 21. 1,2,4-Oxadiazole synthesis on solid support (from resin-bound esters).

are illustrated in Figure 16 (amine and alcohol retrocoupling indicated at dashed line).

Andersson and co-workers described a novel solid-phase synthesis of tertiary methylamines involving iodide- or SmI_2-based cleavage of the N−O bond of resin-bound alkoxyammonium salts.[96] These were prepared via the borane reduction of resin-bound oximes to the corresponding *O*-polystyrene-linked hydroxyamine followed by N-alkylation and quaternization with MeOTf. Purity of the exemplified amine was >90%. The reaction reportedly has broad scope, but details were not disclosed.

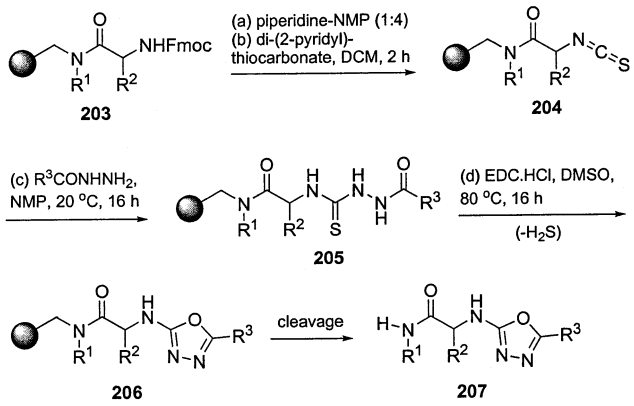


Figure 22. 1,3,4-Oxadiazole synthesis on solid support.[125]

Resin-Bound Triazenes as Reagent and Linker.[44,200,260] Brase and co-workers developed a method for attaching secondary amines onto and detaching secondary amines from solid-support via T2 triazene linkages, e.g., **166**.[313] During investigations of amide bond formation on the resin, it was observed that in cases where acylation was problematic, subsequent cleavage of material from resin with trimethylsilyl chloride (TMS-Cl) gave alkyl chlorides. This observation led to the development of a solid-phase synthesis of alkyl halides and esters from primary amines. The mechanism of the reaction is presented in Figure 17A. Reaction of stable diazonium resin **165** with a primary amine proceeded smoothly to give disubstituted triazenes **166**. Treatment of **166** with a 10% solution of TMS-Cl in DCM for a few minutes at 25 °C, filtration, and evaporation of solvent afforded the alkyl chlorides in excellent yield and purity. TMS-Br and TMS-I gave the corresponding alkyl halides. Alkyl acetates and trifluoroacetates are produced from nucleophilic cleavage with acetic and trifluoroacetic acids, respectively. The method can also be used for the mild and selective synthesis of sulfonic acid esters **173** from sulfonic acids or sodium sulfonates (Figure 17B).[260] Twelve examples of sulfonate esters were reported with yields ranging from 66% to 91%.

One noteworthy application of the triazene linker in library synthesis was reported by Rich in the preparation of putative aspartic acid protease inhibitors (Figure 18).[44] Triazene-linked piperidine **176**, prepared by reacting diazonium resin **174** with **175**, was smoothly alkylated with three different benzyl bromides using potassium *tert*-butoxide as base in THF at 50 °C. Pd^0-mediated deallylation of **177** occurred smoothly to give phenols **178**. Alkylation of **178** with aryl bromomethyl ketones (five inputs) required optimization. Standard reaction conditions (base, DMF) gave only minimal conversion to **179** even in the presence of nBu$_4$NI. An obscure patent citation describing K_2CO_3-mediated O-alkylation of phenols in a 2:1 mixture of CH_3Cl/MeOH[314] prompted the use of these conditions in the current synthesis and afforded conversions of ~90% to the desired bis-ether **179**. Library members **180** were generated upon exposure of **179** to 10% TFA/DCM and free-basing of the trifluoroacetate salts with resin-bound guanidine **132**.

Resin-Bound *N*-Acylimines.[222] Acylimines, the neutral congener of the *N*-acyliminium ion, are generated in situ from α-amino sulfones. Acylimines are reactive intermediates known to undergo Mannich-type addition with a wide variety of nucleophiles including ketone enolates, Reformatsky reagents, nitromethane anion, and vinyl and akynyl organometallic reagents. Enders adapted the synthesis of α-amino sulfones (**182**) to solid phase by condensing carbamate linker **181** with an aldehyde and *p*-toluenesodium sulfinate in the presence of TFA (Figure 19). Upon treatment of with an excess of base, e.g., ester enolate **183**, and elimination of lithium *p*-toluolsulfinate, acylimine species **184** was produced, which immediately underwent a Mannich reaction to give the resin-bound *N*-acyl-*β*-amino ester **185**. Dimethyl sulfide promoted BF_3/Et_2O cleavage of **185** afforded the corresponding amine, which may optionally be acylated to give **186**. Stereoselective reduction of the ketone carbonyl in **185** generates alcohol **187** and yields cyclic carbamates **188** via intracyclative cleavage. The percent diastereomeric excess (% de) for the reduction generally exceeded 94%, and purity of cleaved products was >85%. Treatment of **182** with allylzinc or PhMgCl gave the expected Mannich addition products.

Oxadiazoles.[85,125,203,213,311] 1,2,4-Oxadiazoles are considered metabolically stable ester bioisosteres and are found in a large number of biologically active compounds of pharmaceutical interest. Several solid-phase syntheses of this heterocycle have been reported via cyclodehydration of *O*-acylamidoximes as the key ring-forming step (Figures 20 and 21). Resin-bound *O*-acylamidoximes have been prepared by one of two ways: (i) condensation of hydroxylamine with resin-bound nitriles followed by acylation (Figure 20);[85,213,311] (ii) reaction of resin-bound activated carboxylic acids[203,239] or esters[310] with aldoximes (Figure 21). Thermal cyclodehydration[239,308,310,311] of *O*-acylamidoximes has been the preferred option for heterocyclic ring formation, but recently Kenner (solid-phase),[213] then Gangloff (solution-phase),[85] used tetra-*N*-butylammonium fluoride (TBAF) to cyclize *O*-acylamidoximes **192** at room temperture (**192** and **193**; Figure 20). TBAF-mediated cyclodehydration is compatible with a range of functionality affording diverse collections of 3,5-disubstituted 1,2,4-oxadiazoles.

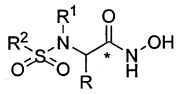
The synthesis of isomeric 1,3,4-oxadiazoles **207** was also reported (Figure 22).[125] Resin-bound thioisocyanates **204** were converted to acylthiosemicarbazides **205**. A survey of dehydrating reagents and conditions to convert **205** to **206** was carried out, and optimal cyclodehydration was effected using EDC·HCl in DMSO at 80 °C. Yields for **207** (six examples) ranged from 44% to 92%; product purities were in excess of 90%. Previous library-based methods for 1,3,4-oxadiazole synthesis include the dehydration of 1,2-diacylhydrazines on solid phase and in solution phase, the latter employing polymer-supported Burgess reagent in combination with microwave heating as the dehydration conditions.[309,312]

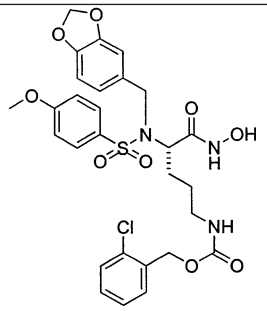
Acknowledgment. Sincere appreciation is expressed to Becca Schaefer for her expert assistance in chemical structure drawing and in the preparation of other portions of this manuscript.

Table 1. Chemical Libraries Targeted for Proteases[a]

Metallo-proteases

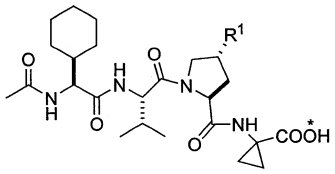
Library: 1.1
Name: Hydroxamic acid
Size: *ca.* 200 members
Affiliation: Roche Bioscience [64]
Note: 1000-fold increase in potency over original lead.

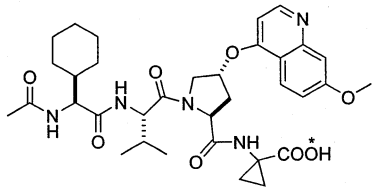




Enzyme: Procollagen C-proteinase
Activity: IC_{50} = 3.9 nM

Library: 1.2
Name: Tetrapeptide
Size: 18 members
Affiliation: Boehringer Ingelheim [206]

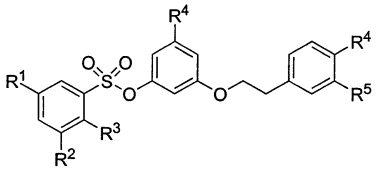


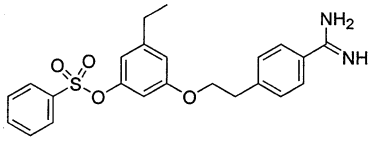


Enzyme: Hepatitis C NS3 protease
Activity: IC_{50} = 0.8 μM

Serine proteases

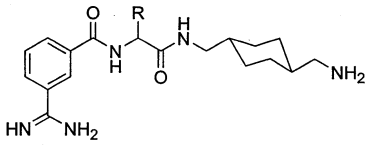
Library: 1.3
Name: Arylsulfonate
Size: 18 members
Affiliation: AstraZeneca [148]

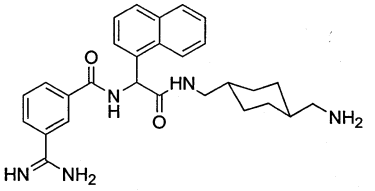




Enzyme: Thrombin
Activity: pIC_{50} = 7.6

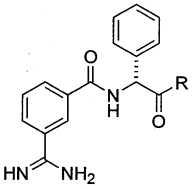
Library: 1.4
Name: Benzamidine
Size: Not defined.
Affiliation: Protherics Mol. Design [117]

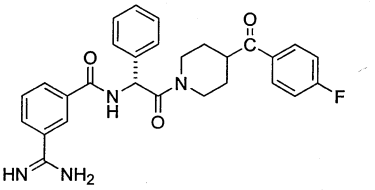




Enzyme: Factor Xa
Activity: K_i = 100 nM (diastereomeric mixture)

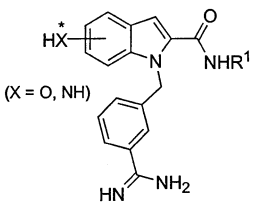
Library: 1.5
Name: Benzamidine
Size: Not defined.
Affiliation: Protherics Mol. Design [117]

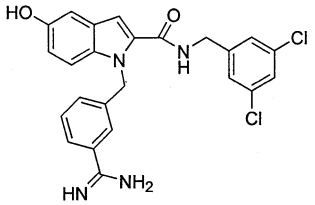




Enzyme: Factor Xa
Activity: K_i = 10 nM

Library: 1.6
Name: Amidinobenzyl indole
Size: ca. 50 members
Affiliation: Aventis Pharm. [101]

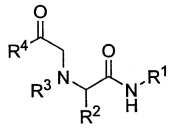


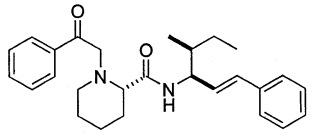


Enzyme: Factor Xa
Activity: K_i = 5 nM

Cysteine proteases

Library: 1.7
Name: Aminoketone
Size: ca. 50 members
Affiliation: Bayer Res. [228]



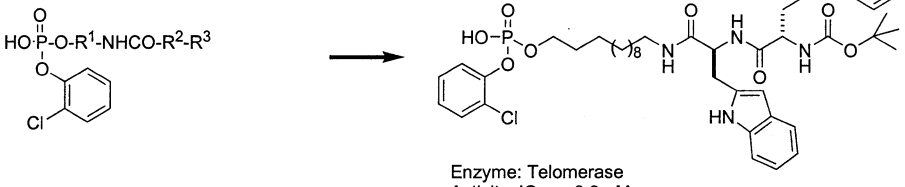


Enzyme: Cathepsin K
Activity: K_i = 230 nM

Table 2 (Continued)

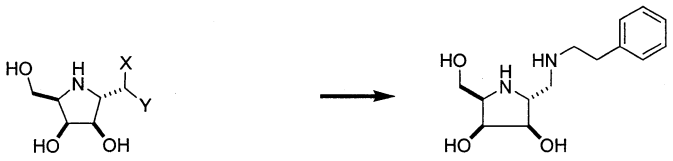
Mammalian enzymes

Library: 2.19
Name: Phosphoric acid mono ester
Size: 52 members
Affiliation: Sasaki, S.; *et al.* [220]



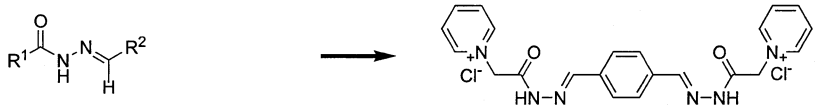
Enzyme: Telomerase
Activity: IC_{50} = 0.3 μM

Library: 2.20
Name: Iminocyclitol
Size: 27 members
Affiliation: Saotome, C.; *et al.* [219]



Enzyme: α-GalNAC-ase (EC 3.2.1.49; chicken)
Activity: K_i = 29 nM

Library: 2.21
Name: Acylhydrazone
Size: 66 members
Affiliation: Bunyapaiboonsri; *et al.* [43]
Note: Dynamic combinatorial library.



