Review

Comprehensive Survey of Combinatorial Library Synthesis: 1999

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Reviews

Comprehensive Survey of Combinatorial Library Synthesis: 1999

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Continuing with this annual series of comprehensive surveys of combinatorial libraries,[1] the present review captures small molecule libraries for pharmaceutical applications reported in the literature during the year 1999. The total number of libraries published in 1999 was 292. There were 85 citations for libraries describing biologically active agents and 207 citations for library constructs without disclosed biological activity.[2−252] Overall, these numbers are quite similar to those reported in last year's review.[1a] Last year, the first example of an efficacious and orally active compound obtained directly from an optimization library was reported.[253] In addition to new examples of orally bioavailable agents coming from chemical libraries,[8,229,252,101] this year marks another milestone: a 500-member optimization library played a defining role in the identification of a clinical candidate.[66,153] The effort was reported by Agouron Pharmaceuticals in their structure-based rhinoviral 3C-protease inhibitor program. Achievements such as these are worth noting as large capital investments have been made in combinatorial chemical technologies.[254] Today combinatorial synthesis pervades many aspects of drug discovery from lead finding and target validation, lead optimization, to enhancing corporate compound collections.

Including the libraries compiled herein, a total of 975 libraries have been abstracted along with their generic structures in this comprehensive review series,[1] beginning in 1992 when the first publications of libraries began to appear in the literature. An analysis of the data collected in the reviews reveals some interesting statistics and trends in combinatorial chemical research (Figures 1−5). Figure 1A graphically illustrates the number of libraries published during the years 1992−1999 as divided into two broad classifications: (1) chemical libraries for which their synthesis and biological assay data is reported (disclosed biological activity), and (2) chemical libraries for which only their synthesis was reported and no disclosure of biological activity (undisclosed biological activity). The number of reports of biologically active libraries grew at a fairly steady pace. The largest single jump (10-fold) occurred in 1995, with a steep rise occurring in 1998−1999. The 1998 library number of 74 is nearly equivalent to the combined total of the preceding 6 years. The number of biologically active libraries for 1992 through 1999 was 240. In contrast, the number of reports of library synthesis without disclosed biological activity rose at a much more dramatic pace as the nascent field began to take root. In 1992−1994, only 15 libraries of this type in total had been reported, comparable in number to the 12 biologically active libraries reported for the same period. Library citations (without biological data) increased by a factor of 3× in 1995 to 43 libraries. In 1996 library publications of this genre more than doubled (2.5×), held steady for 1997, and then doubled again in 1998 to 247 libraries. Libraries with undisclosed biological activity fell back slightly to 207 libraries in 1999. The total number of libraries in this classification is 735, some 70% more than reports of biologically active libraries. This gap is not too surprising since researchers are anxious to demonstrate new chemical methodologies, while safeguarding the structures of active library members. Figure 1B shows the cumulative

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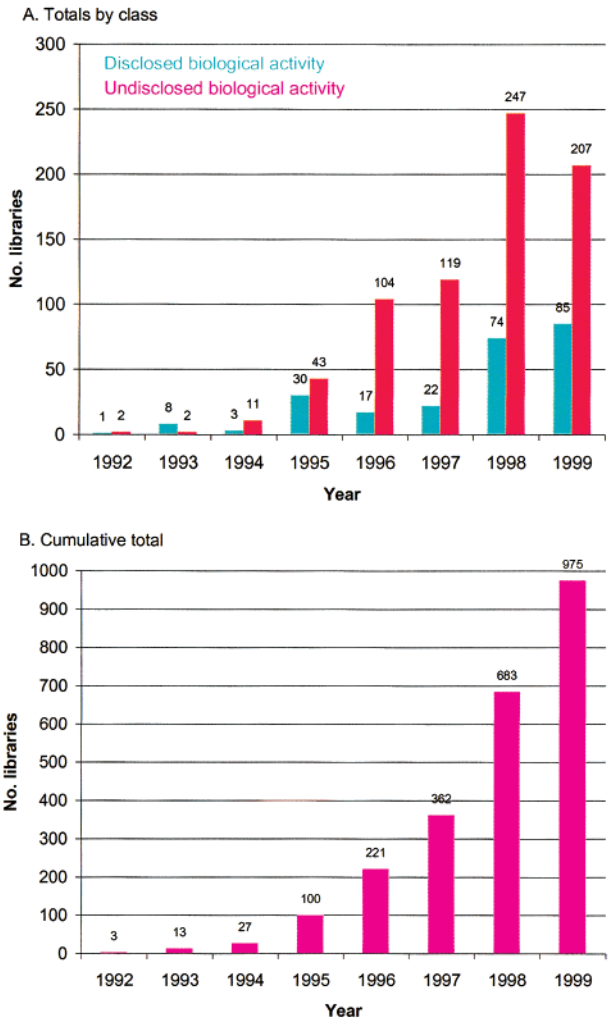


Figure 1. Libraries by major class.

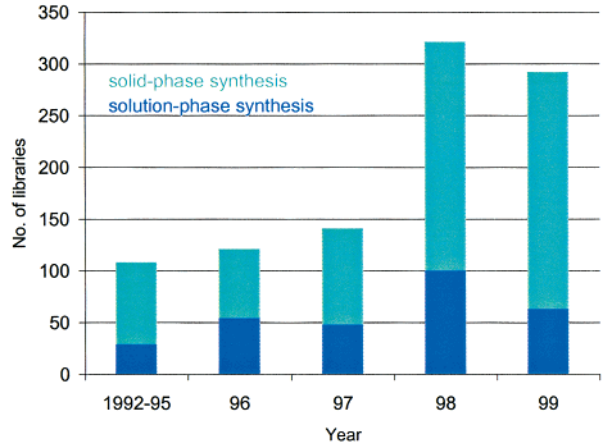


Figure 2. Solid- versus solution-phase for all library constructs (1992−1999).

total of both library classifications, which on balance has increased approximately 1.5× each year.

The early appeal of combinatorial chemistry was creating large discovery-type libraries through synthesis on solid support. In addition to its perceived synthetic advantages, solid-phase synthesis was the overwhelming choice for library construction in 1992−1995 (Figure 2). Some 80% of the libraries produced in this time period were generated on solid support. Solution-phase synthesis surged to 50% of

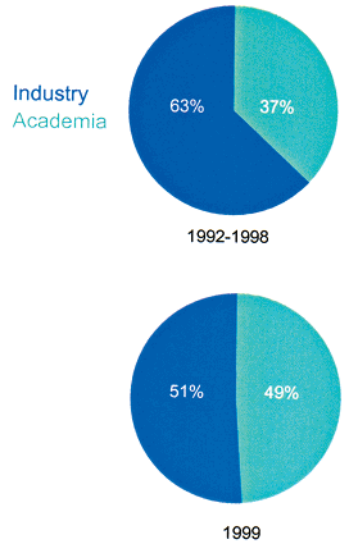


Figure 3. Library contributions by affiliation (1992−1999).

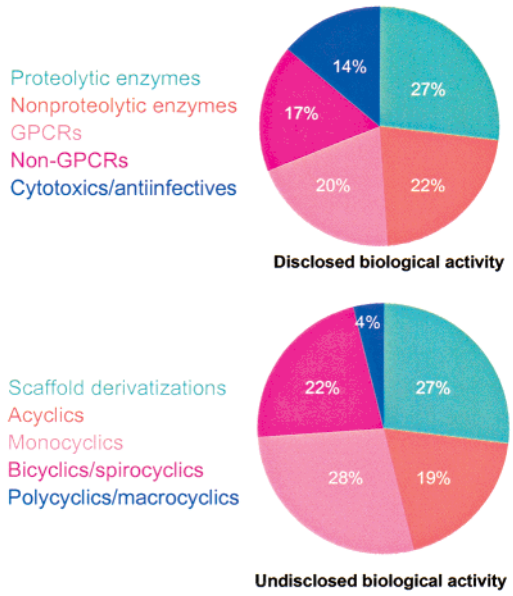


Figure 4. Libraries by subclass (1992−1999).

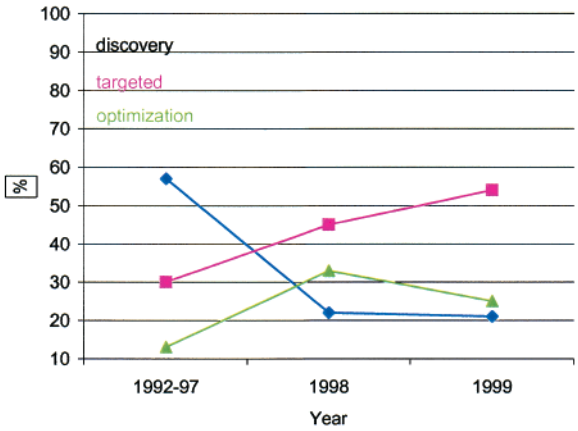


Figure 5. Discovery, targeted, and optimization libraries (biologically active libraries only).

the total reports in 1996. This was led by advances in the development of new solid-phase reagents, scavenger resins, novel fluorous-based separations, and automated liquid−liquid extractions. Publications of solution-phase library

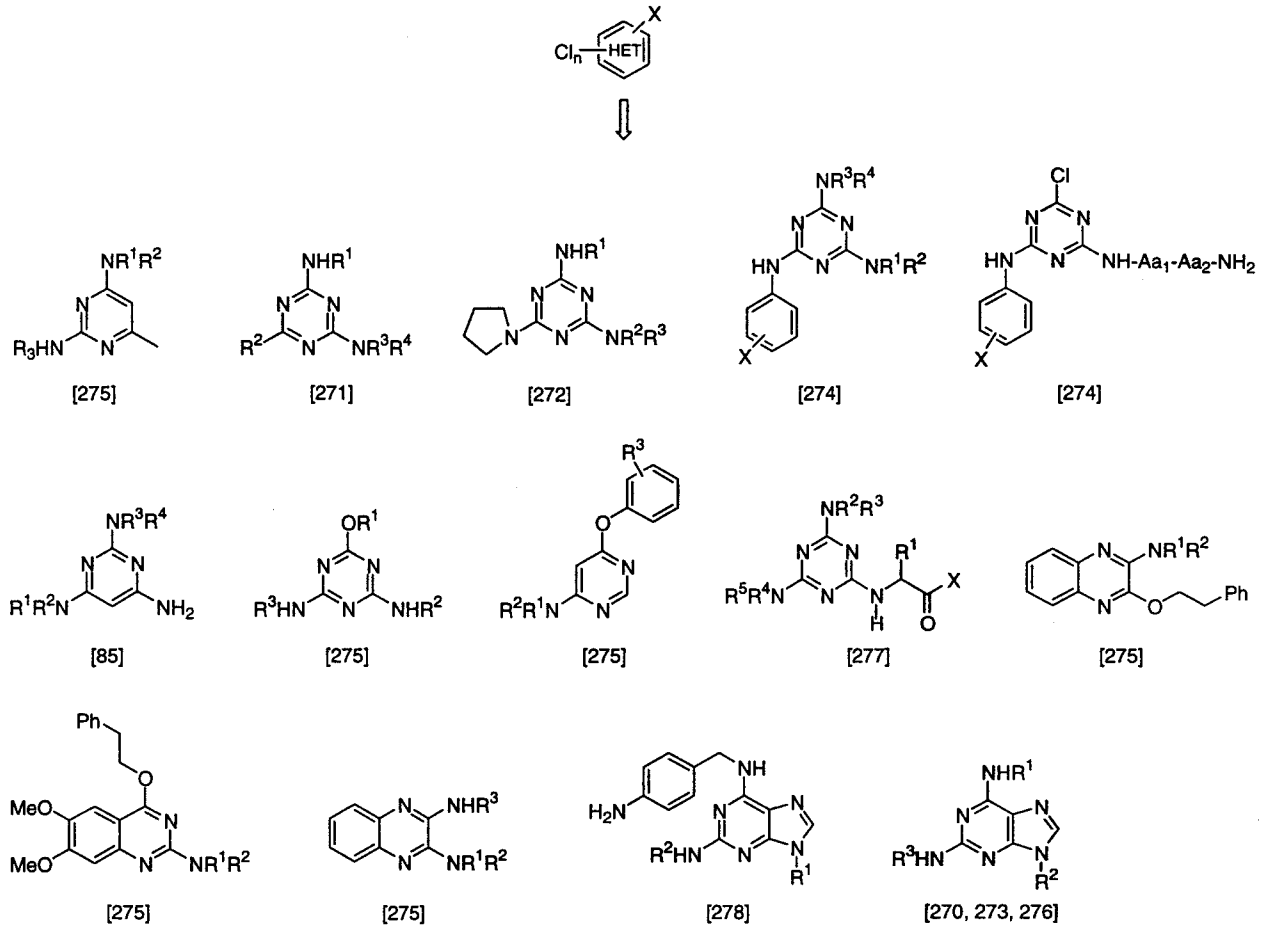


Figure 6. Libraries from polyhalogenated heteroaromatic scaffolds.

synthesis remained steady at ca. 33% in 1997 and 1998, but receded to its 1992−1995 levels (20%) this immediate past year. The data suggest that solid-phase synthesis continues to hold a dominant position in combinatorial synthesis as more and more chemistries are redeveloped on this medium.

Figure 3 indicates the origin of library contributions over the last 8 years, i.e., from the laboratories of academia or industry. In the combined years 1992−1997, two-thirds of the contributions were from industrial laboratories, with this number remaining relatively constant in 1998. This past year library affiliations moved to an industry:academia ratio of 1:1. Overall, pharmaceutical and biotechnology industries appear to be the prevailing players in the game of small molecule combinatorics, motivated by the goal of increasing drug discovery speed and reducing costs. The majority of academic publications showcased new synthetic methodologies.