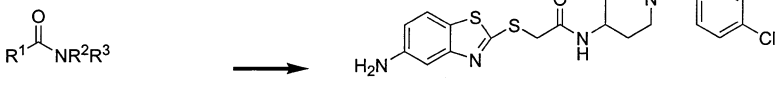
Enzyme: Acetylcholinesterase
Activity: K_i = 1.09 nM

[a] The asterisk (/) indicates point of attachment to the resin.

Table 3. Chemical Libraries Targeted for G-Protein-Coupled Receptors (GPCRs)[a]

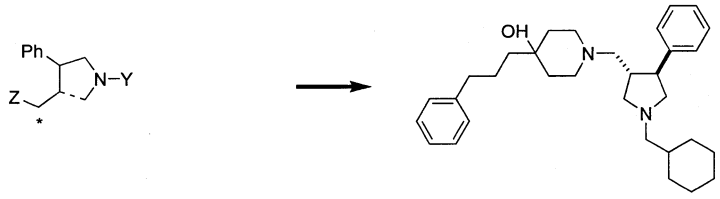
Alphabetical order of target

Library: 3.1
Name: Carboxamide
Size: 770 members
Affiliation: Banyu Tsukuba Inst. [175]



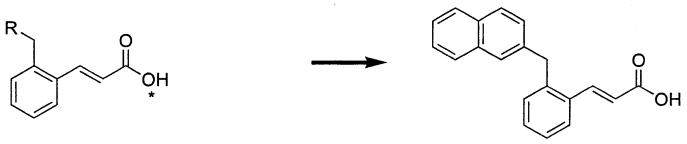
Receptor: CCR3 (chemokine)
Activity: IC_{50} = 750 nM, CCR3 (antagonist); IC_{50} = 7100 nM, CCK1

Library: 3.2
Name: Substituted pyrroline
Size: 11,700 members
Affiliation: Merck Res. Lab. [266]
Note: Kenner safety catch linker used to generate amides which were reduced to amines off resin.



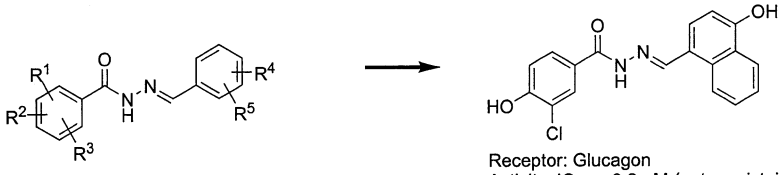
Receptor: CCR5 (chemokine)
Activity: IC_{50} = 1 nM (antagonist)

Library: 3.3
Name: Cinnamic acid
Size: 20 members
Affiliation: Merck Frosst [120]



Receptor: EP_3 prostanoid receptor
Activity: K_i = 20 nM

Library: 3.4
Name: Alkylidene hydrazide
Size: Not defined
Affiliation: Pfizer [147]
Note: Solution-phase synthesis.

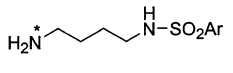


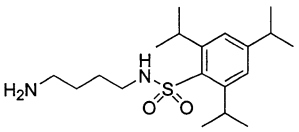
Receptor: Glucagon
Activity: IC_{50} = 0.2 μM (antagonist; inhibition of hyperglycemic effect of glucagon challenge by iv administration in rat)

Table 3 (Continued)

Alphabetical order of target

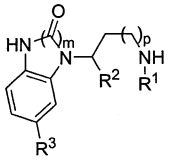
Library: 3.5
Name: Sulfonamide
Size: 8 members
Affiliation: Renault, J.; *et al.* [212]

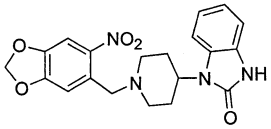




Receptor: 5-HT_6
Activity: IC_{50} = 30 nM; pK_i = 7.4

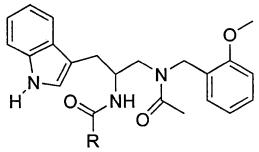
Library: 3.6
Name: Benzimidazolone
Size: 294 members
Affiliation: CEREP [205]
Note: Library design based on computer-assisted comparison of both pharmacophoric patterns and on topological similarity.

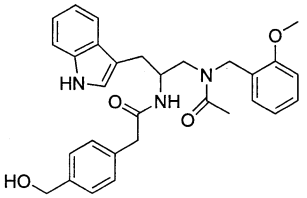




Receptor: μ opioid
Activity: IC_{50} = 1.5 nM, μ; 37 nM, κ; 264 nM, δ

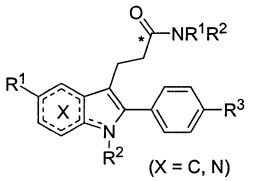
Library: 3.7
Name: Indole
Size: Not defined
Affiliation: Lilly Res. Lab. [83]



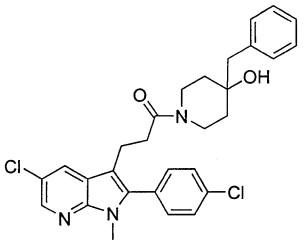


Receptor: Neurokinin-1
Activity: IC_{50} = 0.82 nM (antagonist)

Library: 3.8
Name: Substituted indole
Size: *ca.* 50 members
Affiliation: Merck Sharp & Dohm [59]
Note: Multiple solution- and solid-phase libraries.

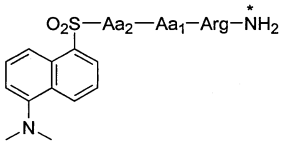


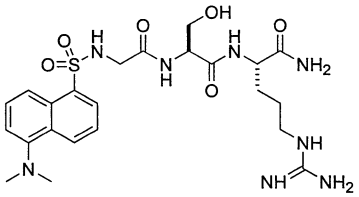
(X = C, N)



Receptor: Neurokinin-1 (human)
Activity: IC_{50} = 0.15 nM (antagonist)

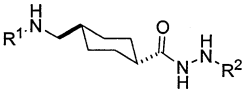
Library: 3.9
Name: Dansyl tripeptide
Size: *ca.* 360 members
Affiliation: Prokai, L.; *et al.* [207]
Note: Focused library derived from dansyl-Pro-Gln-Arg-NH_2 lead.

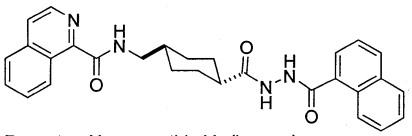




Receptor: Neuropeptide FF (rat)
Activity: K_i = 1.4 μM

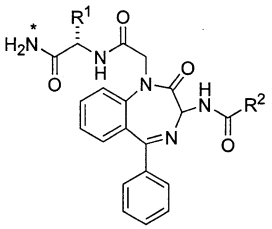
Library: 3.10
Name: Aminomethylcyclohexane
Size: ca. 75 members
Affiliation: Henlin, J. M.; *et al.* [102]
Note:

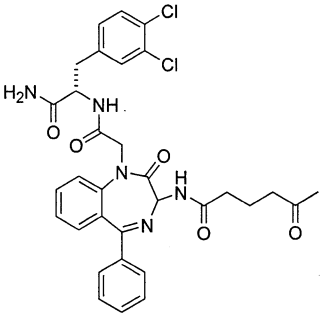




Receptor: Neuropeptide Y_5 (human)
Activity: IC_{50} = 14.5 nM

Library: 3.11
Name: 1,4-Benzodiazepinone
Size: 1296 members
Affiliation: GlaxoSmithKline [80]
Note: Fully encoded differential release library.



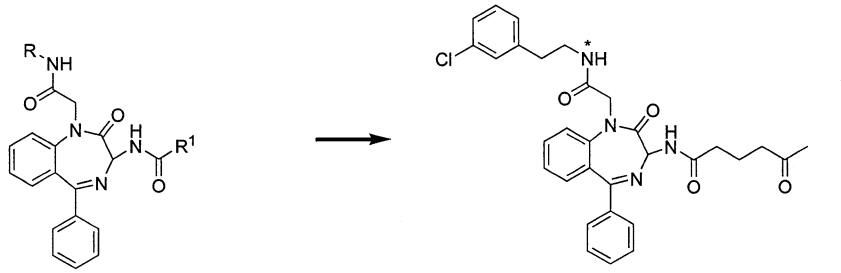


Receptor: Oxytocin (human)
Activity: IC_{50} = 5 nM (pK_i = 8.1)

Table 3 (Continued)

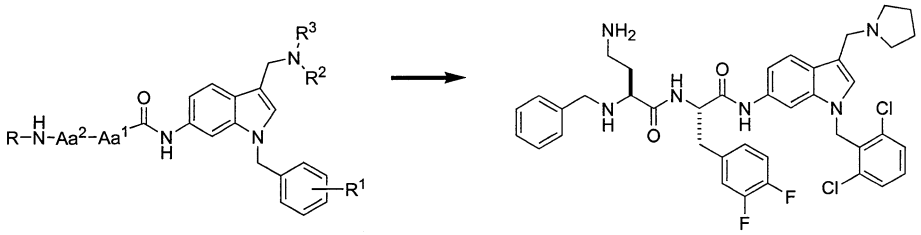
Alphabetical order of target

Library: 3.12
Name: Benzodiazepine
Size: ca. 200 members
Affiliation: GlaxoSmithKline [274]
Note: Multiple solution- and solid-phase libraries. Follow-up to library 3.11.