Figure 4 reveals the breakdown of libraries by subclass. Biologically active libraries are designated into one of five subclasses. These include proteolytic enzymes (27%), non-proteolytic enzymes (22%), GPCRs (20%), non-GPCRs (17%), and cytotoxic and antiinfective agents (14%). Within the proteolytic enzyme subclass, serine proteases, namely the trypsin superfamily, were the most screened molecular targets. For GPCRs, opioid receptors appear to be the perennial favorite, not so much as a serious molecular target, but a convenient demonstration of library utility. Libraries without reported screening data also fall into one of five categories: scaffold derivatizations (27%), acyclic synthesis (19%), monocyclic synthesis (28%), bicyclic and spirocyclic synthesis (22%), and polycyclic and macrocyclic synthesis (4%). A widely used scaffold or template for derivatization is the polyhalogenated heterocycles, e.g., cyanuric chloride and trichoropyrimidine (Figure 6).[270−278] Substituted fluoronitroaromatics have been especially versatile reagents for the construction of mono-, bi-, and macrocycles (Figure 7).[255−269] Many of the classical routes to heterocycles have been reported on solid phase.[290]

Focusing on the 240 biologically active libraries published in 1992−1999, one can readily distinguish between discovery, targeted, and optimization libraries (Figure 5). For the purpose of this discussion, discovery libraries are defined as typically large in size (>5000 members) having no preconceived notions about which molecular target(s) it may be active against. Targeted libraries are biased in their design, defined as those libraries which contain a pharmacophore known to interact with a specific (or family of) molecular target. Optimization libraries are defined as those libraries in which a lead exists and an attempt is being made to improve its potency, selectivity, pharmacokinetic profile, etc. Accordingly, each of the 240 libraries have been examined and binned into one of these three categories. Between the early years 1992−1997, discovery libraries garnered the highest percentage of citations at 57%. This was twice the percentage of targeted libraries and 4 times the reported number of optimization libraries. The number of discovery

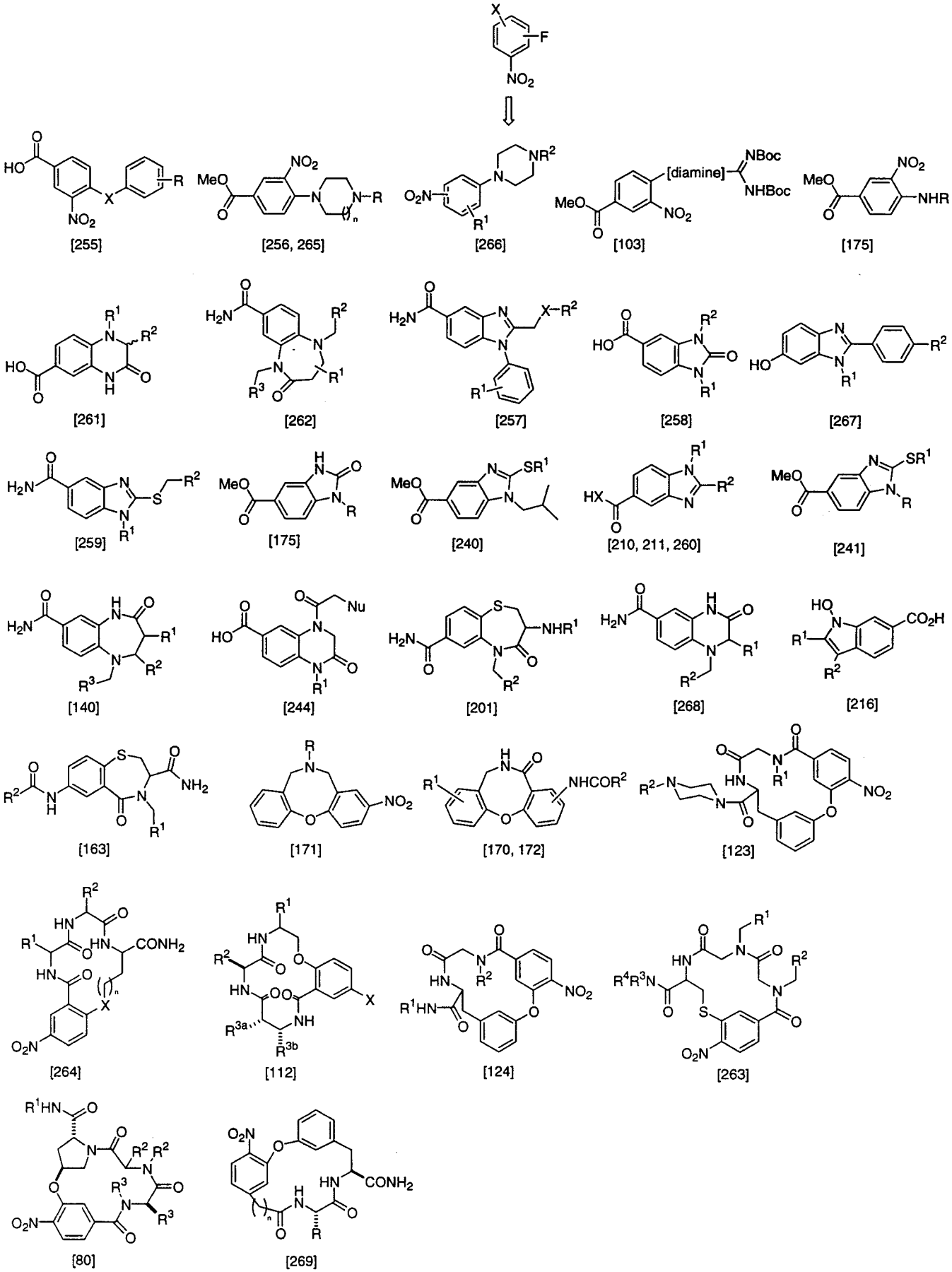


Figure 7. Libraries from fluoronitroaromatic scaffolds.

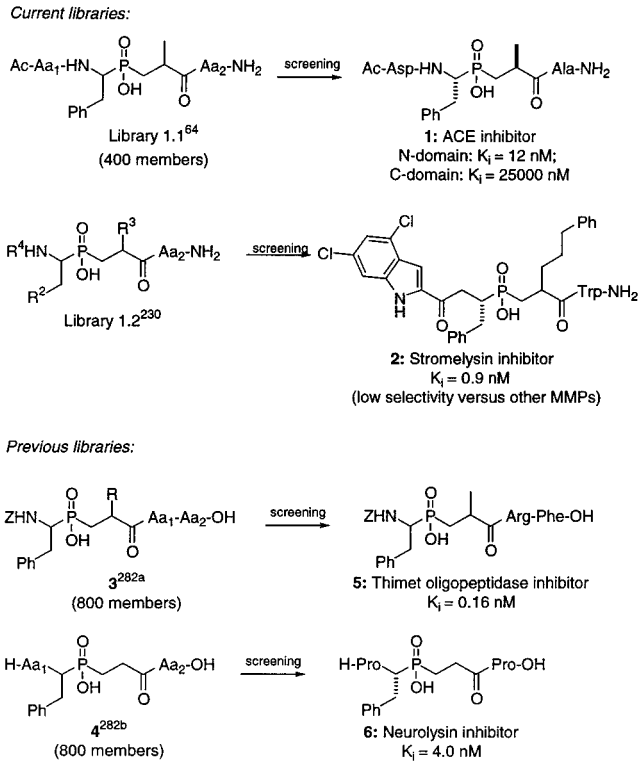


Figure 8. Dive's libraries of phosphinic acids.

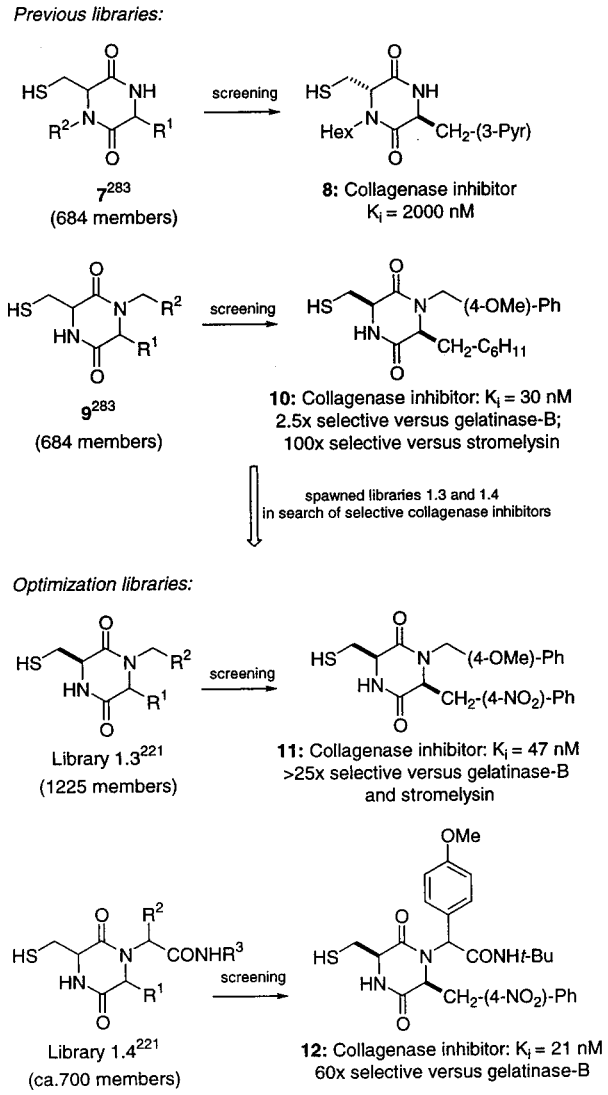


Figure 9. Affymax's thiomethyldiketopiperazine libraries.

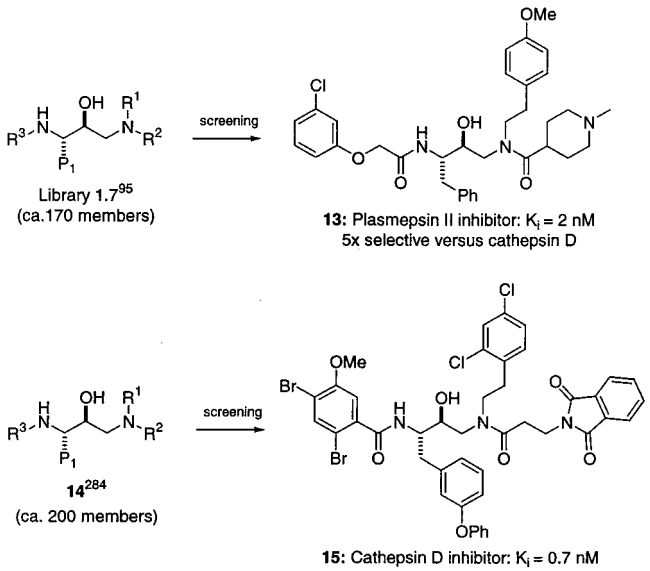


Figure 10. Hydroxyethylamine libraries for cathepsin D and plasmepsin II inhibition.

libraries has fallen rather significantly in the past two years from its 57% high to now the lowest in the group at 21%. In the same 2 year period, targeted libraries now top the charts, rising from 30% → 45% → 54%. Optimization libraries rose from 7% (1992−1997) to ca. 20% (1999), equal to the number of discovery library disclosures. It is tempting to speculate whether this represents a *true* shift in the way the combinatorial chemistry is being valued and applied in drug discovery, or an artifact of industrial research released for external consumption.[2] Anecdotal evidence from discussions at recent conferences and literature commentaries suggest targeted library collections biased toward a specific class or family of molecular targets and "lead explosion" libraries may be preferred over large discovery-type libraries.[254,279,280] Certainly large libraries offer unique advantages over smaller focused collections providing they can be designed with drug-like properties and screened efficiently and the actives can be readily identified.[281]

One of the criticisms leveled against combinatorial chemistry and which may still slow the acceptance of the technology is that the chemistries generally yield structures that are too peptide-like and contain multiple amide bonds. This is a valid concern due to the known pharmacokinetic liabilities, poor drug-like characteristics, and difficulty in optimizing these types of compounds. Data derived from the biologically active libraries show that, of the libraries reported during 1992−1997, ca. 50% were in fact peptide-based (more than three contiguous amino acid residues). Approximately 70% of the libraries incorporated one or more α-amino acids, and ca. 85% of the libraries contained one or more amide bonds (data not shown). In the combined years 1998−1999, the number of reported peptide libraries fell by more than half to ca. 20%, most likely reflecting a bona fide loss in interest in these types of libraries. The use of α-amino acids in library construction remains high at ca. 50%, as these synthons represent an excellent source of chiral, low molecular weight diversity elements.

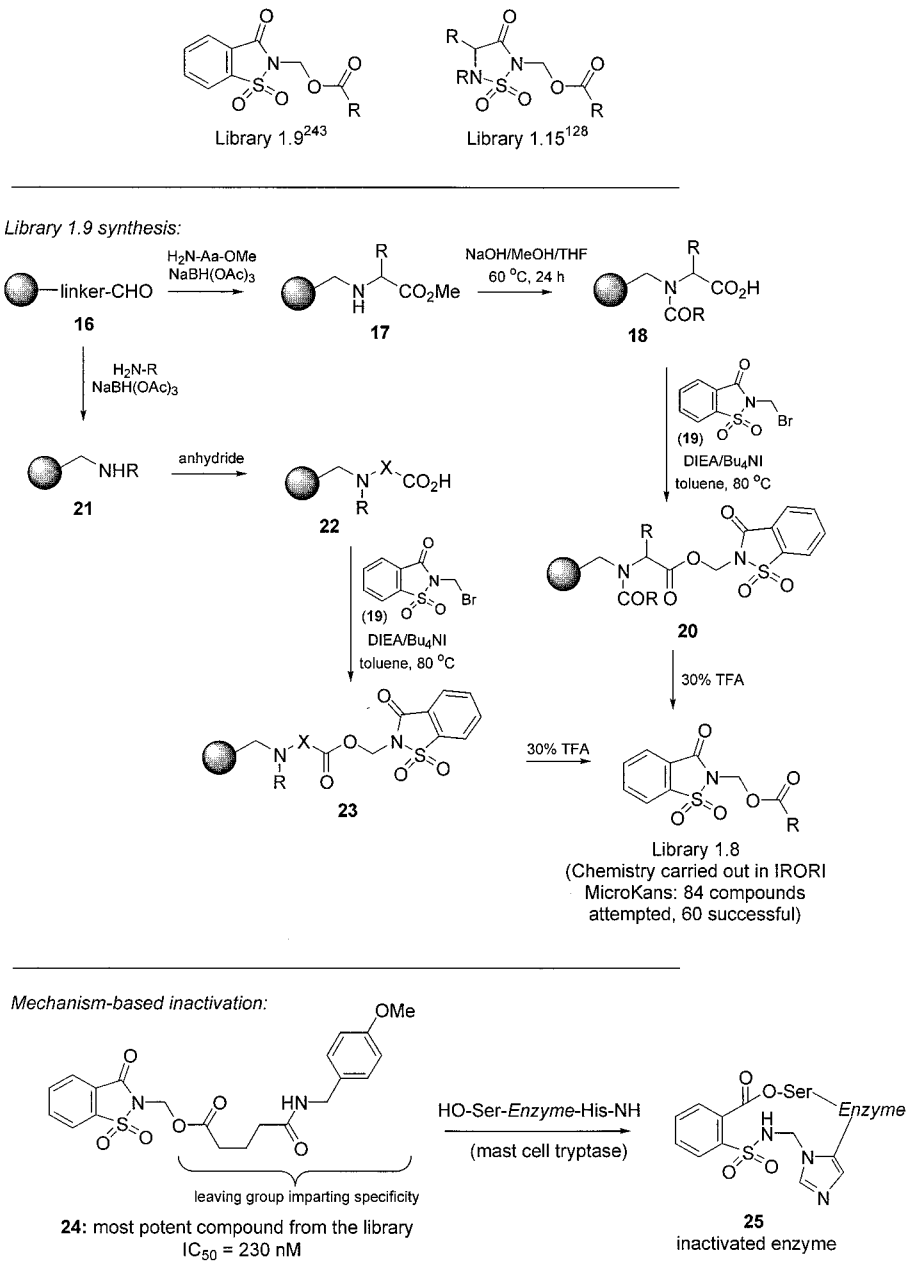


Figure 11. Mechanism-based libraries targeted for (chymo)trypsin serine proteases.

	1992−1997	1998	1999
peptide-based libraries	50%	20%	21%
libraries using ≥1 amino acid	70%	55%	53%
libraries containing ≥1 amide bond	85%	65%	75%

Finally, the notion that combinatorial synthesis acting *alone* will accelerate drug discovery research has not been borne out by experience over this first decade. Ideology of a single universal library as a source of leads against a plethora of molecular targets, purported by some, is not credible. What is evident is that combinatorial synthesis is an important technology among a suite of technologies that can be brought to bear on solving drug discovery problems.