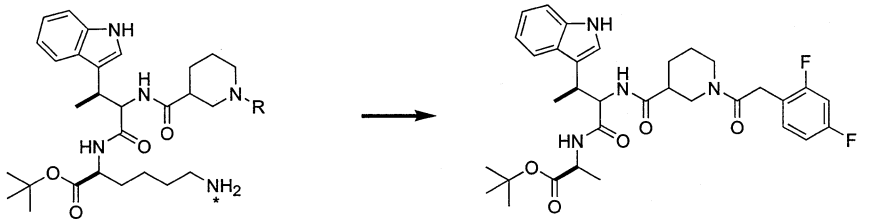
Receptor: Oxytocin (human)
Activity: $pK_i = 7.7$

Library: 3.13
Name: Peptide mimetic
Size: >200 members
Affiliation: R. W. Johnson Pharm. [291]



Receptor: Protease-activated receptor 1 (PAR-1)
Activity: $IC_{50} = 0.44\ \mu M$ (antagonist)

Library: 3.14
Name: Nipecotic amide
Size: 30 members
Affiliation: Merck Res. Lab. [297]



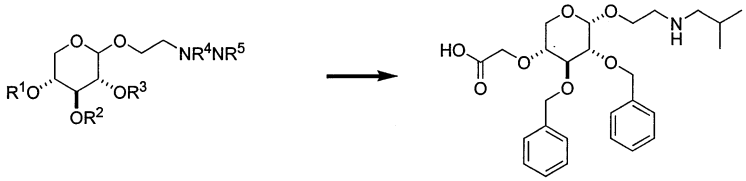
Receptor: Somatostatin-2
Activity: $K_i = 2.3$ nM. (agonist)

[a] The asterisk (/) indicates point of attachment to the resin.

Table 4. Chemical Libraries Targeted for Non-G-Protein-Coupled Receptors (Non-GPCRs)[a]

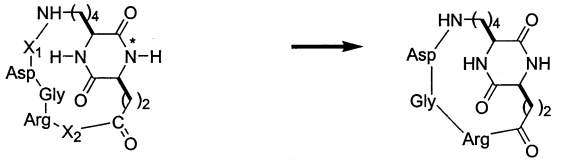
Integrins

Library: 4.1
Name: D-Xylose derivative
Size: 126 members
Affiliation: Moitessier, N.; *et al.* [167]
Note: Liquid-phase, mix and divide synthesis.



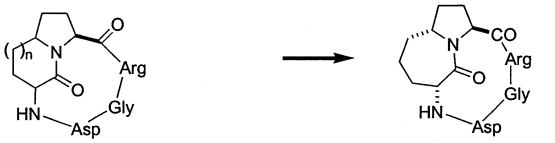
Receptor: $\alpha_v\beta_3$ integrin
Activity: 90% inhibition of cell adhesion at 2 mg/mL

Library: 4.2
Name: Diketopiperazine
Size: Not defined.
Affiliation: Royo, M.; *et al.* [216]



Receptor: $\alpha_v\beta_3$ integrin
Activity: $IC_{50} = 4\ \mu M$

Library: 4.3
Name: Cyclic pseudopeptide
Size: 8 members
Affiliation: Belvisi, L.; *et al.* [25]
Note: Acyclic precursors prepared on solid-phase.

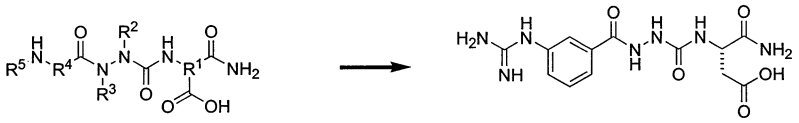


Receptor: $\alpha_v\beta_3$ integrin
Activity: $IC_{50} = 3.7$ nM

Table 4 (Continued)

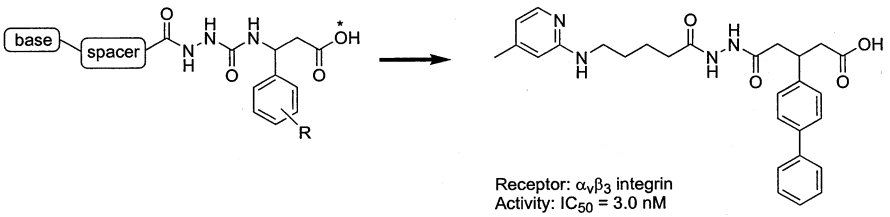
Integrins

Library: 4.4
Name: Azarurea
Size: 990 members
Affiliation: Gibson, C.; *et al.* [88]



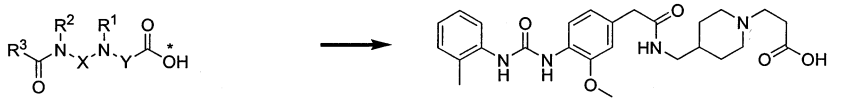
Receptor: $\alpha_v\beta_3$ integrin
Activity: IC_{50} = 150 nM, $\alpha_v\beta_3$; IC_{50} = 7.2 μM, $\alpha_v\beta_5$

Library: 4.5
Name: Aza-RGD mimetric
Size:ca. 25 members
Affiliation: Sulyok, G. A. G.; *et al.* [237]



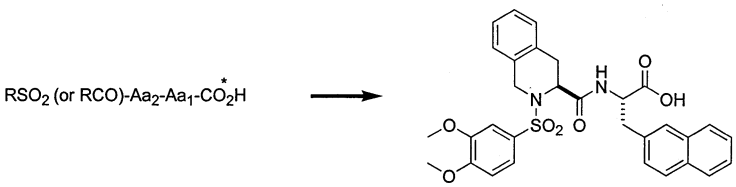
Receptor: $\alpha_v\beta_3$ integrin
Activity: IC_{50} = 3.0 nM

Library: 4.6
Name: Urea carboxylate
Size: ca. 200 members
Affiliation: Aventis Pharm. [14]



Receptor: VLA-4 ($\alpha_4\beta_1$ integrin)
Activity: IC_{50} = 1.7 μM (inhibition of VLA-4 binding to VCAM-1); IC_{50} = 0.1 μM (inhibition of VLA-4 binding to fibronectin)

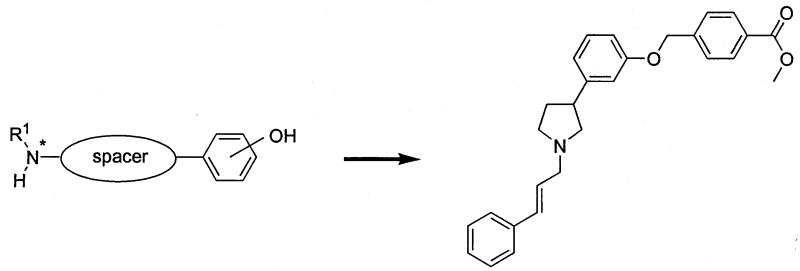
Library: 4.7
Name: Dipeptide acid
Size: ca. 300 members
Affiliation: Merck Res. Lab. [98]



Receptor: VLA-4 ($\alpha_4\beta_1$ integrin)
Activity: IC_{50} = 7 nM

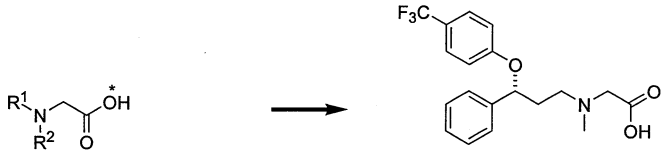
Transporters

Library: 4.8
Name: Aminophenol
Size: 3042 members
Affiliation: Organon Res. [20]
Note: REM resin.



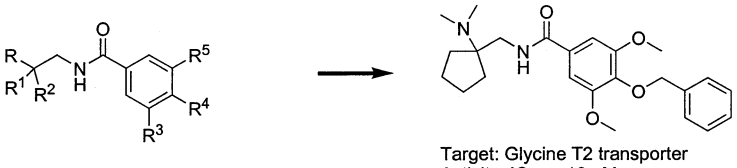
Target: Glycine T_2 transporter (human)
Activity: IC_{50} = 1.0 μM

Library: 4.9
Name: Glycine amides
Size: Not defined
Affiliation: Organon Res. [38]
Note: Amine selection based on known serotonin and monoamine uptake inhibitors. Most active inhibitor identified from the library was resolved.



Target: Glycine transporter-1b (human)
Activity: pIC_{50} = 6.9

Library: 4.10
Name: Benzamide
Size: 288 members
Affiliation: Caulfield, W. L.; *et al.* [49]

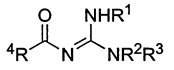


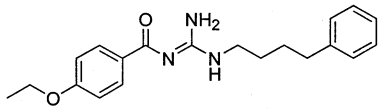
Target: Glycine T2 transporter
Activity: IC_{50} = 16 nM

Table 4 (Continued)

Ion channels

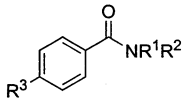
Library: 4.11
Name: Acylguanidine
Size: ca. 200 members
Affiliation: CeNeS Pharm.[190]

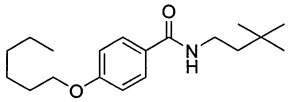




Target: Type II neuronal Na channels
Activity: IC_{50} = 0.76 μM

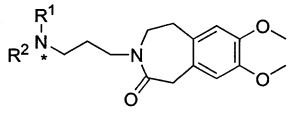
Library: 4.12
Name: Benzamide
Size: Not defined
Affiliation: Bristol-Meyers Squibb [150]

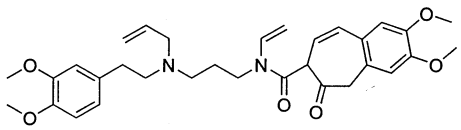




Target: I_{KS} (potassium channel)
Activity: IC_{50} = 0.25 μM

Library: 4.13
Name: Zatebradine analog
Size: 21 members
Affiliation: Organon Lab. [33]

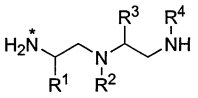


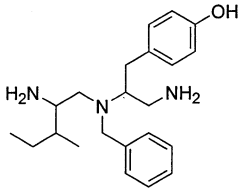


Target: I_f channel
Activity: 80% reduction at 3 μM of beating in guinea-pig atria

Miscellaneous

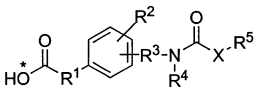
Library: 4.14
Name: N-alkylated thiamine
Size: 42320 members
Affiliation: Tai, K.-K.; *et al.* [242]
Note: Series of positional scanning libraries.



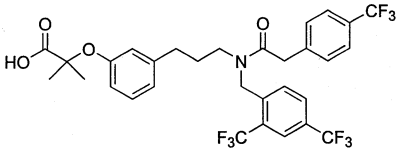


Receptor: NMDA
Activity: IC_{50} = 80 nM

Library: 4.15
Name: Substituted aryl acid
Size: 480 members
Affiliation: GlaxoSmithKline [149]

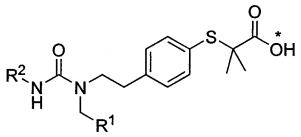


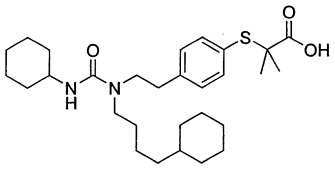
X = single bond, NH



Receptor: Peroxisome proliferator-activated receptor (PPAR)
Activity: K_i = 10 nM, hPPARγ; K_i = 5 nM, hPPARδ; K_i = 420 nM, hPPARα (dual PPARγ/δ agonist)

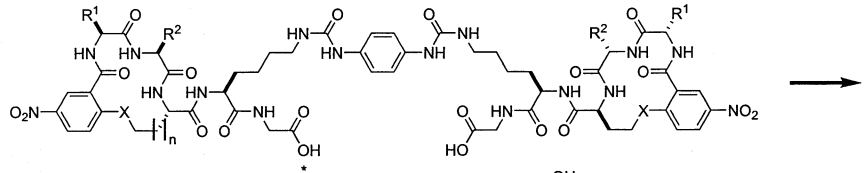
Library: 4.16
Name: Thioisobutyric acid
Size: ca. 160 members
Affiliation: GlaxoSmithKline [39]

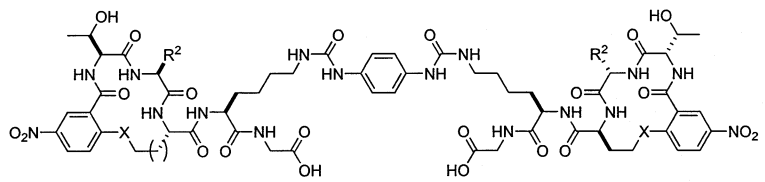




Receptor: PPARα
Activity: EC_{50} = 6.0 nM; 200x selectivity vs PPARγ and PPARδ

Library: 4.17
Name: Dimeric β-turn peptidomimetic
Size: 12 members
Affiliation: Zhang, A. J.; *et al.* [289]



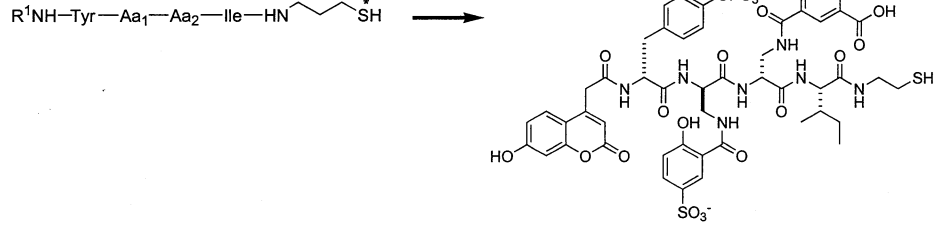


Receptor: Tyrosine kinase-C for neurotrophin-3
Activity: Increase in extracellular acidification rate over baseline.

Table 4 (Continued)

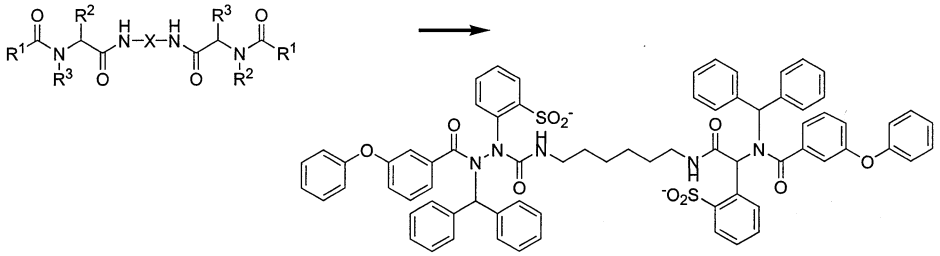
Miscellaneous

Library: 4.18
Name: Tetrapeptide
Size: ca. 1000 members
Affiliation: Yeh, R.-H.; *et al.* [278]
Note: Two libraries.



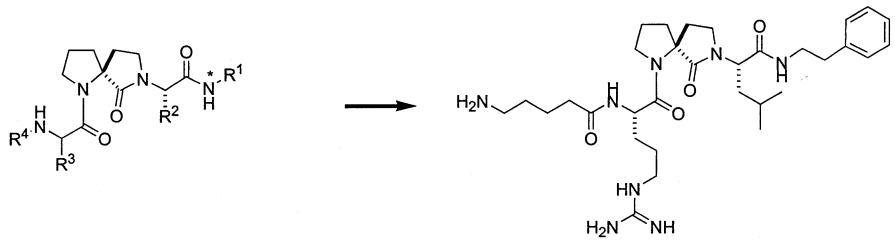
Target: Lck SH2 domain
Activity: IC_{50} = 0.20 nM

Library: 4.19
Name: Amino acid amide
Size: 9600 members
Affiliation: RepliGen Corp. [295]
Note: Multiple chemical libraries based on four-component condensation.



Receptor: Vascular endothelial growth factor (VEGF)
Activity: IC_{50} = 1.65 μM (VEGF-heparin antagonist)

Library: 4.20
Name: Spirolactam
Size: ca. 54 members
Affiliation: Novartis [224]
Note: Photolabile linker used.

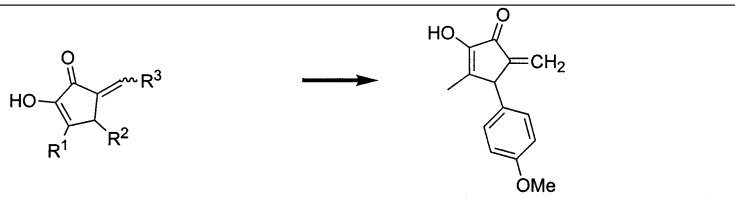


Target: E2F-1/Cyclin A protein-protein interaction
Activity: IC_{50} = 30 μM (antagonist)

Table 5. Chemical Libraries Displaying Cytotoxic and Antiinfective Activity[a]

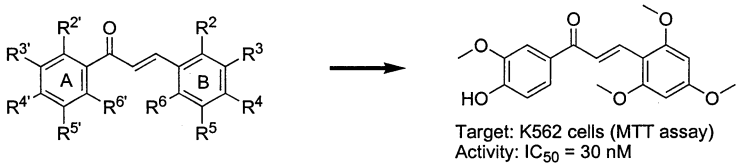
Cytotoxic agents

Library: 5.1
Name: Cyclopentenone
Size: 28 members
Affiliation: Jang, W. B.; *et al.* [116]
Note: Size of the library significantly increased via biocatalytic amplification.



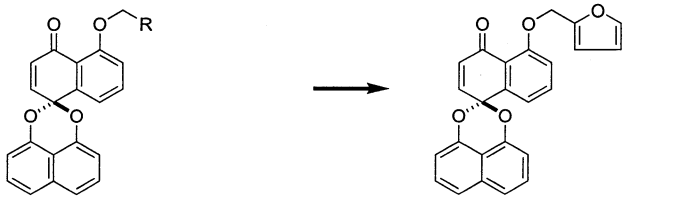
Target: Cytotoxicity assay in KB cells
Activity: IC_{50} = 1.5 μM

Library: 5.2
Name: Substituted chalcone
Size: 644 members
Affiliation: Lawrence, N. J.; *et al.* [139]



Target: K562 cells (MTT assay)
Activity: IC_{50} = 30 nM

Library: 5.3
Name: Palmarumycin CP_1 ether
Size: 13 members
Affiliation: Wipf, P.; *et al.* [270]
Note: Solution-phase Mitsunobu using resin-bound triphenylphosphine reagent.

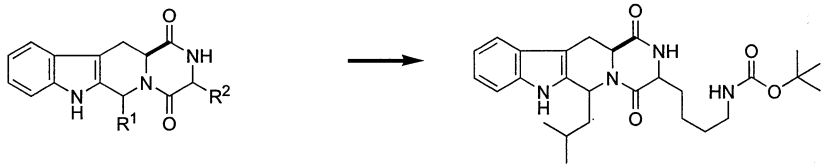


Target: MCF-7 cancer cell line
IC_{50} = 1.1 μM

Table 5 (Continued)

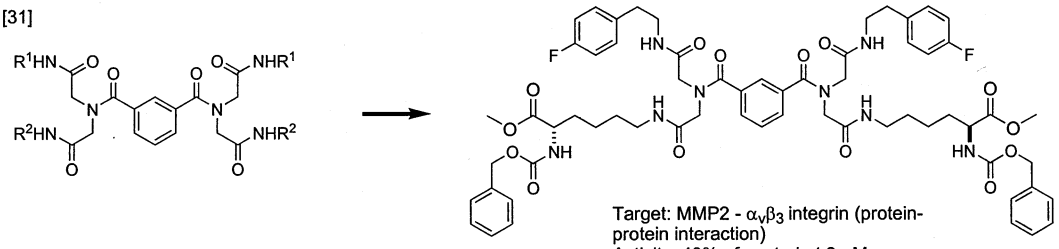
Cytotoxic agents

Library: 5.4
Name: Fumitremorgin analog
Size: 42 members
Affiliation: van Loevezijn, A.; *et al.* [256]



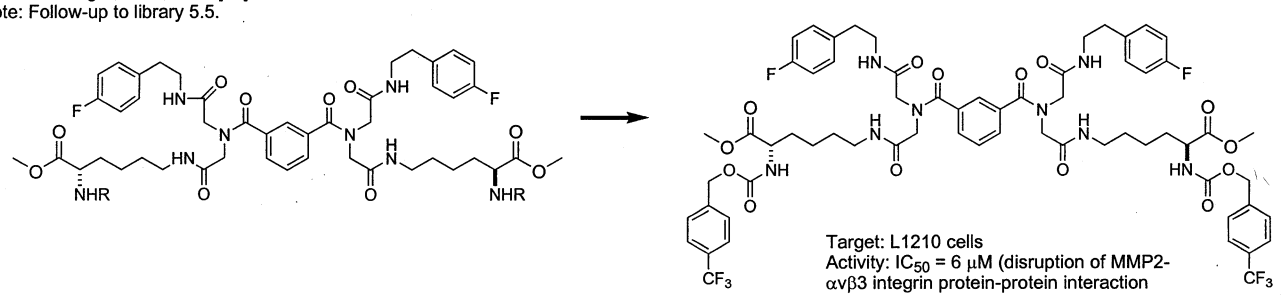
Target: Mitoxantrone accumulation assay (T* human cell line)
Activity: Comparable to fumitremorgin

Library: 5.5
Name: Benzene-1,3-dicarboxylic acid amide
Size: 600 members
Affiliation: Boger, D. L.; *et al.* [31]



Target: MMP2 - $\alpha_v\beta_3$ integrin (protein-protein interaction)
Activity: 40% of control at 3 μM antagonist activity

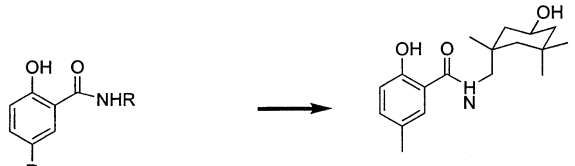
Library: 5.6
Name: Symmetrical tetraamide
Size: 77 members
Affiliation: Boger, D. L.; *et al.* [31]
Note: Follow-up to library 5.5.



Target: L1210 cells
Activity: IC_{50} = 6 μM (disruption of MMP2-αvβ3 integrin protein-protein interaction

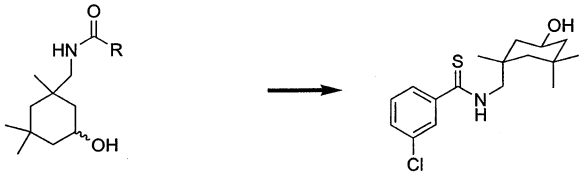
Antiinfective agents

Library: 5.7
Name: Salicylamide
Size: 175 members
Affiliation: Bristol-Meyers Squibb [68]



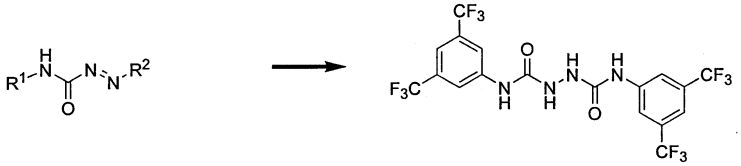
Target: Influenza virus fusion
Activity: EC_{50} = 0.08 ^{3}g/mL

Library: 5.8
Name: Cyclohexylmethylamide
Size: 160 members
Affiliation: Bristol-Meyers Squibb [68]
Note: Follow-up to library 5.7.



Target: Influenza virus fusion
Activity: EC_{50} = 0.02 ^{3}g/mL

Library: 5.9
Name: Hydrazinyl-urea
Size: 80 members
Affiliation: Procter & Gamble Pharm. [268]
Note: By-product from mixture-based synthesis was the active component.

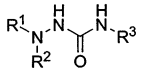


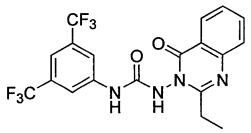
Target: Peptidoglycan biosynthesis (*S. aureus*)
Activity: IC_{50} = 17 μM

Table 5 (Continued)

Antiinfective agents

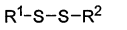
Library: 5.10
Name: Hydrazinyl-urea
Size: 80 members
Affiliation: Procter & Gamble Pharm. [268]
Note: Follow-up to library 5.9.