Library Descriptions

Consistent with the format of previous annual reviews,[1] the abstracted 1999 libraries are sorted into two major categories, libraries with and without associated biological activity. Biologically active libraries are further sorted into five subclasses: proteolytic enzymes (Table 1), nonproteolytic enzymes (Table 2), GPCRs (Table 3), non-GPCRs (Table 4), and cytotoxic and antiinfective agents (Table 5). The name of each library is given, along with its size and affiliation (company name for libraries produced from industry, senior author for libraries reported from academia), as well as the structure of the most active compound from the library. Each library listed in Tables 1−5 is given a library number, e.g., library 2.10 refers to library entry 10 in Table 2. Libraries without accompanying biological data are also segregated into five subclasses. Here each entry is further subdivided as per the mode of synthesis, solid- versus solution-phase synthesis: scaffold derivatization (Table 6a,b), acyclic synthesis (Table 7a,b), monocyclic synthesis (Table 8a,b), bicyclic and spirocyclic synthesis (Table 9a,b), and polycyclic and macrocyclic synthesis (Table 10a,b). The affiliation of each library is provided, along with the number of synthetic examples, range of reported reaction yields, and

a brief description of its synthesis. As indicated previously,[1a] the size of the reported library does not necessarily reflect confirmed library size. Single synthetic transformations, phage display, polysaccharide, and polynucleotide libraries, and libraries for applications in material science or other nonpharmaceutical research areas, are not included in the tables.

Libraries Yielding Proteolytic Enzyme Inhibitors

Each of the four broad classes of proteases—metallo- (libraries 1.1−1.5), aspartyl- (libraries 1.6−1.8), serine- (libraries 1.9−1.18), and cysteine proteases (libraries 1.19−1.20)—were targeted for library synthesis (Table 1). As in previous years, mechanism-based design strategies were generally employed to create protease inhibitor libraries. This approach relies on selecting a functional group or pharmacophore known to engage an enzyme's active site residues and building a library around the scaffold in an effort to obtain potent and selective inhibitors.

In a continuation of their research on the preparation of libraries containing the phosphinic acids, a transition-state isostere for metallo-proteinases,[282] Dive and co-workers described the preparation of two new peptide phosphinic acid libraries, 1.1 and 1.2 (Figure 8). Library 1.1 yielded a selective N-domain inhibitor **1** of angiotensin I converting enzyme (ACE).[64] A selective inhibitor **2** of stromelysin (matrix metallo-proteinase-9) was obtained from library 1.2.[230] The structurally related tripeptide phosphinic acid libraries **3** and **4** were first described by Dive in the identification of potent and selective inhibitors **5** and **6** of the metallo-proteases thimet oligopeptidase and neurolysin 1.[282] The ACE inhibitor **1** is structurally distinct from inhibitors **5** and **6**, and its discovery is significant in that it is the first agent to discriminate between the catalytic N- and C-domains in this enzyme. The C-domain of ACE catalyzes the hydrolysis of angiotensin I and angiotensin II regulating blood pressure, while the N-domain of ACE is thought to be responsible for the specific hydrolysis of other physiologically important substrates, e.g., Ac-Ser-Asp-Lys-Pro, a negative regulator of hematopoietic stem cell differentiation and proliferation. Currently, marketed ACE inhibitors do not discriminate between the enzyme's two catalytic domains, and thus the selective N-domain inhibitor **1** may prove to be a useful pharmacological tool in understanding the role of the N-domain in vivo.

Affymax reported the synthesis of two thiol-containing diketopiperazine libraries (libraries 1.3 and 1.4; Figure 9).[221] The research group previously disclosed these thiol-containing heterocycles as possessing inhibitory action against the matrix metalloproteinases (MMPs).[283] In the earlier work, potent collagenase inhibitors were discovered, but these lacked selectivity (**7** → **8**; **9** → **10**). It was the goal of the new libraries to enhance this aspect of the series. Selectivity was imparted to the class by incorporating nitrophenylalanine as one of the amino acid monomers, furnishing inhibitors **11**, K_i = 47 nM (>25-fold versus gelatinase B and stromelysin), and **12**, K_i = 21 nM (ca. 60-fold selective versus gelatinase-B).

In a full paper, Ellman described further utility of hydroxyethylamine libraries as inhibitors of aspartyl proteases.[95] A series of optimization libraries (library 1.7, Table 1) were systematically prepared, ulitmately furnishing potent inhibitors of plasmepsin, e.g., **13**, although in general, these agents demonstrated weak selectivity against cathepsin D (Figure 10). Throughout the work, particular attention was paid to the physicochemical properties of the libraries and resynthesized compounds as measured against the Lipinski parameters. Earlier work with libraries of this class furnished potent cathepsin D inhibitors (**14** → **15**).[284]

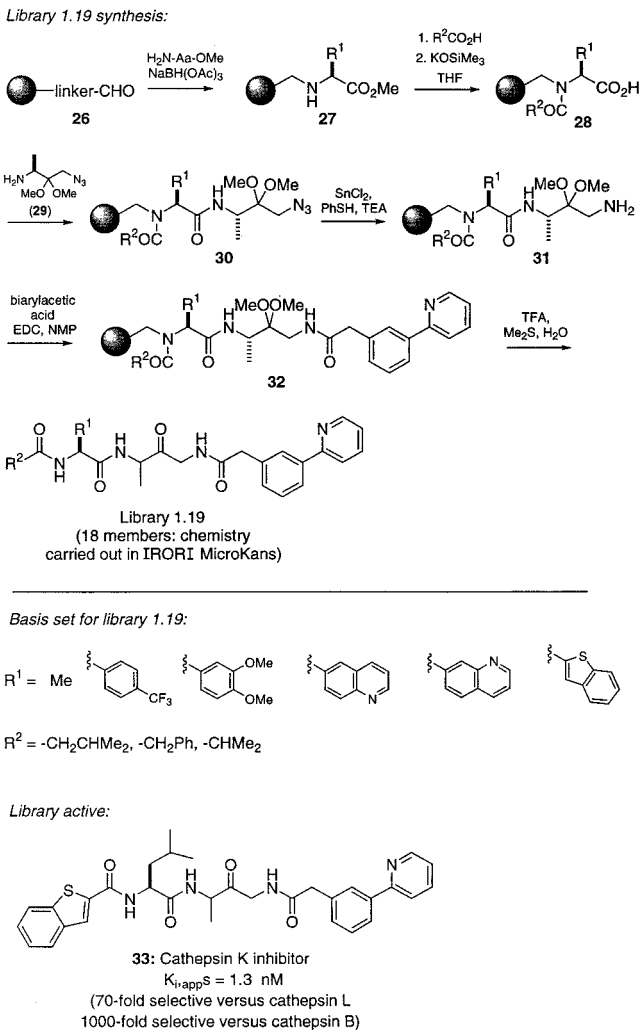


Figure 12. 1,3-Bis(acylamino)-2-butanones library as cysteine protease inhibitors.[239]

Libraries possessing inhibitors of trypsin-like enzymes were reported from several groups. These included δ-ketothiazoles (library 1.10),[3] arylamidines (libraries 1.11 and 1.12),[22,184] benzothiophenes (library 1.13),[114] and aminocyclohexanones (library 1.14).[2] A novel series of amino acid sulfonamides were optimized to yield an orally bioavailable thrombin inhibitor (library 1.18).[252] Two examples of mechanism-based inhibitor libraries of serine proteases leading to covalent adduct formation were reported. These include the benzisothiazolones (library 1.9),[243] yielding inhibitors of tryptase, and thiadiazolidin-3-ones (library 1.15),[128] showing a broad spectrum of affinity for serine proteases with a (chymo)trypsin-like fold (Figure 11).

SmithKline Beecham published on the design and enzymology of a novel class of 1,3-bis(acylamino)-2-butanones

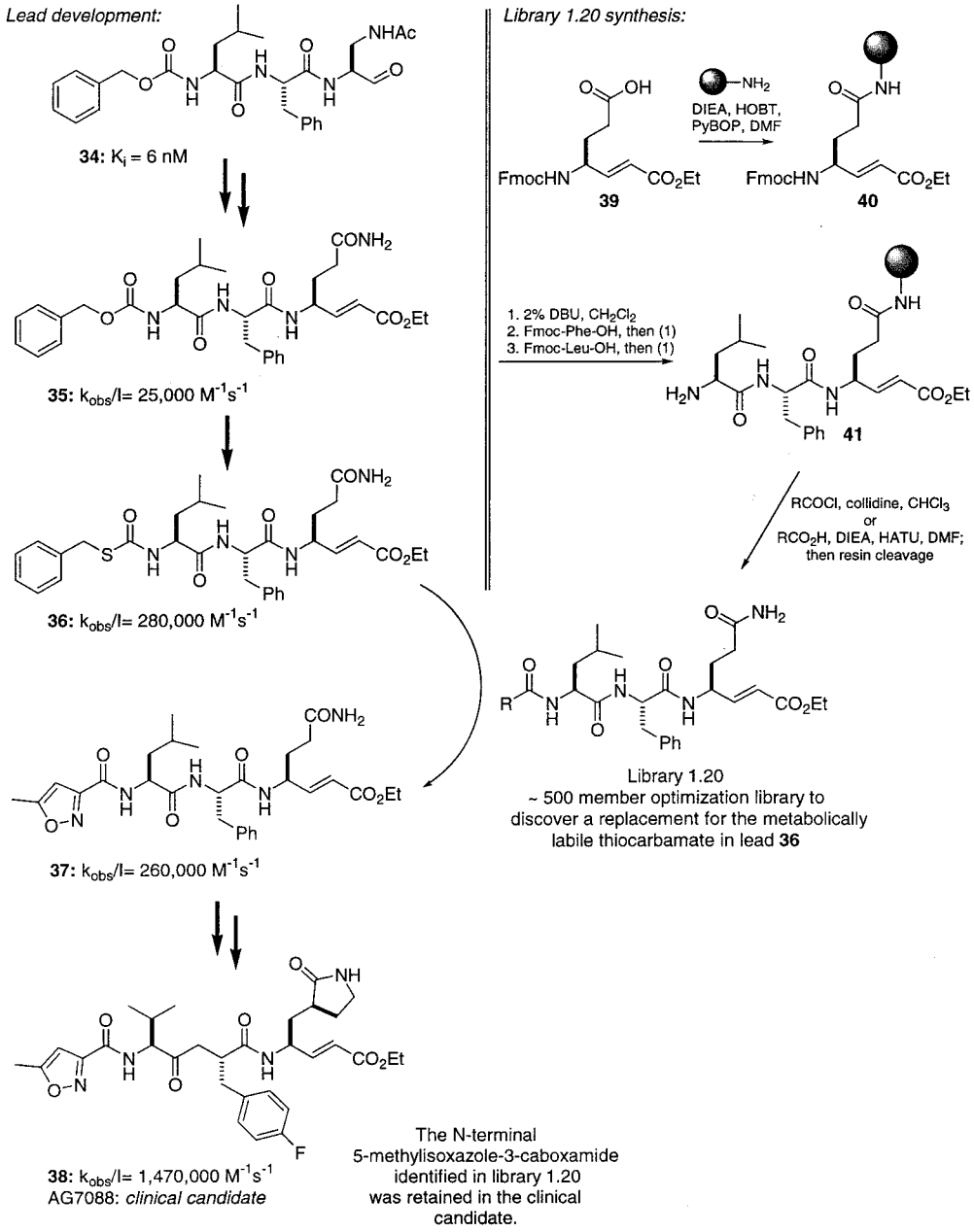


Figure 13. Optimization library 1.20 and the identification of a clinical candidate for human rhinovirus 3C protease.[66,153]

as cysteine protease inhibitors.[239] Their interest in this area is a result of a discovery program aimed at identifying inhibitors of cathepsin K.[285] Cathepsin K is a cysteine protease that degrades collagen at sites of bone remodeling, and inhibitors thereof may represent potential antiosteoporetic agents. In an effort to facilitate the rapid optimization of the 1,3-bis(acylamino)-2-butanone inhibitors, a solid-phase synthesis for this class of compounds was developed (Figure 12). Using the acid labile BAL aldehyde linker on polystyrene resin, the synthesis was initiated via the reductive amidation of amino acid esters onto linker **26**. Acylation of the resulting secondary amine and hydrolysis furnished acid **28**. Coupling **28** to the orthogonal protected azide amine **29** gave resin-bound intermediate **30**. Azide **29** was prepared in solution via a four-step sequence from Boc-alanine methyl ester. Reduction of the azido group in **30**, then acylation with 3-(2-pyridinyl)phenylacetic acid, and acid-mediated cleavage furnished the library compounds. Although optically active synthons were used in the library construction, inspection of the final products showed that epimerization had occurred to some extent. This was thought to take place during the coupling of azide **29** with resin-bound acid and upon the hydrolysis of the dimethyl ketal protecting group. Library synthesis was carried out using the IRORI R_f tags. Evaluation of the library against cathepsins K, L, and B revealed interesting SAR. The library was essentially devoid of cathepsin B activity. This was believed to be due to an unfavorable interaction of the heterobiaryl with an insertion loop present on the S′ side of the enzyme. Cathepsin K had a strong preference for leucine versus phenylalanine at the P_2 position, while cathepsin L showed a slight preference for phenylalanine. The most potent cathepsin K inhibitor was compound **33**: K_i = 1.3 nM, ca. 70-fold selective versus cathepsin L.

A beautiful example of the application of solid-phase chemistry in drug discovery is found in the optimization of

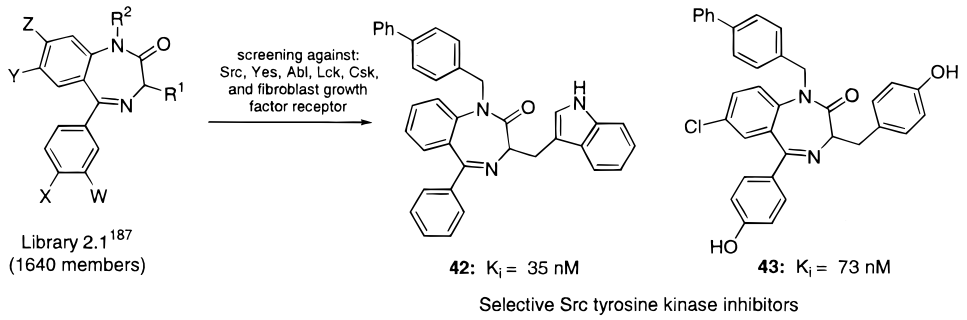


Figure 14. 1,4-Benzodiazepines as inhibitors of Src protein tyrosine kinase.[187]

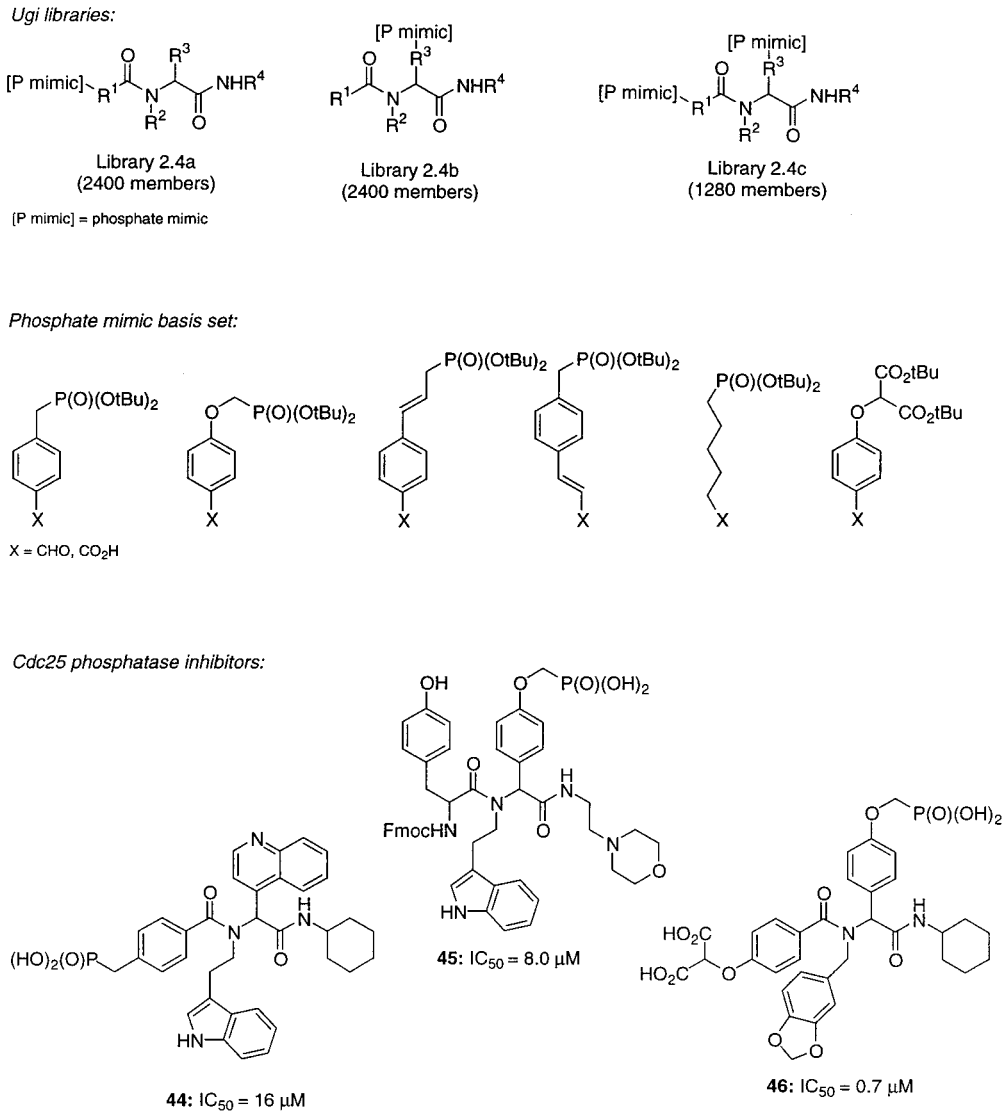


Figure 15. Ugi libraries of Cdc25 phosphatase inhibitors.[14]

irreversible human rhinovirus 3C protease inhibitors leading to a clinical candidate.[66,153] Researchers at Agouron Pharmaceuticals had shown that substrate-based peptide aldehydes, represented by **34**, were potent, reversible inhibitors of 3C protease. Due to the well-known pharmacological limitations of peptide aldehydes as viable drug candidates, the group turned to peptide Michael acceptors as covalent, irreversible inhibitors of the cysteine protease with the belief that the electrophilicity of these agents could be sufficiently modulated through high enzyme specificity. The lead compound **35**, based on the enzyme's P_1 and P_2 specificity preferences, possessed a second-order rate constant $k_{obs}/I =$ 25 000 M^{-1} s^{-1}. Exchange of the N-terminal benzyloxycarbamoyl group in **35** for the benzylthiocarbamoyl group led to a *10-fold increase* in the second-order rate constant (**36**: $k_{obs}/I =$ 280 000 M^{-1} s^{-1}). The rationale for the boost in affinity was provided through analysis of the X-ray crystal structure of inhibitor **36** bound to serotype-2 3C protease. The crystal structure revealed that the thiocarbamate sulfur atom lies deep in the enzyme's S_4 pocket and is in van der Waals contact with the S_4 subsite's Phe residue. This is in contrast to the oxygen analogue **35**. However, there was

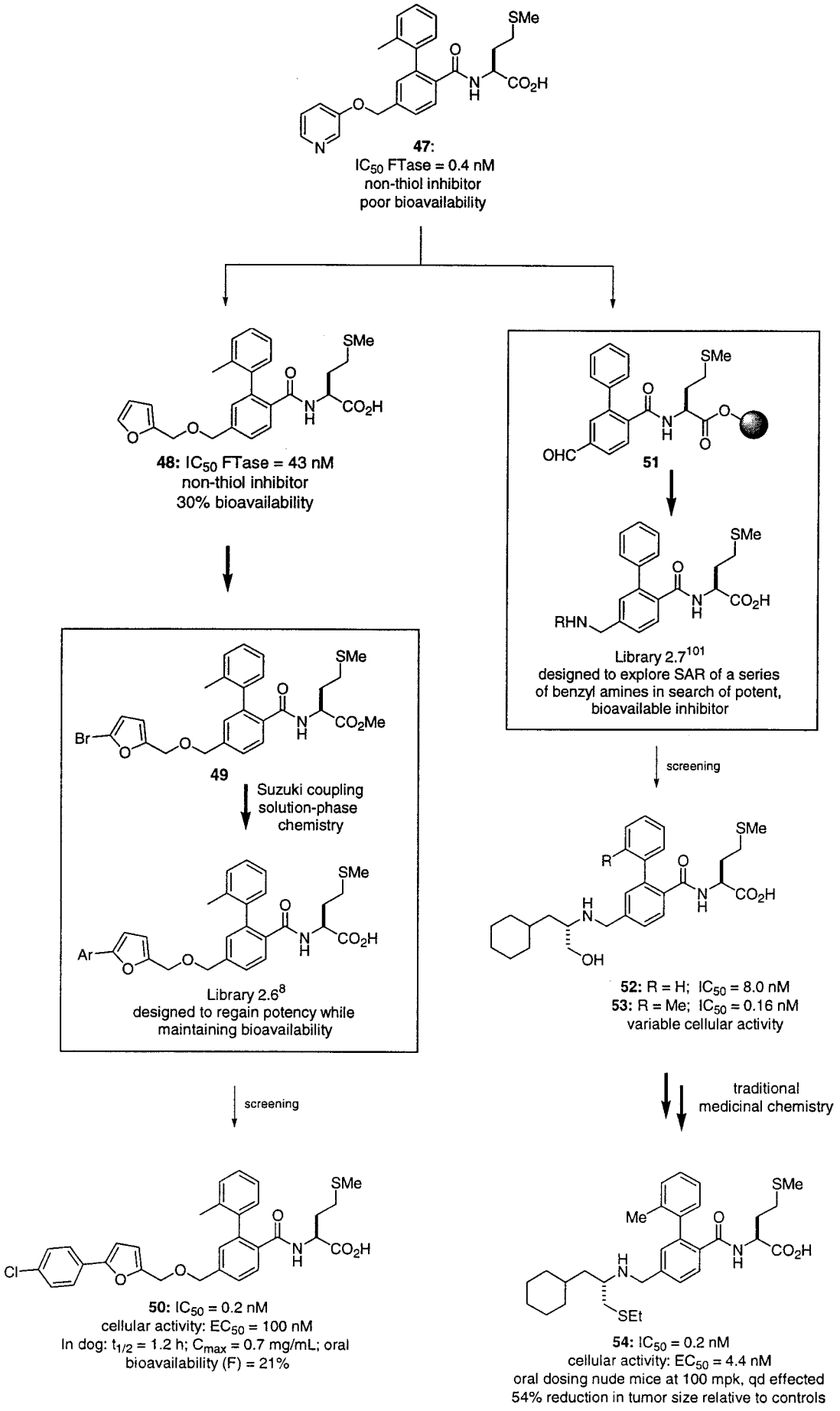


Figure 16. Abbott's FTase libraries.[8,101]

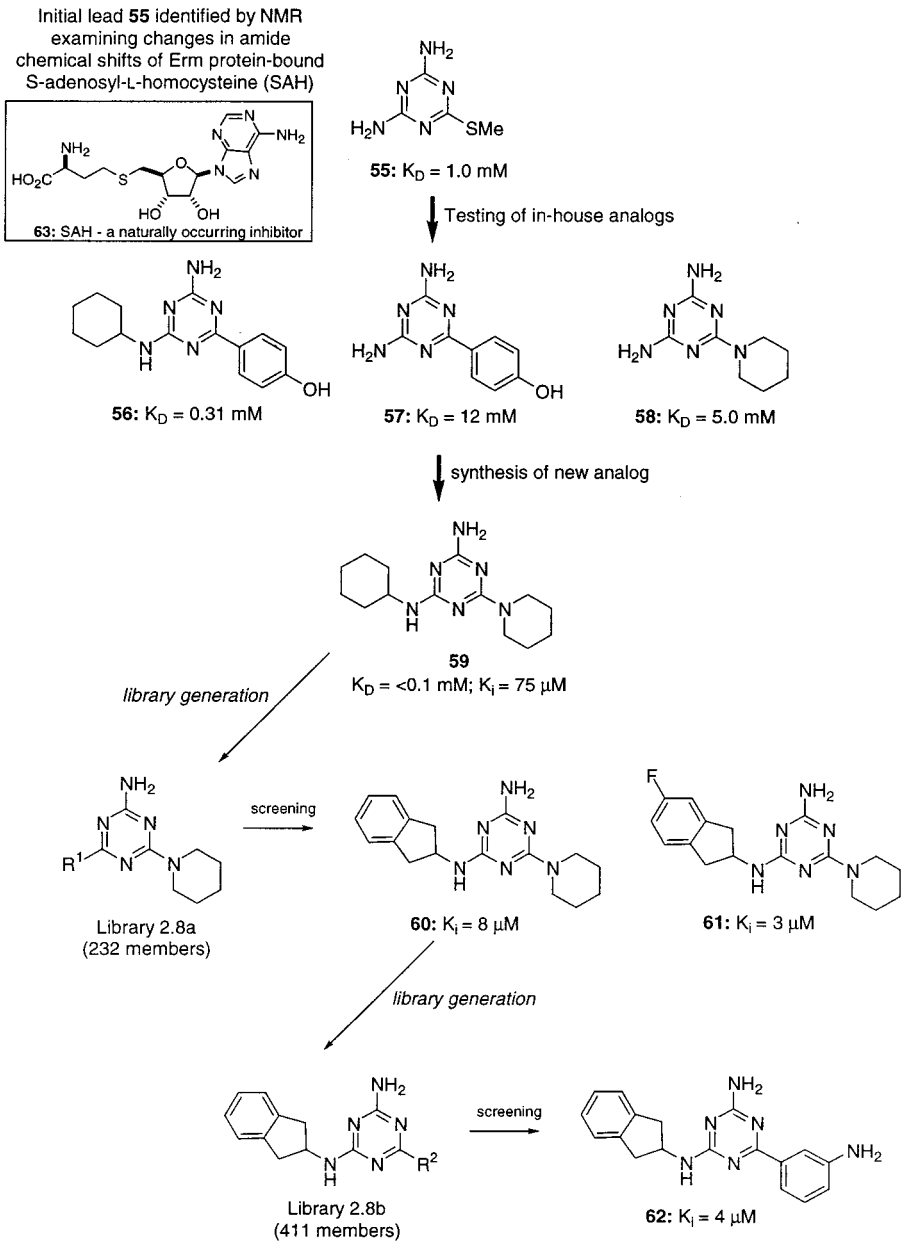


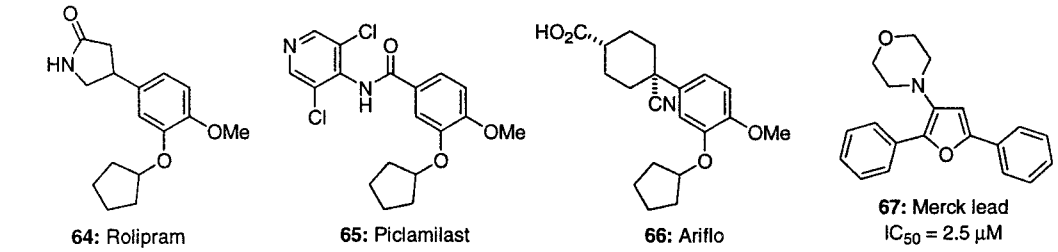
Figure 17. Inhibitors of Erm methyltransferase by NMR and parallel synthesis.[14]

concern that the thiocarbamate moiety would prove to be a metabolic and/or toxicologic liability, and thus an N-terminal surrogate was sought. This was carried out through solid-phase chemical optimization. Library 1.20 was created by attaching glutamic acid analogue **39** to Rink resin (Figure 13). Amide **40** so obtained was deprotected and subjected to amino acid couplings to furnish **41** after Fmoc-deprotection. Amine **41** was a key intermediate derivatized with some 500 acylating reagents to generate the optimization library. Evaluation of library 1.20 using a high throughput assay identified the 5-methylisoxzole-3-carboxyl group as the preferred N-terminal surrogate. This heterocycle was incorporated into the main series (**36** → **37**). Compound **37** (k_{obs}/I = 260 000 M^{-1} s^{-1}) was essentially equipotent with thiocarbamate **36** (k_{obs}/I = 280 000 M^{-1} s^{-1}). Further analogues produced inhibitor **38** (AG7088; k_{obs}/I = 1 470 000 M^{-1} s^{-1}) with reduced peptide character. AG7088 is currently undergoing clinical evaluation for the treatment of rhinoviral-mediated infections, e.g., the common cold. This research effort represents a prime example of the value of combinatorial chemistry (solid-phase synthesis) in lead optimization. In this instance, the N-terminal capping element 5-methylisoxazole-3-carboxamide identified in library 1.20 was retained in the clinical candidate.

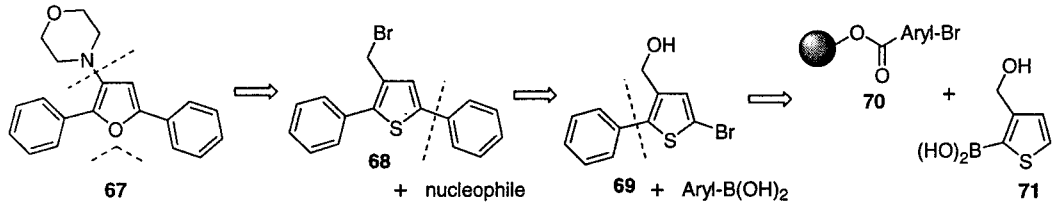
Libraries Yielding Nonproteolytic Enzyme Inhibitors

Table 2 lists 19 libraries displaying activity against nonproteolytic-type enzymes. The table is subdivided into kinases and phosphatases (entries 2.1−2.4), transferases (entries 2.5−2.8), reductases and dehydratases (entries 2.9−2.12), and miscellaneous mammalian and nonmammalian enzymes (entries 2.13−2.19).