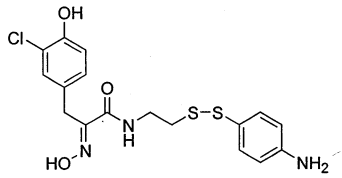




Target: Peptidoglycan biosynthesis (*S. aureus*)
Activity: IC_{50} = 36 μM (vancomycin, IC_{50} = 0.4 μM)

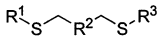
Library: 5.11
Name: Psammaplin A analog
Size: 3828 members
Affiliation: Nicolaou, K. C.; *et al.* [180, 181]

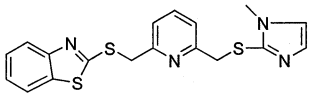




Target: Methicillin-resistant *S. aureus*
Activity: MIC = 0.78 μg/mL (MRSA 43300)

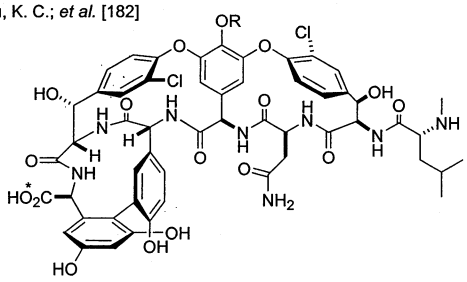
Library: 5.12
Name: Bis-sulfide
Size: ca. 100 members
Affiliation: Joseph-McCarthy, D.; *et al.* [119]
Note: Computational methods used to design structure-base libraries.

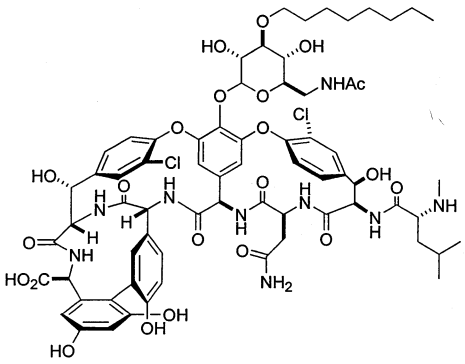




Target: PI/Mahoney poliovirus
Activity: MIC = 0.26 μM

Library: 5.13
Name: Vancomycin analog
Size: ca. 11 members
Affiliation: Nicolaou, K. C.; *et al.* [182]



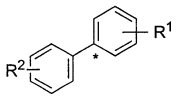


Target: Methicillin-resistant *S. pneumoniae*
Activity: MIC = 0.25 μg/mL (Sa8520) vs. MIC = 4.0 μg/mL, vancomycin

[a] The asterisk (/) indicates the point of attachment to the resin.

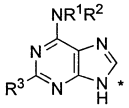
Table 6. Scaffold Derivatization

(a) Solid Phase[a]

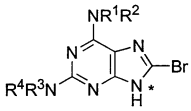


- Affymax [193]
- 22 ex; 62-89%
- Suzuki cleavage of resin-bound aryl perfluoroalkylsulfonates

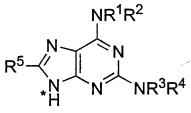
- Affymax [192]
- 12 ex; 63-90%
- Pd-catalyzed deoxygenation of resin-bound per aryl-perfluoralkyl sulfonate



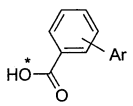
- Novartis [37]
- ca. 16 ex; high purity
- purine derivatives via substitution and Suzuki chemistry



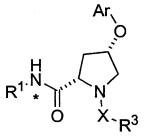
- Novartis [35]
- 14 ex; 61-97%
- bromination of resin-bound purines



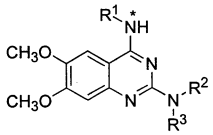
- Novartis [36]
- 8 ex; ca. 50%
- sequential displacement of C2-and C6-Cl atoms, bromination at C8 then Stille coupling



- Aventis [293]
- 12 ex; 33-100%
- Suzuki reaction on colored dendrimer, soluble support

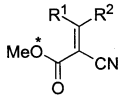


- ChemRx [32]
- 17,000 members
- from hydroxy proline



- ChemRx [67]
- 12 ex; 17-67%
- from dichloro-quinazoline

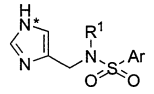
- Rigby, J. H. [214]
- ca. 6 ex; 61-78%
- traceless release of resin-bound functionalized arene chromium carbonyls



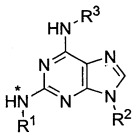
- Takaya, H. [243]
- 7 ex; 49-95%
- Aldol condensation

Table 6 (Continued)

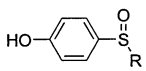
(a) Solid Phase[a] (Continued)



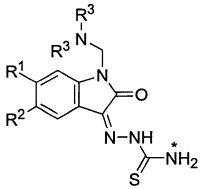
- Janssen Res. [217]
- 96 members
- from resin-bound imidazole-4-carbox-aldelyde



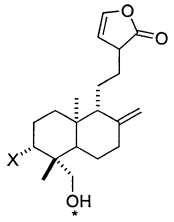
- Ding, S. [70]
- 9 ex; high purity
- from N(9)-substituted 2-fluoro-6-thiophenyl purine



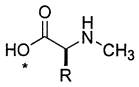
- Rolland, C. [215]
- 7 ex; 40-100%
- reaction of resin-bound *p*-hydroxyphenyl menthyl sulfinate with C-nucleophiles



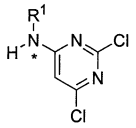
- Pirrung, M. C. [202]
- 5 ex; good yield
- isostatins and trityl-isothiocyanate resin



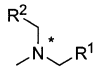
- Biabani, M. [28]
- 20 members
- derived from resin-bound labdane diterpenoid-based scaffold X = OCOR; =NOCOR



- Laplante, C. [137]
- 6 ex; 74-95%
- mono-N-methylation via Matteson rearrange-ment of α–aminoalkyl boronic esters

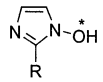


- Zucca, C. [298]
- 6 ex; high purity
- alkylation of 2,4,6-trichloropyrimidine with N-potassium carbamates

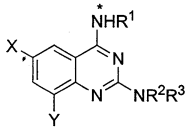


- ACADIA. [96]
- ca. 6 ex; good purity
- cleavage of quaternary salts of O-benzylhydroxyl-amines with LiI or SmI_2

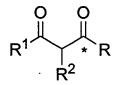
- Pilot, C. [200]
- ca. 10 ex; high yield
- cleavage of resin-bound disubstituted triazenes (diazoalkane equivalent) with electrophiles; X = halogen, OAc, OTf



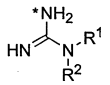
- Havez, S. [99]
- ca. 10 ex; 0-93%
- Pd-catalyzed cross-coupling of aryl iodides with resin-bound imidazol-2-yl-zinc chlorides



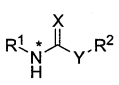
- 3-D Pharm [273]
- 12 ex; 82-95%
- reaction of 2,4-dichloro-quinazolines to resin-bound amine then addition of HNR^2R^3; X,Y = H or Cl



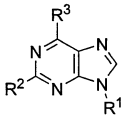
- Katritzky, A. R. [124]
- 8 ex; 47-77%
- C-acylation of ketones using acylated benzo-triazole resin



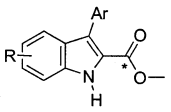
- Zapf, C. W. [287]
- 8 ex; 33-100%
- single-step guanidinylation of amines



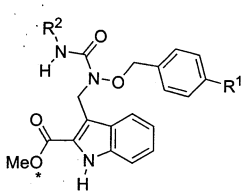
- Phoon, C. W. [199]
- 20 ex; 68-95%
- from amines loaded onto SynPhase lanterns



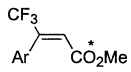
- Brun, V. [40-42]
- ca. 12 members
- from 2-iodo-6-thiopurine



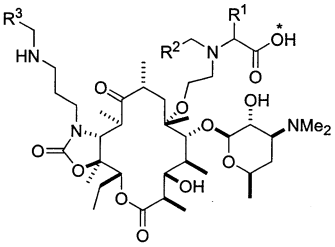
- Tois, J. [251]
- 7 ex; 42-98%
- bromination of resin-bound 2-carboxyindoles then Suzuki coupling



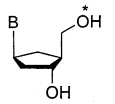
- Tois, J. [252]
- 10 ex; 30-75%
- Vilsmeier formylation of resin-bound 2-carboxy-indoles and derivatization with H_2NOCH_2Ar



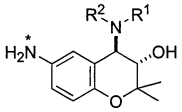
- Wang, H.-J. [264]
- 8 ex; 27-49%
- Suzuki coupling of resin-bound 3-Br-3-CF_3-acrylate



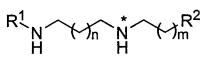
- Abbott Lab. [8]
- 11 ex; 9-33%
- reductive amination using macrolide aldehyde



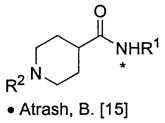
- Choo, H. [55]
- 4 ex; 39-88%
- from resin-bound triol



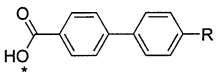
- Gong, Y.-D. [90]
- 9 ex; 13-33%
- epoxidation of resin-bound benzopyran then ring-opening with HNR^1R^2



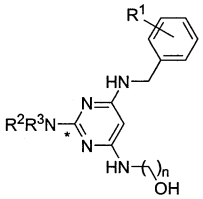
- Manov, N. [160]
- 5 ex; 43-69%
- from resin-bound mono-protected diamines



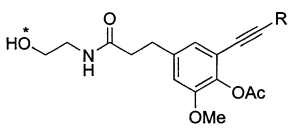
- Atrash, B. [15]
- 100 members
- use of "resin plugs"



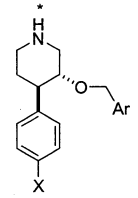
- Homsi, F. [107]
- 8 ex; good yield
- cross-coupling of resin-bound aryl iodides with aryl(halo)silanes



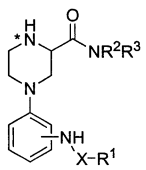
- Yoo, K.-H. [279]
- 8 ex; 8-10%
- from 4,6-dihydroxy-2-mercaptopyrimidine



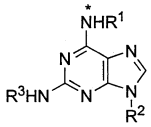
- Liao, Y. [146]
- 12 ex; >95%
- Sonogashira cross-coupling of resin-bound aromatic iodide and alkyne



- Bursavich, G. M. [44]
- ca. 20 ex; good yields
- functionalization of 3,4-disubstituted piperidine scaffolds on triazine linker



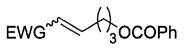
- Nilsson, J. W. [184]
- 160 members
- functionalization of 4-phenyl-2-carboxy-piperazines



- Pfizer [76]
- 4 ex; 69-96%
- coupling 2-fluoro-6-chloropurine to amine resin, Mitsunobu, then addition of R^3NH_2

Table 6 (Continued)

(b) Solution Phase



- Randl, S. [210]
- 6 ex; 86-98%
- cross metathesis using polymer-bound Grubb's catalyst

R−COOH

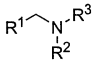
- Takemoto, T. [244]
- 18 ex; 83-98%
- RCHO oxidation using solid-support reagent

RCHO, RCOR

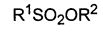
- Mulbaier, M. [171]
- 11 ex; 80-100%
- 1^o and 2^o alcohols oxidized to RCHO and RCOR via resin-bound IBX

RCHO, RCOR

- Sorg, G. [229]
- 17 ex; good yields
- 1^o and 2^o alcohols oxidized to RCHO and RCOR via resin-bound IBX

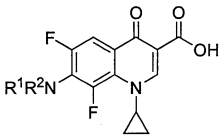


- Novo Nordisk [288]
- 8 ex; 68-83%
- phosphonium iodide mediated alkylation of secondary amines by ROH (2 ex on solid-phase)

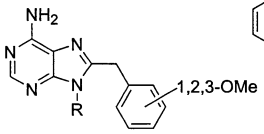


- Vignola, N. [260]
- 12 ex; 66-91%
- sulfonic esters from resin-bound triazenes

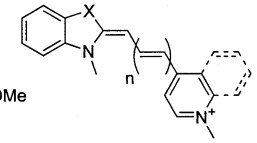
- Aberle, N. S. [2]
- 12 ex; good yields
- parallel modification of tropanol



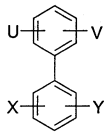
- Hoffmann-La Roche [106]
- 200 members
- S_NAr with amines using Amberlite 900-Cl as base



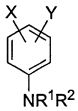
- Lucas, B. [151]
- ca. 45 ex; 65-80%
- N(9)-derivatives prepared by Mitsunobu coupling of alcohols



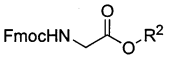
- Isacsson, I. [115]
- 4 ex; good yield
- condensation of pyridinium salts with N- methylated benzothiczoles



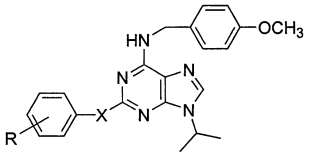
- Parrish, C. A. [196]
- 9 ex; 92-99%
- Suzuki cross-coupling using resin-bound phosphine ligand



- Parrish, C. A. [196]
- 13 ex; 79-95%
- Pd-catalyzed amination using resin-bound phosphine ligand



- Zander, N. [286]
- 13 ex; >90%
- esterification using polystyryl sulfonyl chloride resin

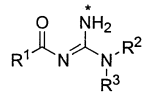


- Ding, S. [69]
- 12 ex; 90-97%
- from 2-Cl purines; X = O, N, single bond

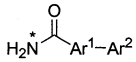
[a] The asterisk (/) indicates the point of attachment to the resin.

Table 7. Acyclic Synthesis

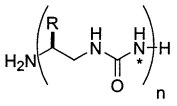
(a) Solid Phase[a]



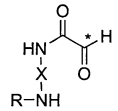
- BMS [71]
- 12 ex; 75-85%
- N-acylation of resin-bound *S*-methylisothiourea with RCOOH using PyAOP coupling reagent



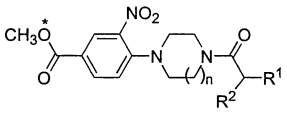
- Atrash, B. [15]
- 10 ex; good yield
- Suzuki chemistry on "resin plugs"



- Boeijen, A. [30]
- 2 ex; good purity
- oligourea peptidomimetics from diamines

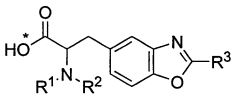


- Melnyk, O. [163]
- ca. 11 ex.
- application of 2,3-O-isopropylidine tartrate based linker

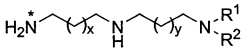


- Huang, K.-T. [112]
- 12 ex; 85-98%
- urea formation via liquid-phase synthesis

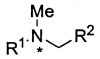
- Affymax [153]
- 14 ex; 10-95%
- reversed Kenner safety-catch linker



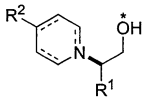
- Abbott [24]
- 6 ex; 25-60%
- derived from 3-nitrotyrosine



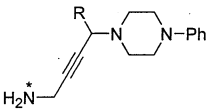
- Renault, J. [211]
- ca. 11 ex; 50-85%
- amino alcohol building blocks via carbanate linkage on SynPhase lanterns



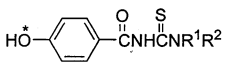
- Alhambra, C. [10]
- 15 ex; 28-97%
- two-resin method for cleavage of tertiary amines from REM resin



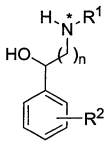
- Welfide Corp. [77]
- 18 ex; 33-93%
- coupling of resin-bound amino ethers with 2,4-dinitrophenyl pyridinium salts to give Zincke products



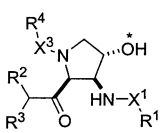
- R. W. Johnson [280]
- 35 ex; good purity
- Mannich condensation of amines, aldehydes and resin-bound alkynes



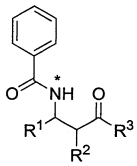
- Chen, Z. [53]
- 19 ex; good yields
- acylation of resin-bound *p*-hydroxybenzoic acid with ammonium rhodanate then reaction with amines and cleavage



- Srinivasan, T. [230]
- 11 ex; 75-92%
- alkylation of immobilized carbamates with bromo ketones, reduction and cleavage



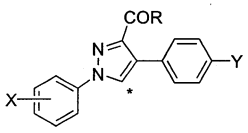
- Hoffmann-La Roche [233]
- 800 members
- derived from a resin-bound bicyclic β-lactam alcohol



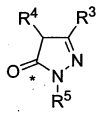
- Schunk, S. [222]
- 8 ex; 23-80%
- Mannich-type reaction of resin-bound N-acylimines

Table 8 (Continued)

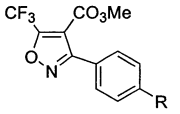
(a) Solid Phase[a] (Continued)



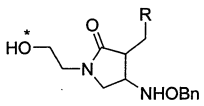
- Donohue, A. C. [75]
- 7 ex; 52-79%
- 1,3-dipolar cycloaddition of nitrile imines and resin-bound enamines



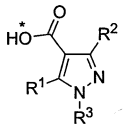
- Tietze, L. F. [249]
- 30 ex; 40-96%
- condensation of hydrazines with resin-bound β-keto esters then intracyclative cleavage



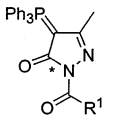
- Wang, H.-J. [264]
- 7 ex; 21-48%
- 1,3-dipolar cycloaddition reaction of resin-bound 3-Br-3-CF_3 acrylate with oximes



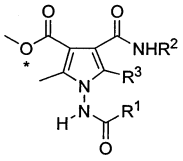
- Miyabe, H. [166]
- 4 ex; 54-89%
- tandem radical addition cyclization of oxime ethers



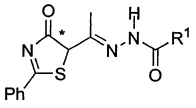
- Schmid, D. G. [221]
- 144 members
- condensation of resin-bound acetoacetate with RCHO then hydrazines



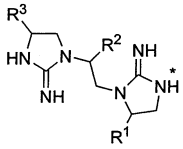
- Attanasi, O. A. [17]
- 5 ex; 12-42%
- from resin-bound 1,2-diaza-1,3-butadienes



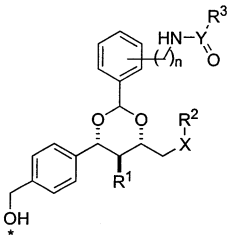
- Attanasi, O. A. [17]
- 12 ex; 17-64%
- from resin-bound 1,2-diaza-1,3-butadienes



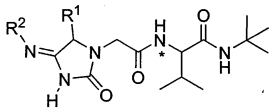
- Attanasi, O. A. [17]
- 3 ex; 11-42%
- from resin-bound 1,2-diaza-1,3-butadienes



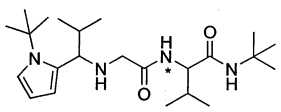
- Acharya, A. N. [7]
- 13 ex; 53-75%
- from resin-bound reduced tripeptides



- Sternson, S. M. [234]
- 1800 members
- from resin-bound diol and Fmoc-protected amino methylbenzaldehyde acetal



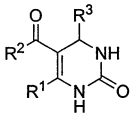
- Constabel, F. [58]
- 4 ex; 35-50%
- repetitive Ugi reactions



- Constabel, F. [58]
- 2 ex; 83-85%
- repetitive Ugi reactions

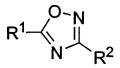
(b) Solution Phase

- Uehlin, L. [254]
- 3 ex; 54-72%
- intramolecular selenenyl etherification using resin-bound chiral selenenyl bromide

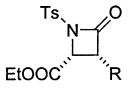


- Dondoni, A. [74]
- 32 ex; 61-80%
- Biginelli reaction using Yb(III)-resin and polymer-supported scavengers

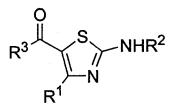
- Axys Pharm.[85]
- 24 ex; <5-98%
- nitriles to acyl aldoximes then ring closure with TBAF



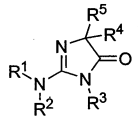
- Poulain, R. F. [203]
- 24 members
- uronium-based activation of RCOOH then acylation of aldoximes and cyclo-dehydration in DMF, 110° C



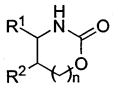
- Hafez, A. M. [97]
- 5 ex; 53-65%
- asymmetric synthesis via sequentially linked columns



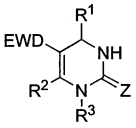
- Hoffmann-La Roche [162]
- 8 ex; 65-99%
- three-component condensation of amidines and thiouronium salts with RNCS then alkylation with α-bromoketones and ring closure



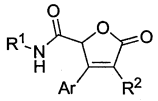
- Heras, M. [104]
- ca. 20 ex; 15-98%
- condensation of α–iminomethylene amino esters and amines



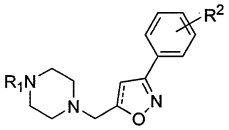
- Yu, C. [281]
- 4 ex; 96-100%
- from β–hydroxypropion-amides via Hofmann re-arrangement using a hyper-valent iodobenzene



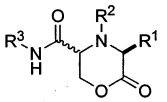
- Stadler, A. [231]
- 48 members
- microwave-assisted Biginelli multicomponent condensation; Z = O, S



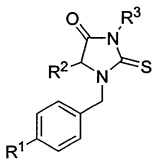
- Morphochem [23]
- 9 ex; 13-87%
- three component condensation



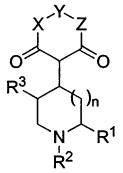
- Kang, K. H. [123]
- 40 ex; 65-100%
- nitrile oxide cycloaddition



- Kim, Y. B. [126]
- 8 ex; 30-81%
- Ugi multicomponent condensation using glycoaldehyde dimer



- Personal Chem. [186]
- ca. 10 ex; good yield
- thiohydantoins using microwave heating

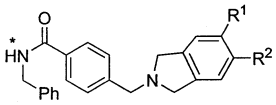


- Tietze, L. F. [250]
- 15 ex; 45-69%
- multicomponent domino Knoevenagel/hetero-Diels-Alder reaction of 1,3-dicarbonyl compounds with amino aldehydes and enol ethers

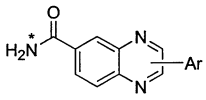
[a] The asterisk (/) indicates the point of attachment to the resin.