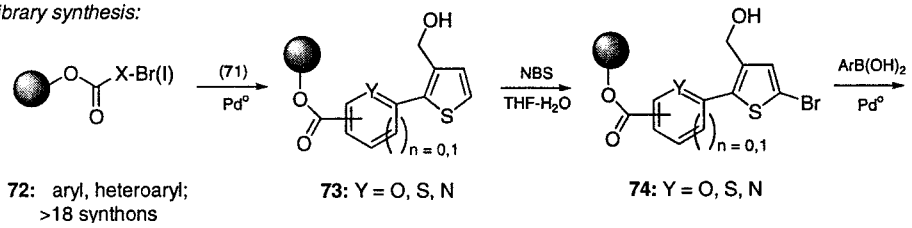
Benzodiazepine library 2.1, composed of 1640 members and prepared in the Ellman group, was screened against a wide variety of protein tyrosine kinases including Src, Yes, Abl, Lck, Csk, and fibroblast growth factor receptor (Figure 14).[187] Binding was observed only against the Src family (mixed against the peptidic substrate, K_i = 35 μM; noncom-

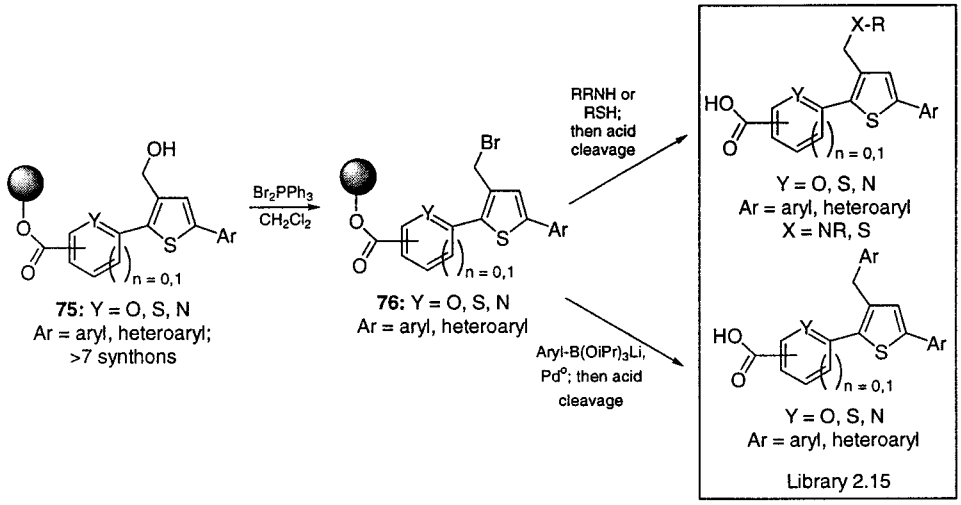


Retrosynthetic library analysis:



Library synthesis:





PDE – 4 inhibitors from library 2.15

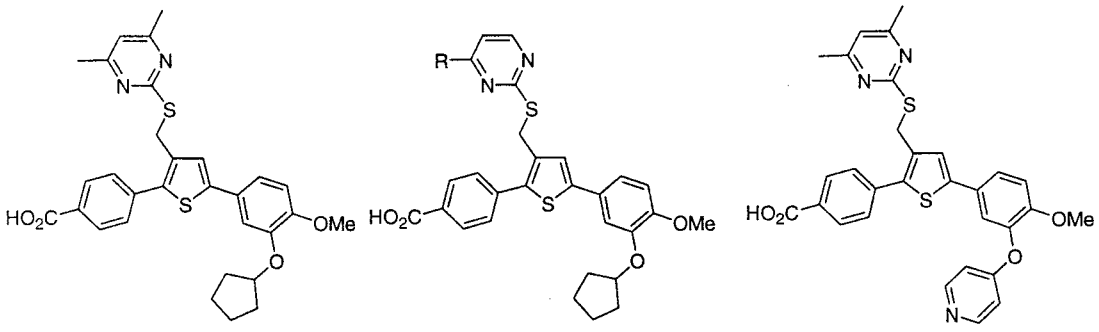


Figure 18. Merck's PDE-4 optimization library 2.15.[93]

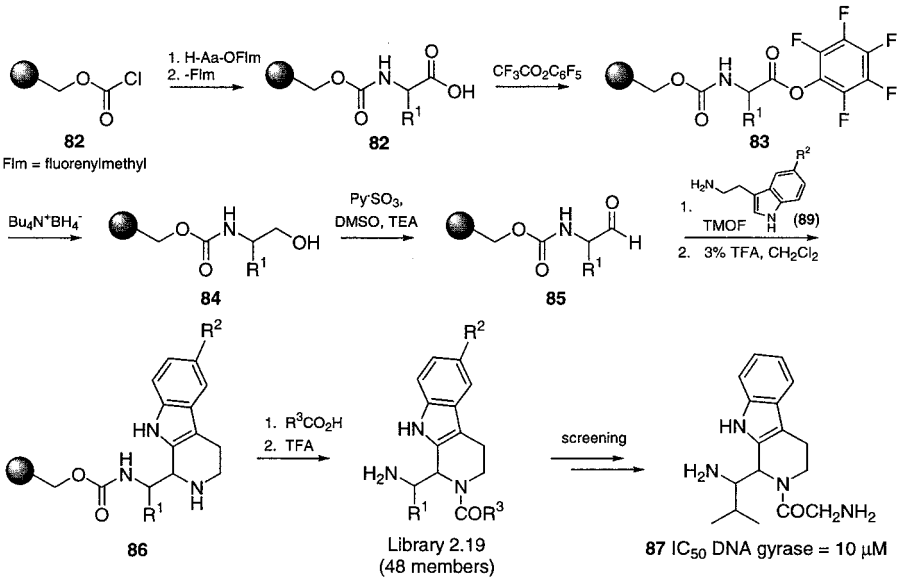


Figure 19. Tetrahydro-β-carboline library yielding DNA gyrase inhibitors.[250]

petitive against ATP-Mg, K_i = 17 μM). Preferred ring substituents include the *p*-hydroxyphenyl and *p*-hydroxybenzyl groups. The small nonpeptide, nonnucleotide class of compounds is structurally unique among known kinase inhibitors. Lead **42** is an inhibitor of colony formation of HT-29 colon adenocarcinoma cells that are dependent on Src activity.

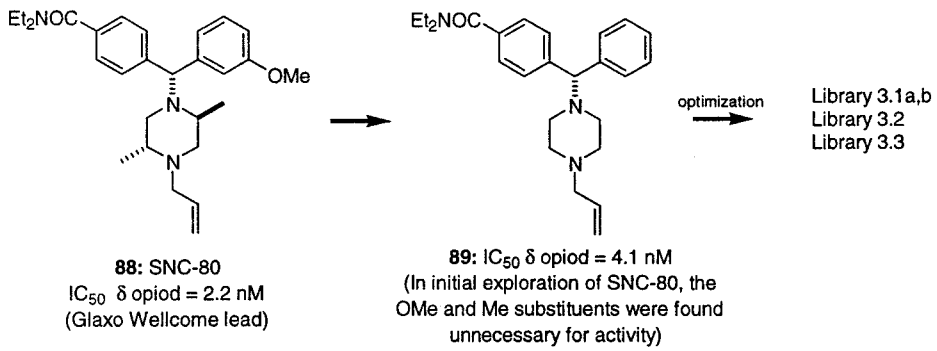
A four-component Ugi condensation was used to create three libraries (2.4a−c) containing potential phosphatase inhibitors (Figure 15).[14] These libraries incorporated a selection of known phosphate mimics as either the aldehyde or acid Ugi reaction partners. Libraries were screened against cell cycle phosphatase Cdc25, an oncology target. A number of structures (e.g., **44**−**46**) were found to be active. Potencies of resynthesized compounds ranged from 0.7 to 35 μM.

Protein farnesyltransferase (FTase) is responsible for the farnesylation of oncogenic Ras proteins, a posttranslational modification required for membrane association and signal transduction. Inhibitors of FTase block mitogenic signaling pathway leading to uncontrolled cell division; hence, the enzyme is an attractive target for cancer chemotherapy. Abbott produced two optimization libraries 2.6[8] and 2.7[101] in an effort to enhance the pharmacokinetic properties of their lead **47** (Figure 16). Biaryl **47** is a potent, non-cysteine, inhibitor of FTase (IC_{50} = 0.4 nM) and active in whole cells. In-house studies suggested the pyridinyl ether in **47** is a metabolic liability, presumably through unwanted formation of the pyridine *N*-oxide. Evidence for this was obtained upon replacement of the pyridinyl ring with a furfuryl moiety, which afforded ether **48** having 30% oral bioavailability in the rat, albeit reduction in enzyme affinity. Bromide **49** was an advanced intermediate used for the generation of a library of furanylbiaryls (library 2.6) via solution-phase Suzuki coupling. A number of potent FTase inhibitors were found in the library. In particular, the 5-(4-chlorophenyl)furfuryl ether **50** restored enzyme and cellular potency and was found to have reasonable pharmacokinetic properties.

In library 2.7, benzylamines were explored as replacements of the pyridinyl ether in **47**.[101] Resin-bound aldehyde **51** was subjected to reductive amination with a host of amines. Inhibitor **52**, derived from cyclohexylalaninol, demonstrated nanomolar activity (IC_{50} = 8 nM). Modification of the biaryl to append an *o*-methyl substituent and replacing the hydroxyl with a thioethyl group furnished inhibitor **54** having high in vitro (IC_{50} = 0.2 nM) and cellular activity (EC_{50} = 4.4 nM). Compound **54** was also active in vivo.

Erm (erythromycin-resistance) family of methyltransferases catalyzes the mono- and dimethylation of the N6-amino group in adenine using S-adenosylmethionine (Ado-Met) as a methyl source. This action results in base-specific 23S ribosomal RNA methylation, preventing the binding of certain macrolide antibiotics, and is the mechanism by which pathogenic bacteria may become resistant to these antibiotics. Studies have shown that inhibitors of Erm methyltransferase in combination with a broad-spectrum macrolide antibiotic may be useful in treating resistant bacteria. Using SAR by NMR, triazine **55** (and several other classes of small molecules) was identified as a weak inhibitor of ErmAM methyltransferase (Figure 17).[89] The compound caused chemical shift changes in Erm protein-bound *S*-adenosyl-L-homocysteine (**63**; SAH), and its binding was competitive with this naturally occurring Erm inhibitor. In-house analogues of **55** showed that the activity of this class could be modulated by varying ring substituents (e.g., **56**−**58**), leading to the synthesis of the piperidinylaminotriazine **59** (K_i = 75 μM). Keeping the amino and piperidinyl substituents in **59** constant, library 2.8a of 232 members was created. Evaluation of the library revealed the 2-aminoindanyl as a particularly effective synthon, yielding an ErmAM inhibitor **60**: K_i = 8 μM. The corresponding 1-aminoindanyl congener was 10-fold less active. Library 2.8b further explored the SAR of the class wherein the amino and indanyl substituents were held constant while varying the piperidinyl group. Thislibrary led to a further 2-fold increase in potency; the anilino group was preferred over piperidine (**60** → **62**). Further NMR and X-ray crystallographic studies indicated that the anilino group in **62** partially fills the space occupied by the ribose ring of SAH (**63**), while the amino acid portion

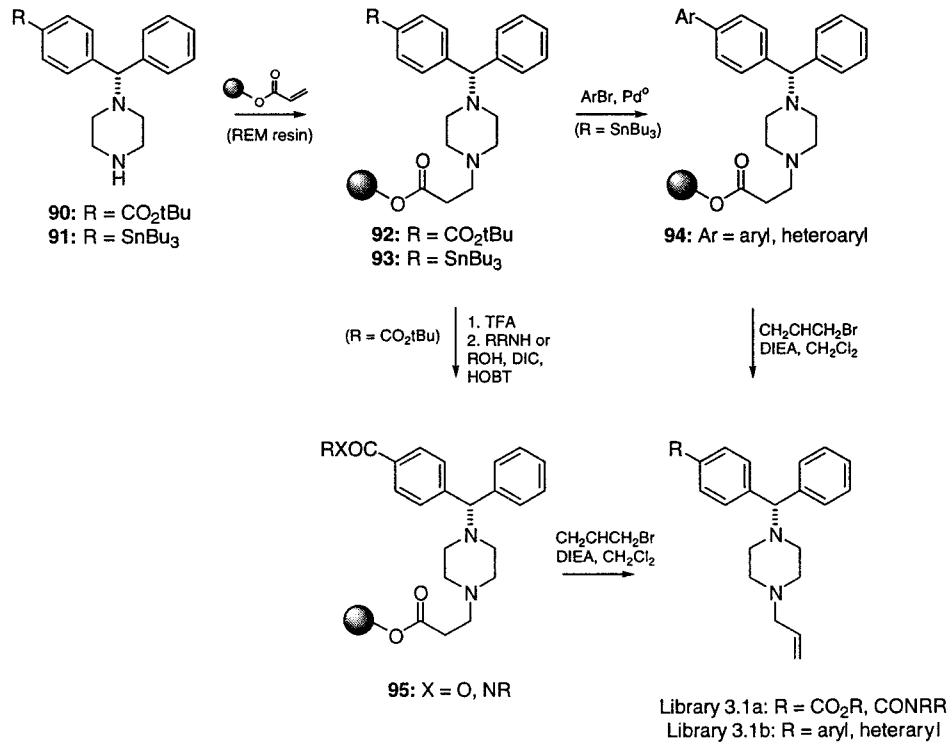
Lead structures:



88: SNC-80
IC_{50} δ opiod = 2.2 nM
(Glaxo Wellcome lead)

89: IC_{50} δ opiod = 4.1 nM
(In initial exploration of SNC-80, the OMe and Me substituents were found unnecessary for activity)

Library 3.1a,b synthesis:



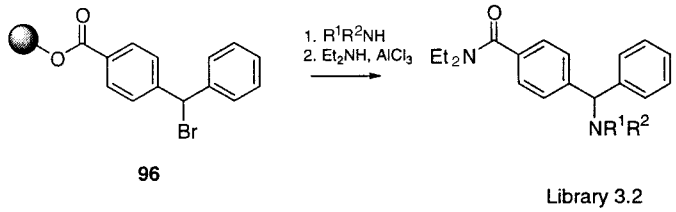
90: R = CO_2tBu
91: R = $SnBu_3$

92: R = CO_2tBu
93: R = $SnBu_3$

94: Ar = aryl, heteroaryl

95: X = O, NR

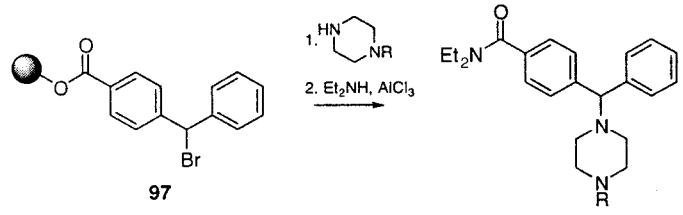
Library 3.2 synthesis:



96

Library 3.2

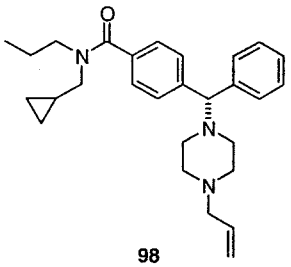
Library 3.3 synthesis:



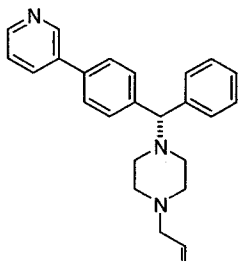
97

Library 3.3

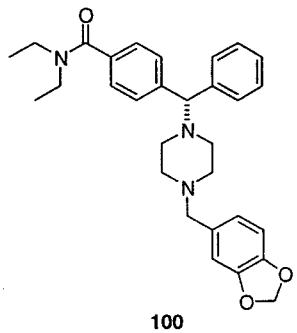
Library actives:



98
IC_{50} δ opioid = 4.0 nM

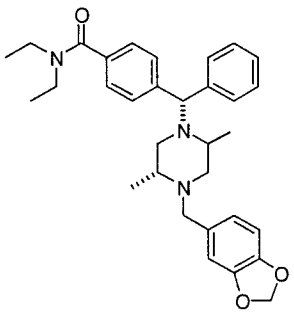


99
IC_{50} δ opioid = 250 nM



100
IC_{50} δ opioid = 1.4 nM

analog synthesis



101
IC_{50} δ opioid = 0.54 nM

Figure 20. Delta opioid ligands from Organon's libraries 3.1a,b−3.3.[11,55]