Table 9. Bicyclic and Spirocyclic Synthesis

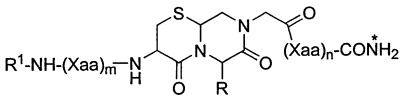
(a) Solid Phase[a]



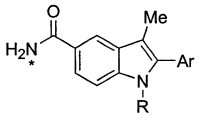
- Purdue Pharm. [238]
- 8 ex; 20-85%
- isoindolines via Rh-catalyzed [2+2+2] cycloaddition



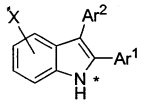
- Mimetopes [272]
- 10 ex; ca. 80%
- from resin-bound 4-fluoro-3-nitrobenzoic acid; multi-step sequence on SynPhase lanterns



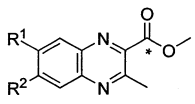
- Lilly [132]
- 14 ex; 40-50%
- intramolecular bicyclic ring closure



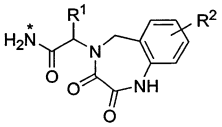
- R. W. Johnson [292]
- 7 ex; 65-96%
- Pd-mediated hetero-annulation of (1-alkyl-2-TMS)acetylene with amide resin-bound *o*-iodoaniline, electrophilic iodination and Suzuki reaction



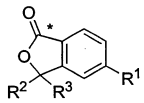
- R. W. Johnson [292]
- 7 ex; 65-96%
- heteroannulation of sulfonamide resin-bound *o*-iodoaniline electrophilic bromination then Suzuki reaction



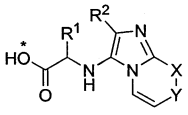
- Attanasi, O. A. [17]
- 3 ex; ca. 50%
- reaction of resin-bound 3-diazenylbut-2-enes and 1,2-diamines



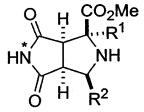
- Nefzi, A. [178]
- 41 ex; good purity
- reductive alkylation of resin-bound amine with *o*-nitrobenzaldehydes, acylation with $ClCOCO_2Me$, reduction and intramolecular cyclization



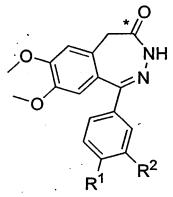
- Novo Nordisk [86]
- 84 members
- ortho-lithiation of resin-bound benzamides, reaction with RCOR or RCHO and intracyclative cleavage



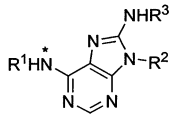
- Proctor & Gamble [51]
- 10 ex; 25-76%
- multicomponent condensation with resin-bound α-isocyano esters



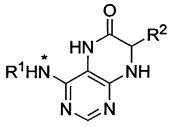
- Barrett, A. G. M. [21]
- 120 members
- 1,3-dipolar cyclo-addition of azomethine ylide and resin-bound maleimide



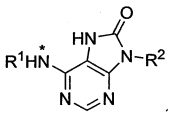
- Bevacqua, F. [27]
- 5 ex; 27-62%
- Friedel-Crafta acylation of resin-bound 3,4-di-OMe-Ph then intracyclative cleavage via H_2NNH_2



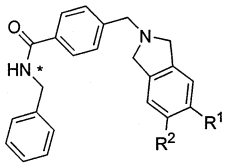
- NeoGenesis [155]
- 18 ex; 0-85%
- from resin-bound 4,6-dichloro-5-nitro-pyrimidine



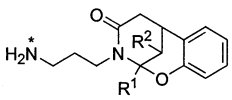
- NeoGenesis [155]
- 4 ex; 50-90%
- from resin-bound 4,6-dichloro-5-nitro-pyrimidine



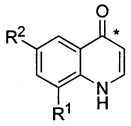
- NeoGenesis [155]
- 5 ex; 70-95%
- from resin-bound 4,6-dichloro-5-nitro-pyrimidine



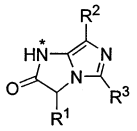
- Purdue Pharm. [238]
- 8 ex; 20-85%
- Rh-catalyzed [2+2+2] cyclo-addition of alkynes



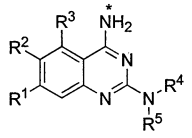
- Jonsson, D. [118]
- 8 ex; 0-70%
- condensation of resin-bound diamine with coumarin-3-carboxylic acid and ketones



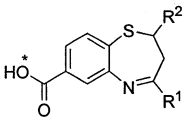
- Huang, X. [114]
- 47-62%
- thermal cyclative cleavage of arylamino methylene cyclic malonic esters



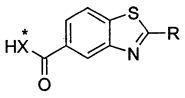
- Yu, Y. [282]
- 10 ex; 41-62%
- from acylated dipeptides via Bischler-Napieralski cyclization conditions



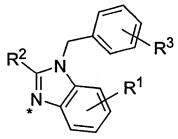
- Proctor & Gamble [267]
- 16 ex; 0-76%
- condensation of 2-amino-benzonitriles and amines with acyl isothiocyanate resin and traceless cleavage and cyclization



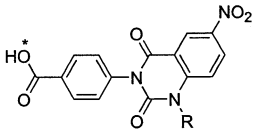
- Lee, C. L. [142]
- 3 ex; 29-34%
- from resin-bound bis-(2-nitro-4-carboxyphenyl) disulfide and α,β-unsaturated ketones



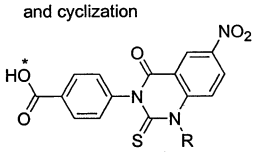
- Lee, C. L. [142]
- 7 ex; 49-91%
- from resin-bound bis-(2-nitro-4-carboxyphenyl) disulfide and RCHO; X = O, NH



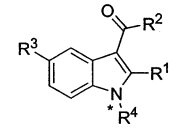
- Affymax [253]
- 25 ex; 10-93%
- reaction of o-nitrofluoro-arenes with ethylsulfide amine resin, NO_2 reduction, cyclization with RCHO then oxidative release



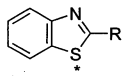
- Ajinomoto [158]
- 13 ex; 44-79%
- S_NAr reaction of resin-bound 2-fluoro-5-nitrobenzoic acid with amines, reduction, cyclization with CDI then cleavage



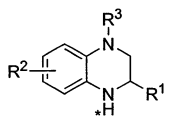
- Ajinomoto . [157]
- 10 ex; 59-100%
- S_NAr of resin-bound 2-fluoro-5-nitrobenzoic acid with amines, NO_2 reduction, cyclization with TCDI then cleavage



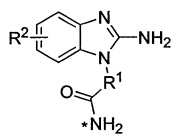
- Wu, T. Y. H. [271]
- *ca.* 40 ex; good yield
- three-step sequence from resin-bound 4-bromo-2-iodoaniline



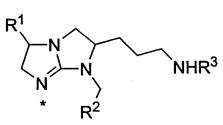
- Mourtas, S. [170]
- ca. 10 ex; good yield
- N-acylation of resin-bound 2-amino benzene-thiol then intracyclative cleavage



- SIDDCO [170]
- 10 ex; 76-96%
- resin-bound amino alcohols reacted with *o*-fluoronitro-benzenes, mesylation, NO_2 reduction, cyclization then cleavage



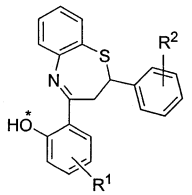
- Boehr. Ingelheim [143]
- 9 ex; 84-99%
- resin-bound amino acids reacted with *o*-fluoronitro benzenes, NO_2 reduction, cyclization with BrCN then cleavage



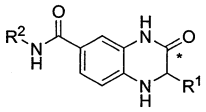
- Acharya, A. N. [3]
- 21 ex; 60-90%
- ring system generated upon reaction of resin-bound tri-amines with thiocarbonyl-dimidazole and $Hg(OAc)_2$

Table 9 (Continued)

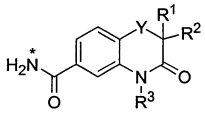
(a) Solid Phase[a] (Continued)



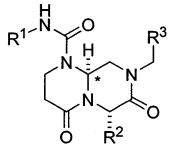
- Glaxo Wellcome [165]
- 400 members
- resin-bound chalcones cyclized with *o*-amino thiophenols



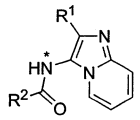
- Telik [136]
- 14 ex; 24-66%
- resin-bound amino acids N-derivatized with 4-fluoro-3-nitro benzoic acid then amide formation, NO_2 reduction and intracyclative cleavage



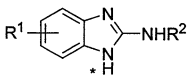
- Lee, C. L. [141]
- 10 ex; 26-86%
- alkylation of resin-bound nitro-phenols and-thiophenols with α-bromo acetates then reduction, cyclization, and further alkylation



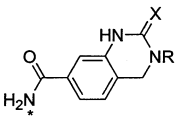
- Moelcumetics [78]
- 12 ex; 26-76%
- from bromoacetal resin, amine, Fmoc-amino acids, and Fmoc-β-alanine



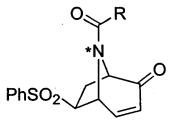
- Proctor & Gamble [52]
- 7 ex; 23-64%
- three-component condensation on Rink-isonitrile resin then acylation and spontaneous release



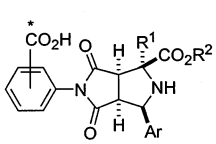
- SIDDCO [134]
- 6 ex; 40-50%
- from *o*-fluoronitro-benzenes



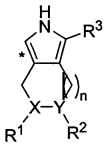
- Purdue Pharm. [240]
- 11 ex; 70-100%
- treatment of resin-bound 4-bromomethyl-3-nitroben-zoic acid with amines, reduction and cyclization; X = O, S



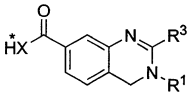
- Caix-Haumesser, S. [46]
- 3 ex; 51-58%
- 1,3-dipolar cycloaddition of resin-bound 3-oxido-pyridinium bromide to activated olefins



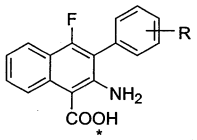
- Hoveyda, H. R. [111]
- 11 ex; 50-95%
- 1,3-dipolar cycloaddition reaction of resin-bound N-arylmaleimides



- Cheng, W.-C. [54]
- ca. 15 ex; 20-40%
- traceless cleavage of resin-bound vinyl sulfones with TOSMIC or ethyl isocyano-acetate

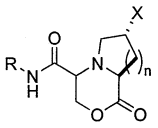


- Adv. SynTech [294]
- 13 ex; 69-95%
- from resin-bound 4-bromomethyl-3-nitro benzoate; X = O, NH

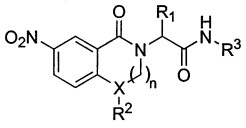


- Imclone Sys. [128]
- 8 ex; 30-67%
- novel reaction of resin-bound (2-CF_3)-phenylacetic acid with aromatic nitriles

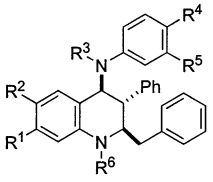
(b) Solution Phase



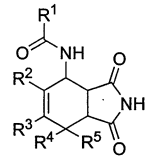
- Kim, Y. B. [126]
- 6 ex; 68-90%
- Ugi multicomponent condensation using glyco-aldehyde dimer



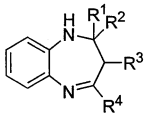
- Amgen [246]
- 1280 members
- Ugi reaction of 2-fluoro-5-nitro benzoic acid then S_NAr cyclization



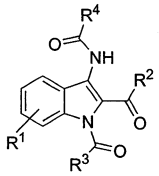
- Talukdar, S. [245]
- 9 ex; 82-89%
- use of polymer-supported benzotriazoles as catalyst for condensation of aldehyde and aniline



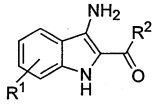
- von Wangelin, A. J. [261]
- 12 ex; 56-91%
- three-component coupling of α,β-unsaturated aldehyde, amine and maleimide



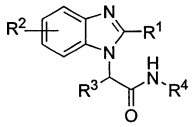
- Balakrishna, M. S. [19]
- 5 ex; 65-90%
- *o*-phenyldiamine and ketones on solid surface



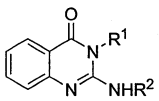
- Hoffmann-La Roche [179]
- 159 members
- from 2-aminobenzo-nitriles



- Hoffmann-La Roche [179]
- 80 members
- from 2-amino benzonitriles



- Amgen [247]
- 960 members
- Ugi reaction of 2-fluoro-3-nitrobenzoic acid then S_NAr cyclization

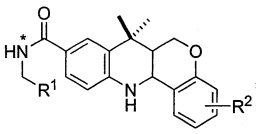


- Sphinix [296]
- 7 ex; 74-89%
- N-substituted benzamides subjected to Kirsanov reaction using polystyryl triphenyl-phosphine resin

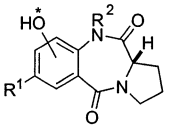
[a] The asterisk (/) indicates the point of attachment to the resin.

Table 10. Polycyclic and Macrocyclic Synthesis

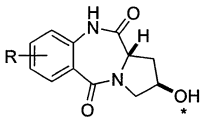
Solid Phase[a]



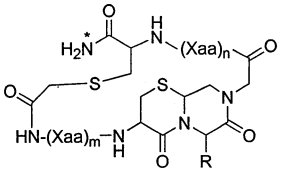
- Amgen [290]
- 9 ex; 61-81%
- reaction of immobilized anilines with derivatives of salicylic aldehyde



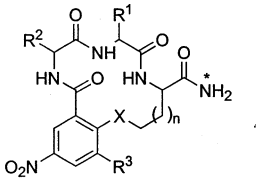
- Kamal, A. [121]
- 14 ex; 52-84%
- from resin-bound 2-nitro-3(or 4)-hydroxy-benzoic and proline



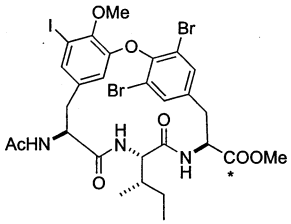
- Kamal, A. [122]
- 4 ex; 82-92%
- indium-mediated reduction of azide and intracyclative cleavage



- Lilly [132]
- 12 ex; 40-50%
- intramolecular ring closure via amide bond formation



- Park, C. [194]
- 16 ex; 45-71%
- macrocyclic ring closure via S_NAr reaction; X = NH, S, O



- Nakamura, K. [174]
- 1 ex; ca. 10%
- macrocyclic ring closure via cyclic diarylether formation

[a] The asterisk (/) represents point of attachment to the resin.

Table 11. Resin-Bound Reagents and Scavengers Reported in 2001

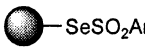
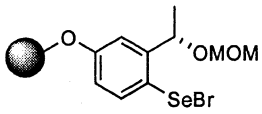
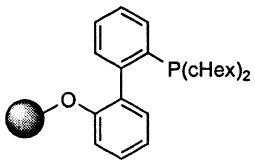
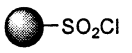
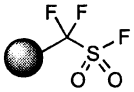
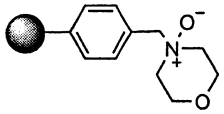
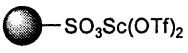
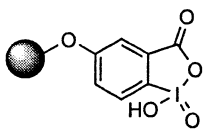
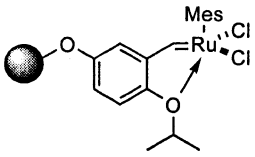
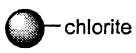
Reagent	Application [reference]	Reagent	Application [reference]
	Vinyl sulfones from olefins. [208]		Resin-bound iminophosphoranes from anilines; preparation of quinazolines. [296]
	Chiral ethers from olefins. [254]		Pd-catalyzed aminations and Suzuki reactions. [196]
	Esterification of carboxylic acids. [286]		
	Formatino of resin-bound aryl triflates from phenols. [192, 193]		Co-oxidant in the TPAP oxidation of alcohols. [333]
	Nucleophilic addition to *N*-acylimino esters. [131]		Oxidation of alcohols to alehydes and ketones. [171, 229]
	RCM with electron deficient olefins. [210]		Oxidation of aldehydes to acids. [244]

Table 11 (Continued)

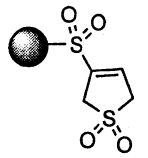
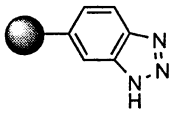
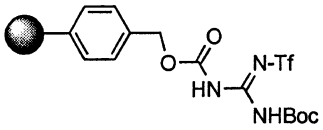
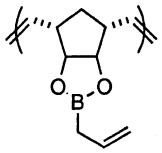
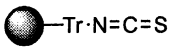
Reagent	Application [reference]	Reagent	Application [reference]
	Vinyl sulfone as Diels-Alder diene precursor. [54]		(a) Ureas from phosgene and amines. [191]; (b) Tetrahydroquinolines from aldehydes and aromatic amines. [245]; (c) Comparison to related triazole and benzotriazole leaving groups. [124]
	Rink-isonitrile resin for multi-component reactions. [52]		Traceless guanidinylating reagent for secondary amines to prepare *N,N*-disubstituted guanidines. [287]
	Purification-free method for the peparation of homoallylic alcohols. [13]		
	Trityl isothiocyanate resin as precursor for resin-bound trityl thiosemicarbazide for preparation of heterocycles. [202]		

Table 12. Solid-Phase Linkers Reported in 2001

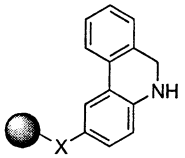
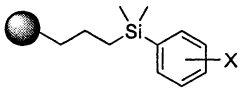
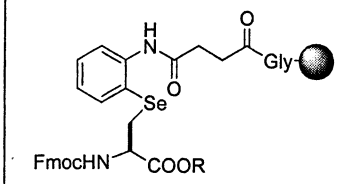
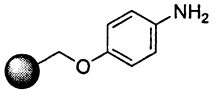
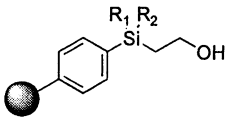
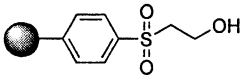
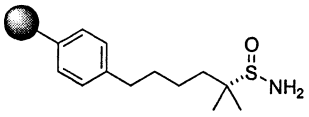
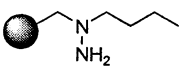
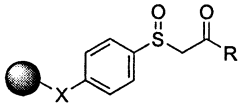
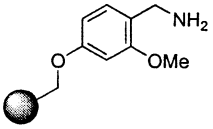
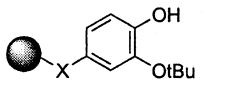
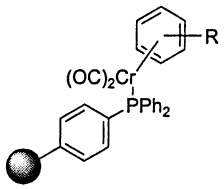
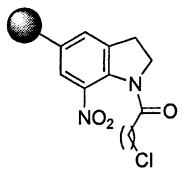
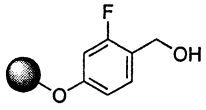
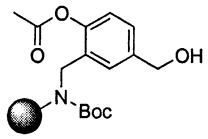
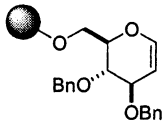
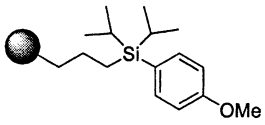
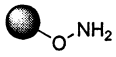
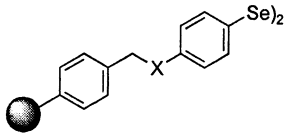
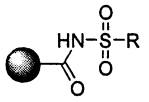
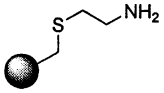
Linker	Application [reference]	Linker	Application [reference]
	Phenanthridine-based linker. Release of carboxylic acids upon treatment with cerium ammonium nitrate (CAN). Stable to acids, bases, reductive amination. [318]		General synthesis of functionalized arylsilanes. [324]
	Preparation of dehydroamino acid amides. [319]		Linker that uses CAN as a cleavage reagent. Applied to the synthesis of β-lactams. [92]
	Resistant to basic and moderately acidic media, oxidation, and elevated thermal conditions. [320] Synthesis of Tryprostatin B. [262]		Couples to acids to form ester linkage which can be cleaved by using both aqueous acidic and basic conditions. Intramolecular release to form hydantoins. [113]
	Synthesis of chiral amines in near quantitative yields in high enantiomeric purities. [321]		Synthesis of α-branched primary amines. [127]
	Synthesis of 1,2-diols via Pummerer cleavage strategy. [322]		BOMBA resin for the traceless cleavage of heterocycles. [138]
	'Safety-catch' ester linker. Linked esters are stable to nucleophilic chemistry. TFA-treatment gives the activated 2-hydroxyphenyl ester which readily reacts with amines to give amide cleavage products. [323]		Chromium carbonyl linker for attaching arenes to resin via π-bond ligand chemistry. [214, 325]

Table 12 (Continued)

Linker	Application [reference]	Linker	Application [reference]
	Photolabile linker for photoactivation of carboxyl groups. [326]		Fluoro-Wang resin for solid-phase reaction monitoring by ^{19}F NMR. [331]
	Acylation of alcohol gives esters that are released from resin upon Boc removal via a 1,6-elimination process. [327] Intramolecular variation also reported. [330]		Glucal-based linker for immobilization of alcohols. [332]
	Treatment with TfOH gives silyl triflate for loading alcohols. [146, 328]		SmI_2-mediated reductive N-O bond cleavage. Used in the synthesis of β-lactams. [164]
	Source of selenide anion which functions as traceless linker for electrophiles. [329]		Reversed Kenner 'safety-catch' linker for sulfonamide synthesis. [153]
			Base-labile linker following sulfide to sulfone oxidation used in preparation of heterocycles. [253]

References and Notes

(1) (a) Dolle, R. E. Comprehensive survey of combinatorial library synthesis: 2000. *J. Comb. Chem.* **2001**, *3*, 477−517. (b) Dolle, R. E. Comprehensive survey of combinatorial library synthesis: 1999. *J. Comb. Chem.* **2000**, *2*, 383−433. (c) Dolle, R. E.; Nelson, K. H., Jr. Comprehensive survey of combinatorial library synthesis: 1998. *J. Comb. Chem.* **1999**, *3*, 235−282. (d) Dolle, R. E. Comprehensive survey of chemical libraries yielding enzyme inhibitors, receptor agonists and antagonists, and other biologically active agents: 1992−1997. *Mol. Diversity* **1998**, *3*, 199−233. (e) Dolle, R. E. Comprehensive survey of combinatorial libraries with undisclosed biological activity: 1992−1997. *Mol. Diversity* **2000**, *4*, 233−256. (f) As combinatorial chemistry becomes integrated into mainstream drug discovery, it has become increasing difficult to discern which optimization programs have benefited from high-throughput synthesis because key words such as parallel-, library-, solid-phase synthesis, etc. are no longer included in titles and abstracts of research papers. Simply searching public databases, e.g., SciFinder, for these key words can no longer be relied upon to ensure a complete and accurate literature search. It has become necessary to scan the chemistry discussion and experimental sections of publications for combinatorial chemistry terms to create this comprehensive survey of libraries; thus, if omissions are found, please notify the author.

(2) Aberle, N. S.; Ganesan, A.; Lambert, J. N.; Saubern, S.; Smith, R. Parallel modification of tropane alkaloids. *Tetrahedron Lett.* **2001**, *42*, 1975−1977.

(3) Acharya, A. N.; Nefzi, A.; Ostresh, J. M.; Houghten, R. A. Tethered libraries: solid-phase synthesis of substituted urea-linked bicyclic guanidines. *J. Comb. Chem.* **2001**, *3*, 189−195.

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(7) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. Solid-phase synthesis of bis-cyclic guanidines from tripeptides. *Tetrahedron* **2001**, *57*, 9911−9914.

(8) Akritopoulou-Zanze, I.; Sowin, T. J. Solid-phase synthesis of macrolide analogues. *J. Comb. Chem.* **2001**, *3*, 301−311.

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(11) Apfel, C.; Banner, D. W.; Bur, D.; Dietz, M.; Hubschwerlen, C.; Locher, H.; Marlin, F.; Masciadri, R.; Pirson, W.; Stalder, H. 2-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)- and 2-(2,2-dioxo-1,4-dihydro-2*H*-2λ^6-benzo[1,2,6]thiadiazin-3-yl)-*N*-hydroxy-acetamides as potent and selective peptide deformylase inhibitors. *J. Med. Chem.* **2001**, *44*, 1847−1852.

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