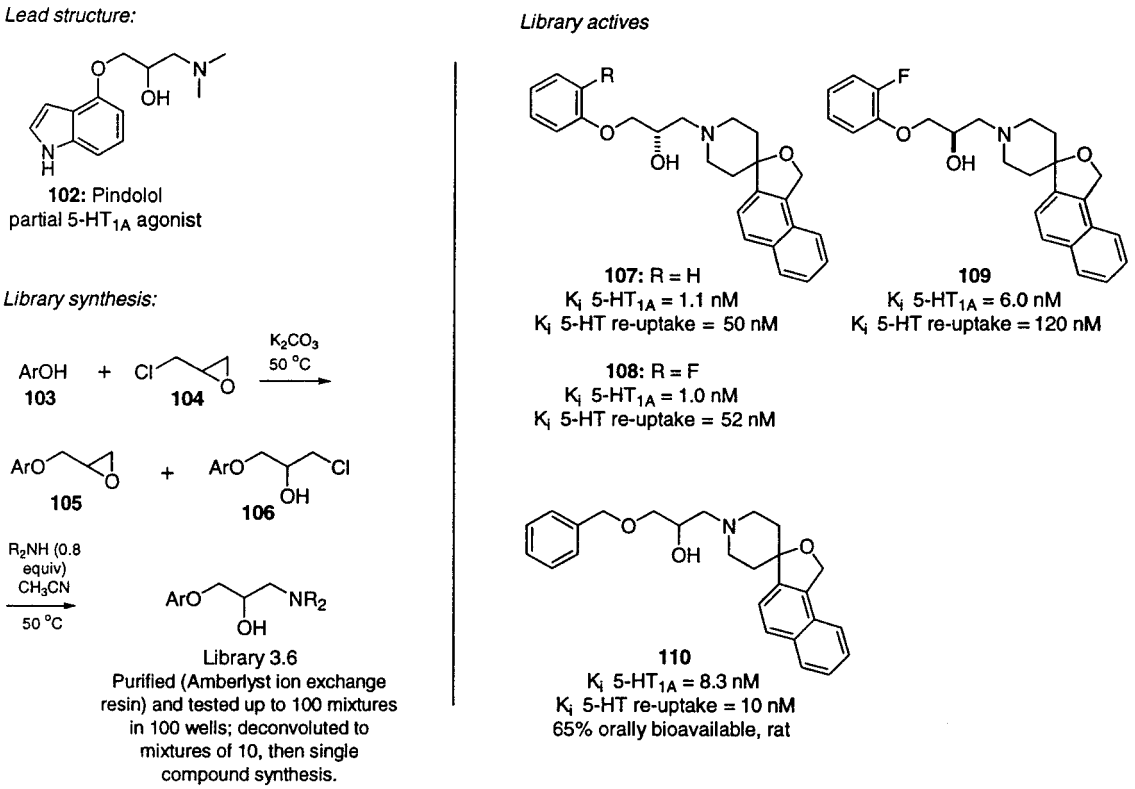


Figure 21. Merck's library of 3-aryloxy-2-propanolamines.[229]

of SAH is completely unoccupied. This suggests that additional gains in potency may be achieved by further structural modifications of **62**, engaging unoccupied binding sites in ErmAM.

The solid-phase synthesis of highly substituted thiophene derivatives and their activity against the cyclic nucleotide phosphodiesterase-4 (PDE-4) enzyme were described by researchers at Merck Frosst (Figure 18).[93] PDE-4 is a member of a broad class of hydrolases and is primarily responsible for the hydrolysis of cAMP in inflammatory and immune cells. Rolipram **64**, piclamilast **65**, and ariflo **66** are examples of PDE-4 inhibitors currently in development for the treatment of depression, rheumatoid arthritis, and asthma, respectively. Library 2.15 was based on the lead structure **67**, a trisubstituted furan, presumably identified through screening an internal compound collection, possessing an $IC_{50} = 2.5\ \mu M$ against PDE-4. Initial SAR revealed that furan and thiophene cores were interchangeable providing that the 2- and 5-aryl rings remained intact. In contemplating a library design, the biaryl rings were thought to be introduced by Suzuki-type couplings. A bromomethyl group was fixed at position C(3) to facilitate the introduction of a broad range of substituents at this position via nucleophilic substitution. For the actual solid-phase synthesis, bromo- and iodo-substituted aromatic carboxylic acids were first attached to Wang resin to give **72**. Suzuki coupling to readily available boronic acid **71** furnished hydroxymethylthiophene intermediate **73**. Bromination of the resin-bound **73** using 2 equiv of NBS in THF containing 2% water occurred in high yield *without* compromising the linker. Bromide **74** in turn was subjected to a second Suzuki coupling with a host of aryl and heteroaryl boronic acids to give the 2,5-biaryl-3-hydroxymethylthiophenes **75**. Conversion of the hydroxy group to the corresponding bromide was accomplished using bromotriphenylphosphine bromide in methylene chloride (**75** → **76**). Bromomethyl intermediate **76** was treated with a range of nitrogen and sulfur nucleophiles, affording library 2.15. Alternatively, carbon−carbon bond formation via Pd-catalyzed coupling of **76** with lithoaryltriisopropylboronates led to the direct exchange of the bromine atom for an aryl ring. One of the more potent PDE-4 inhibitors identified from the library was **77**, $IC_{50} = 8.0$ nM. This inhibitor contained the 3-cyclopentyloxy-4-methoxyphenyl ring at C(5), a substituent shared by known PDE-4 inhibitors **64-66**.

DNA gyrase inhibitors were identified from a library of tetrahydro-β-carbolines (library 2.19, Figure 19).[250] The key intermediate for the library was the resin-bound amino acid aldehyde **85** prepared by sequentially attaching amino acid fluorenylmethyl esters to chlorocarbonate resin, followed by deprotection, reduction of the corresponding activated pentafluorophenyl esters with tetrabutylammonium borohydride, and oxidation with sulfur trioxide-pyridine complex (**82** → **83** → **84**). Pictet−Spengler reaction of **85** with a series of tryptamines and then derivatization of the resulting secondary amino function of the tetrahydro-β-carboline furnished library 2.19.

Libraries Yielding G-Protein Coupled Receptor Agonists and Antagonists

Entries in Table 3 refer to those libraries that have yielded agents with binding affinity toward G-protein coupled receptors (GPCRs). Within the table are libraries active against opioid receptors (libraries 3.1−3.5), serotonin receptors (libraries 3.6 and 3.7), somatostatin receptors (libraries 3.8−3.9), and assorted miscellaneous receptors (libraries 3.10−3.15).

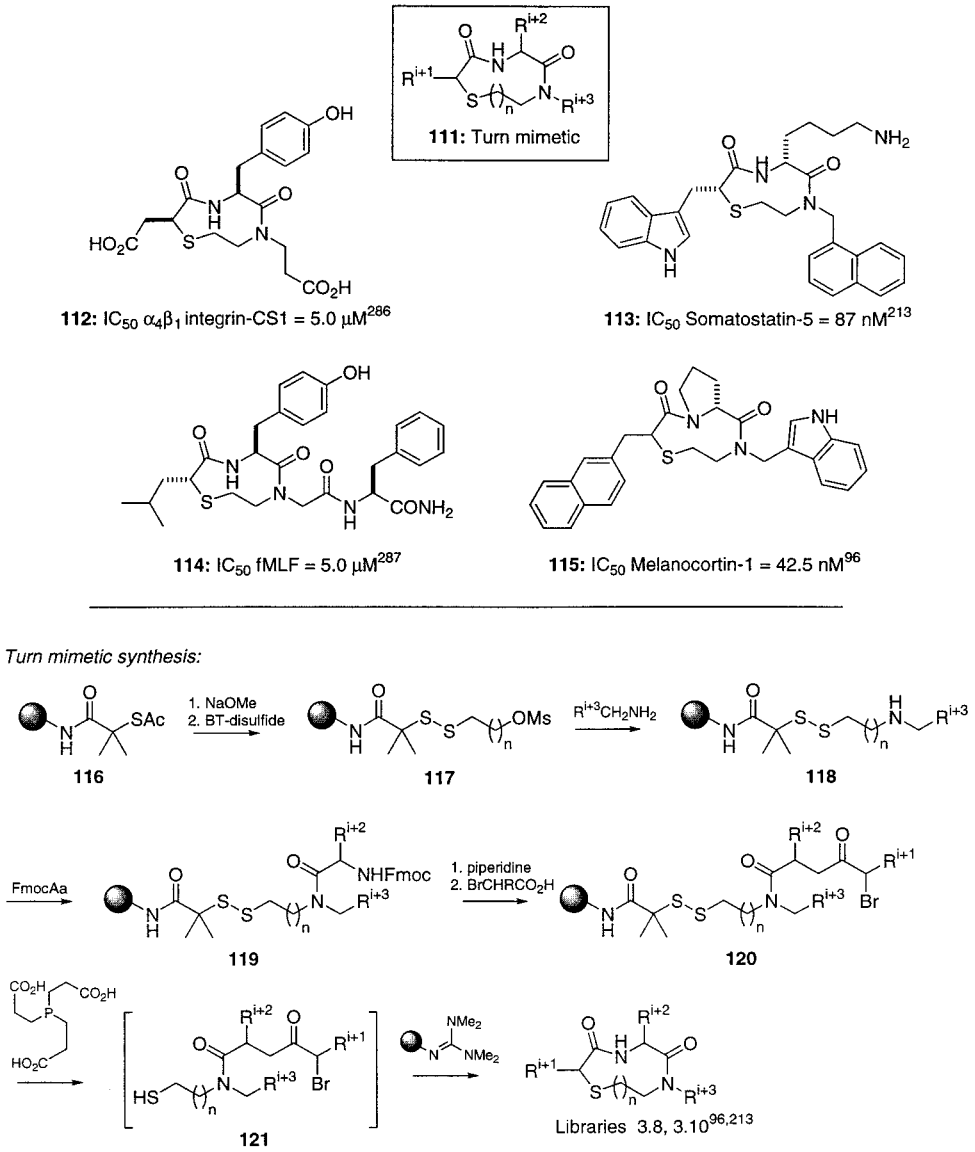


Figure 22. Biological activities of Ellman's turn mimetic library.[213]

Several focused libraries of δ opioid ligands based on the Glaxo Wellcome lead SNC-80 **88** were synthesized at Organon (Figure 20).[11,55] Initial SAR studies indicated that the aryl methoxy and piperazinyl methyl groups were not critical for δ opioid affinity, but the *N*,*N*-diethylcarboxamide was an essential structural feature. This is represented by structure **89**: δ opioid $IC_{50} = 4.1$ nM, and >1000-fold selective versus the μ and κ opioid receptors. In an effort to further explore the SAR, four optimization libraries were prepared. Libraries 3.1a and 3.1b relied on REM resin methodology to strategically target the carboxamide group for modification. In this chemistry, piperazines **90** and **91** were coupled to REM resin to give ester **92** and stannane **93**, respectively. Selective deprotection of the *tert*-butyl ester group with TFA furnished the corresponding acid, which in turn was converted to either an ester or amide (**92** → **95**). Stannane **93** was subjected to Stille coupling to 10 aryl and heteroaryl bromides (**93** → **94**). Release of library compounds was achieved after quaternization of resins **94** and **95** with allyl bromide and Hofmann elimination (Hunig's base, 18 h, 20 °C). No significant improvement in activity was observed.

In complementary optimization libraries 3.2 and 3.3, piperazine replacements (cyclic diamines) and *N*-substituted piperazines were investigated (Figure 20).[11] In these libraries the diethylcarboxamide group was retained. None of the cyclic diamines were as active as piperazine, but a 4-fold improvement in binding affinity was observed when piperonyl was substituted for allyl; **100**: $IC_{50} = 1.4$ nM. Reintroducing the dimethyl groups and piperazine stereochemistry as per SNC-80, gave **101** with subnanomolar potency against the δ opioid receptor.

A solution-phase synthesis was developed for the preparation of 3-aryloxy-2-propanolamine libraries (library 3.6, Figure 21).[229] Specific interest in this class of compound stems from an interest in identifying dual affinity 5-HT_{1A} and 5-HT re-uptake ligands as potential antidepressants with improved side effects. The library design focused on modifying pindolol **102** (partial 5-HT_{1A} agonist). A diverse set of amine and phenol synthons were utilized in the library. These were obtained from commercial sources and in-house "privileged structures", as well as selections based on amine fragments from serotonin re-uptake blockers and substituted phenols from 5-HT_{1A} ligands. Binding data were first

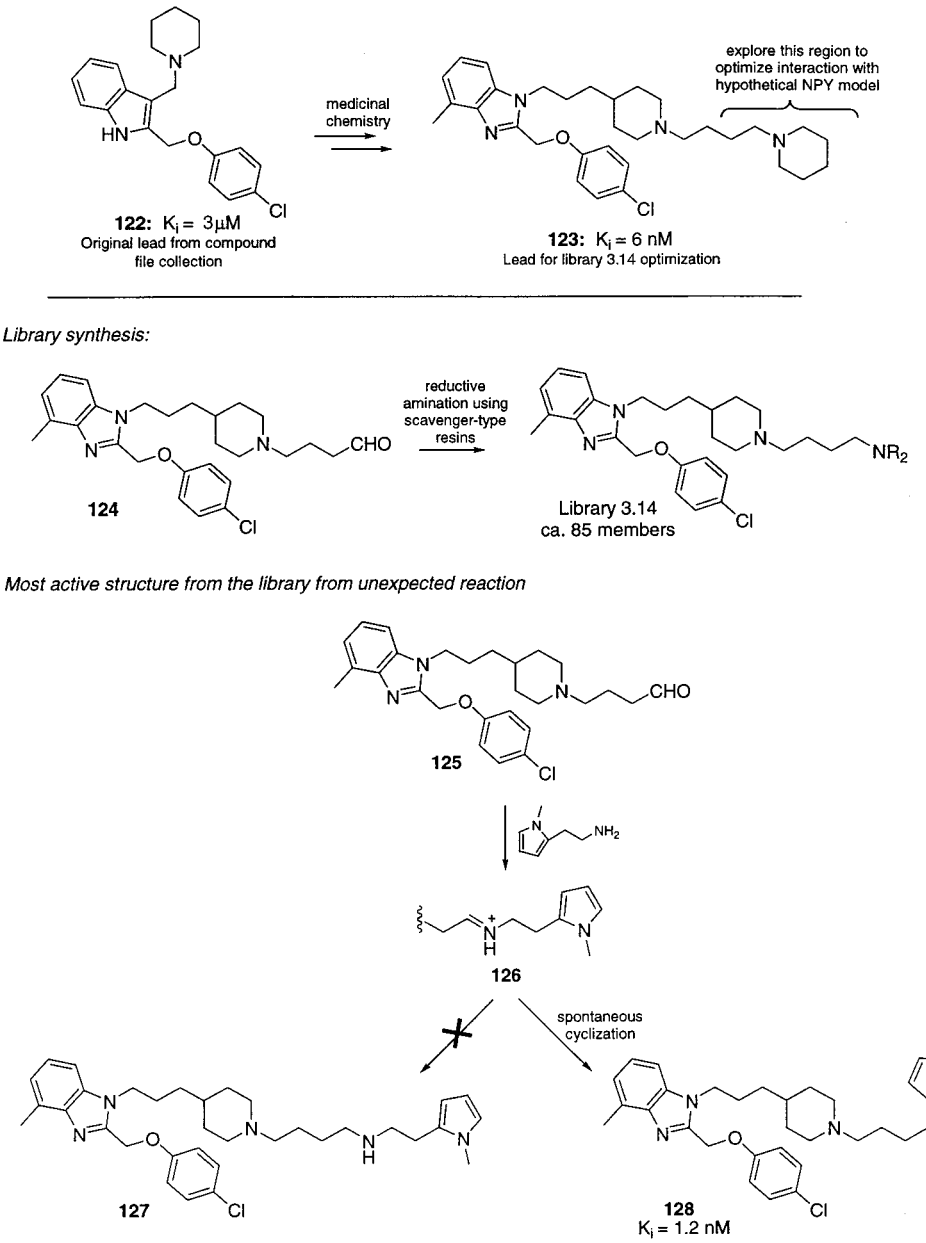


Figure 23. Neuropeptide Y-1 antagonists from library 3.14.[205]

obtained on purified mixtures containing up to 100 compounds per well, then deconvoluted to yield single compounds. Several potent 5-HT_{1A} ligands were identified. The simple substituted phenols were found to be superior to the indole in pindolol **102**. The spirocyclic amine found in **107**−**110** was the only amine to give consistent levels of dual activity (binding at serotonin re-uptake receptors and 5-HT_{1A} receptors). Compound **110** demonstrated nearly full agonism at 5-HT_{1A} and potent re-uptake blocking properties. Compound **110** was found to be 65% orally bioavailable in the rat (3 mg/kg) possesing a $t_{1/2} = 3.0$ h.

Ellman published a full report on the synthesis of a turn mimetic library (libraries 3.8 and 3.10; Figure 22).[96,213] The synthesis takes advantage of a facile intramolecular-cyclative thiol S_N2 displacement, simultaneously cleaving material from resin and creating the penultimate 9- and 10-member rings. Preliminary reports of this chemistry have appeared in the literature as well as multiple biological activities associated with this interesting class of medium-sized heterocycles. Turn mimetics have shown activity as integrin antagonists,[286] human neutrophile receptor (fMLF) inhibitors,[287] and selective agonists against somatostatin-5 [213] and melanocortin-1.[96]

A full disclosure of the library synthesis (library 3.9) and screening of Merck's selective somatostatin receptor agonists was published this past year.[158, 288]

Neuropeptide Y, found in both the peripheral and central nervous systems, is believed to be involved in the regulation of feeding, energy metabolism, vascular tone, learning and memory, and the release of pituitary hormones. To date, six receptors of this family have been characterized pharmacologically. Several antagonists of the NPY-1 receptor have been reported in the literature. One class of compounds discovered at Lilly is the benzimidazoles, represented by structure **123** (Figure 23).[205] The potent NPY-1 antagonist was obtained following extensive medicinal chemical optimization, starting from the 3 μM in-house screening hit **122**. Using the combined applications of computational chemistry

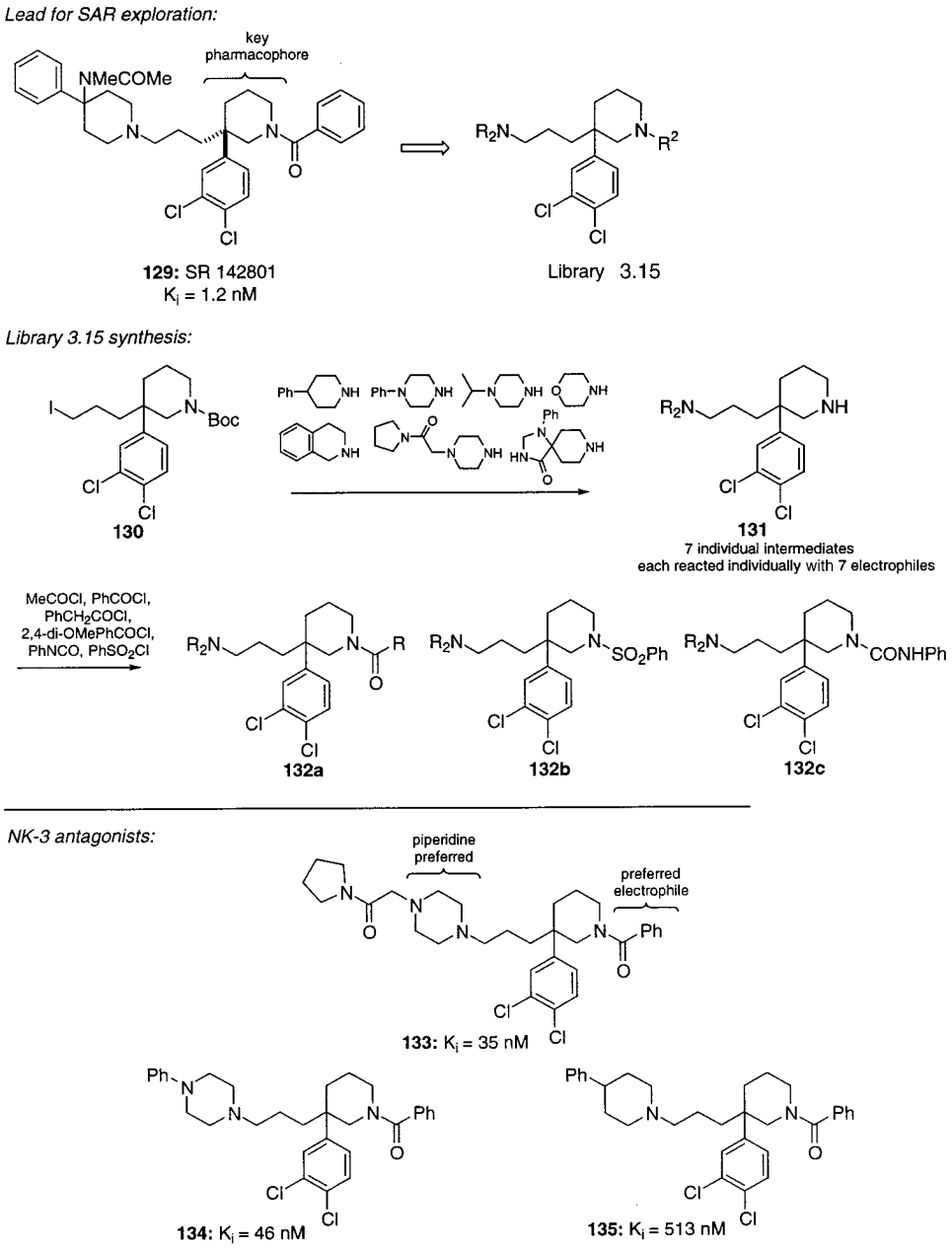


Figure 24. Human neurokinin-3 receptor antagonists.[188]

and parallel solid-phase synthesis, further optimization of **123** was undertaken. Computer modeling suggested that the interactions between the distal piperidine group and salient residues in the operative NPY-1 model may not be optimal for high affinity binding. With this hypothesis in mind, library 3.14 was constructed to explore alternative amines. Chemistry was carried out via the reductive amination using resin-bound aldehyde **124** and ca. 100 amines. Amines were selected by initially searching the ACD database of commercially available primary amines (6642 matches). The "master list" was reduced in a first round by discarding amines containing carboxylic acids and MW >250 (1636 matches) and in a second round by similarity clustering (577 matches). A final list of amine synthons was generated by human selection to <100 amines. Some 85−90 compounds were prepared in the library and each evaluated against NPY-1. Only one compound appeared more active than **123**, and that was a compound obtained from the reductive amination of aldehyde **124** with *N*-methyl-2-aminoethylpyrrole. However, the structure of the expected product **127** was inconsistent with its spectroscopic data. It turned out that, in this particular case, the intermediate imine **126** undergoes a spontaneous Pictet−Spengler cyclization affording tetrahydro-5-aza-indole **128**. This is the *second* solid-phase synthesis example where the occurrence of an unanticipated side reaction yielded a biologically active agent.[289]

An interesting application of combinatorial library synthesis is in the rapid evaluation of "competitor compounds". It is not uncommon in the pharmaceutical industry to have multiple companies simultaneously pursue drug discovery programs focused on an identical molecular target in the race to be first to market with a breakthrough drug. For this reason, when a competitor publishes the structure and biological activity of a "hot target", other research groups will prepare this compound and use it as a benchmark against their own series. In many instances however, much of the

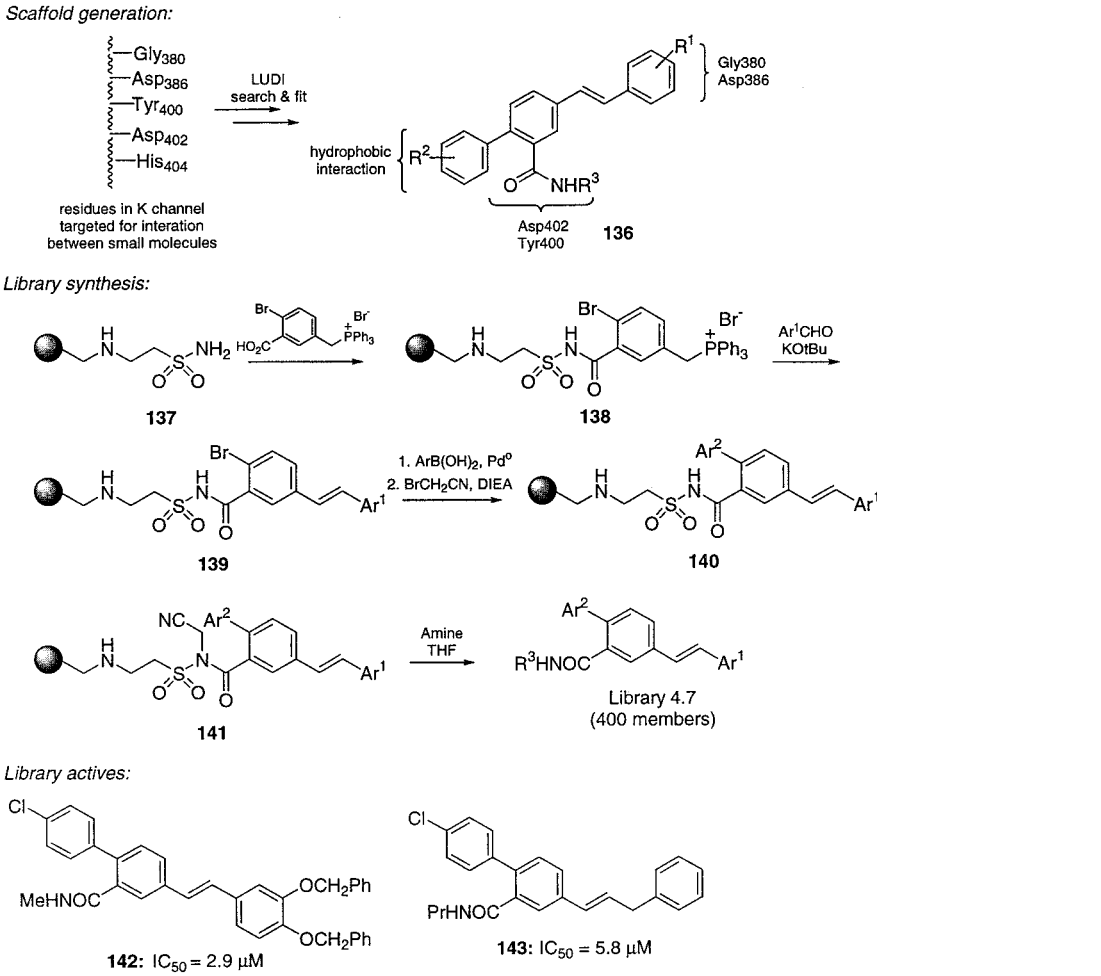


Figure 25. Potassium channel blockers obtained from Biosym/MSI's ligand design program LUDI and parallel synthesis.[145]

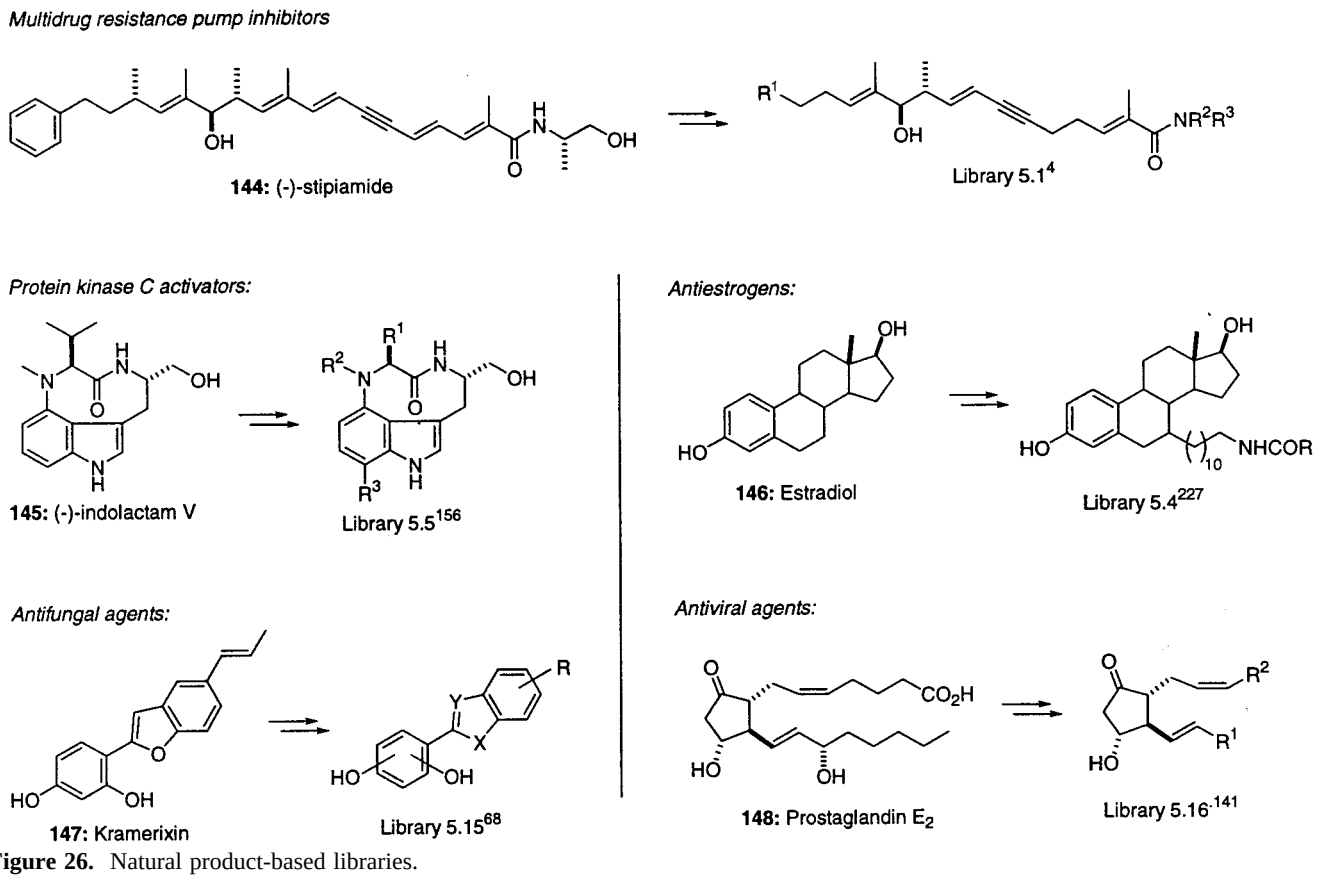


Figure 26. Natural product-based libraries.

SAR around the structure is unpublished and kept secret, although this information can be invaluable in enhancing one's own lead series. Library 3.15 is an optimization library synthesized at SmithKline Beecham and designed to explore the SAR requirements of the 3,4-diclorophenylpiperidine class of NK-3 receptor antagonists (Figure 24).[188] This class of agent was first reported by Sanofi (e.g., SR 142801: **129**), but SAR data was virtually nonexistent in the literature. Using a combinatorial chemical approach, SmithKline was able to rapidly generate analogues of interest. This was carrried out synthetically by sequential reaction of the bifunctional derivative **130**, derived from the key (3,4-dichlorophenyl)-3-propylpiperidine pharmacophore, with amines and electrophiles (library 3.15: **132a**−**c**).[188]

Libraries Yielding Non-GPCR Ligands

Libraries yielding active structures against non-GPCR molecular targets are delineated in Table 4. Table 4 is subdivided into integrin receptors (libraries 4.1−4.5), ion channels (libraries 4.6 and 4.7), and miscellaneous targets (libraries 4.8−4.12).

Three of the five libraries describing integrin antagonists were direct takeoffs of the well-known -Arg-Gly-Asp-binding motif linking basic guanidyl and carboxylic acid residues through an optimal spacer. Library 4.1 utilizes an azapeptide-type spacer[77] while isoxazole linkers were utilized by DuPont (libraries 4.3 and 4.4).[190] A new binding motif, D-Pro-D-Tyr-D-Leu-, identified in Selectide's library 4.2 is of interest as it is a neutral ligand,[223] although its affinity is rather weak (14 μM) compared to classical charged ligands possessing nanomolar affinity. Optimization library 4.5 was part of a broad-based medicinal chemistry effort to identifiy potent integrin antagonists incorporating piperidine as a surrogate for the guanidyl residue.

An interesting new series of phenyl substituted stilbenes as voltage gated potassium channel blockers were described by Lew and Chamberlin (library 4.7, Figure 25).[145] The stilbene pharmacophore was computationally designed using LUDI, a Biosym/MSI ligand design program, and predicted to block the potassium channel. A combinatorial library of LUDI hits was generated furnishing μM leads **142** and **143** for further studies.

Libraries of Cytotoxic and Antiinfective Agents

Table 5 contains 17 libraries subdivided into two categories demonstrating cytotoxic activity (libraries 5.1−5.5) and antiinfective activity, including antibacterials (libraries 5.6−5.13), antifugals (libraries 5.14−5.15), and antivirals (libraries 5.16 and 5.17). One reoccurring theme in this set of entries is the use of natural products as templates or starting points for library design. Examples of this include (−)-stipiamide-based library 5.1,[4] estradiol-based library 5.4,[227] (−)-indolactam V-based library 5.5,[156] kramerixin-based library 5.15,[68] and the prostanoid-based library 5.16 (Figure 26).[141]

Isis described a series of libraries using a technique of "simultaneous addition of fuctionality" in which chemically reactive polyhalogenated heterocycles are treated with excess nucleophiles to create libraries possessing antibacterial activity (libraries 5.11−5.13).[119] No specific compounds were identified from the libraries. Polyhalogenated heteroaromatics as well as the corresponding reactive fluoronitroaromatics have been used extensively over the past several years in the synthesis of biologically active libraries and other library constructs of medicinal interest (Figures 6 and 7).

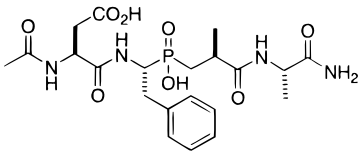
Acknowledgment. Many thanks to Ms. Karen Rivera for her invaluable assistance in the preparation of this manuscript and for her expertise and perseverance in chemical structure drawing.

Table 1. Chemical Libraries Targeted for Proteases[a]

Metallo-proteases

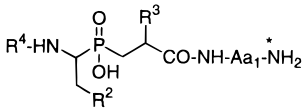
Library: 1.1
Name: Phosphinic peptide
Size: 400 members
Affiliation: Dive, V.; *et al.* [64]
Note: Twenty peptide mixtures each containing a single Aa_1 with a mixture of 20 Aa_2.

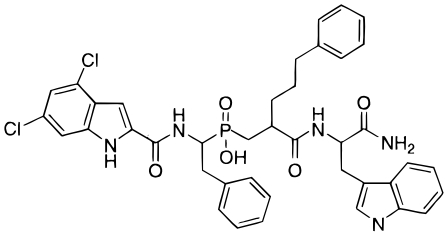
Ac-Aa_1-Pheψ(PO_2-CH_2)Ala-Aa_2-NH_2



Enzyme: Somatic angiotensin converting enzyme (ACE)
Activity: K_i = 12 nM, ACE (N-domain); K_i = 25 μM, ACE (C-domain)

Library: 1.2
Name: Phosphinic tripeptide
Size: Not defined
Affiliation: Dive, V.; *et al.* [230]
Note: Several libraries prepared.

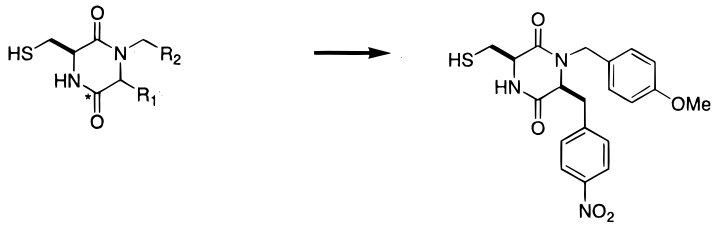




Enzyme: MMP-11 (stromelysin-3)
Activity: K_i = 0.9 nM (K_i = 24 nM, MMP-2; K_i = 7 nM, MMP-9; K_i = 32 nM, MMP-14; K_i = 36 nM, MMP-1; K_i = 117 nM, MMP-7; K_i = 5 nM, MMP-8)

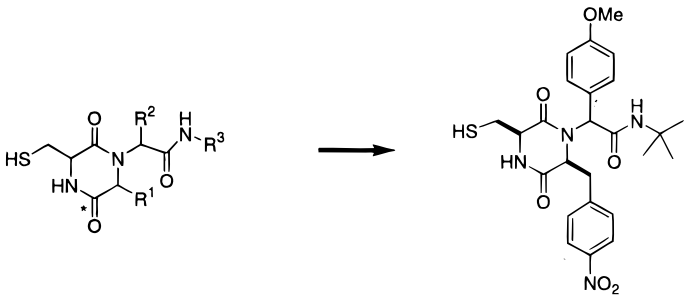
Table 1. (Continued)

Library: 1.3
Name: Diketopiperazine
Size: 1225 members
Affiliation: Affymax Res. Inst. [221]



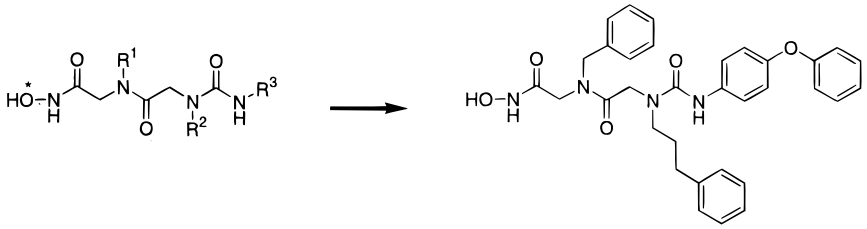
Enzyme: Collagenase-1
Activity: IC_{50} = 47 nM (IC_{50} = 1200 nM, gelatinase-B; >4000 nM, stromelysin)

Library: 1.4
Name: Diketopiperazine
Size: ca. 700-900 members
Affiliation: Affymax Res. Inst. [221]
Note: Three-component Ugi condensation.



Enzyme: Collagenase-1
IC_{50} = 21 nM (IC_{50} = 1300 nM, gelatinase-B)

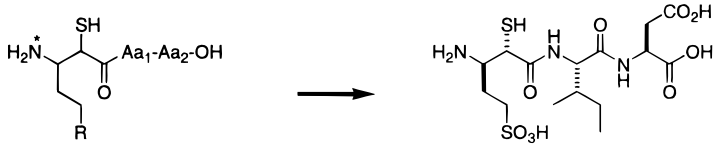
Library: 1.5
Name: Urea-based hydroxymate
Size: Not defined
Affiliation: Lauhon, C. T.; *et al.* [247]



Enzyme: Gelatinase (MMP-2)
Activity: IC_{50} = 300 nM

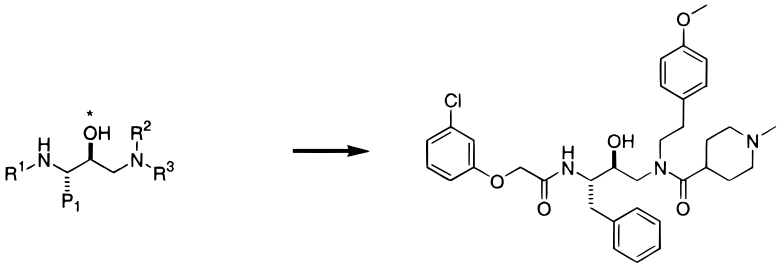
Aspartic acid proteases

Library: 1.6
Name: Pseudotripeptide
Size: 380 members
Affiliation: Roques, B. P.; *et al.* [59]
Note: Two positional scanning libraries.



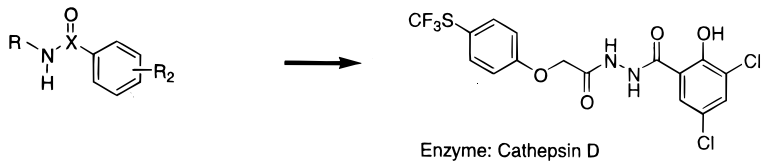
Enzyme: Aminopeptidase A
Activity: K_i = 3.2 nM

Library: 1.7
Name: Hydroxyethylamine
Size: ca. 170 members
Affiliation: Ellman, J. A.; *et al.* [95]
Note: Six iterative libraries for lead optimization.



Enzyme: Plasmepsin II (*P. falciparum*)
Activity: K_i = 2 nM (K_i = 9.8 nM, cathepsin D)

Library: 1.8
Name: Amide derivative
Size: 300 members
Affiliation: Bayer Corp. [47]
Note: Solution-phase synthesis using polymer bound reagents.

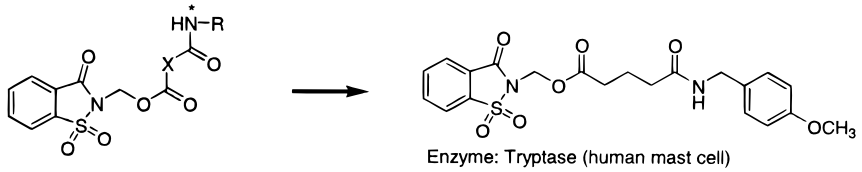


Enzyme: Cathepsin D
Activity: IC_{50} = 320 nM

Table 1. (Continued)

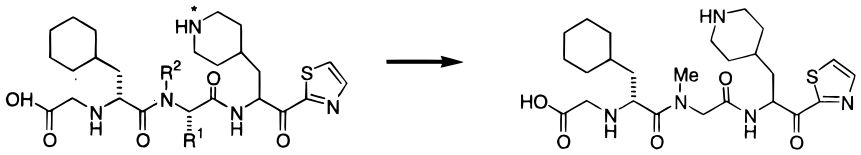
Serine proteases

Library: 1.9
Name: Benzisothiazolone
Size: 60 members
Affiliation: Bristol-Myers Squibb [243]
Note: Encoded split-pool library using R_f tags.



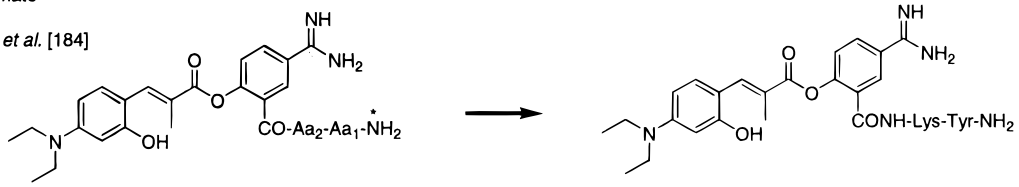
Enzyme: Tryptase (human mast cell)
Activity: IC_{50} = 0.23 μM

Library: 1.10
Name: Peptide ketothiazole
Size: ca. 150 members
Affiliation: Organon Labs [3]



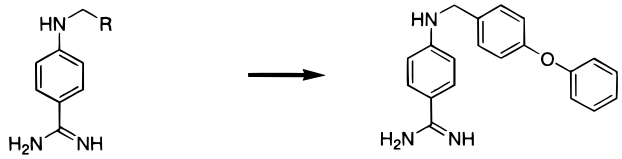
Enzyme: Factor Xa
Activity: IC_{50} = 0.43 μM
(IC_{50} = 4.8 μM, thrombin)

Library: 1.11
Name: *o*-Hydroxycinnamate
Size: 112 members
Affiliation: Porter, N. A.; *et al.* [184]



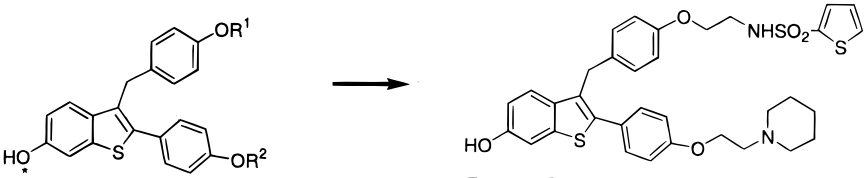
Enzyme: Thrombin
Activity: Photo-reversible inactivation

Library: 1.12
Name: Phenylamidine
Size: 10 members
Affiliation: Hoffmann-La Roche [22]
Note: Combinatorial docking procedure led to selection of library compounds.

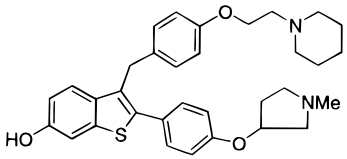


Enzyme: Thrombin
Activity: K_i = 9.5 nM
(K_i = 520 nM, trypsin)

Library: 1.13
Name: Benzothiophene
Size: 346 members
Affiliation: Sphinx Pharm. [114]
Note: Solid-phase Mitsunobu chemistry and parallel purification.

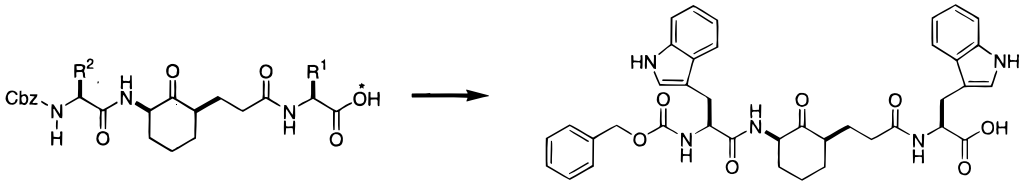


Enzyme: Thrombin (human)
Activity: K_{ass} = 1μM (0.02 μM, Factor Xa)



Enzyme: Factor Xa (human)
Activity: K_{ass} = 5.0 nM (2.3 μM, thrombin)

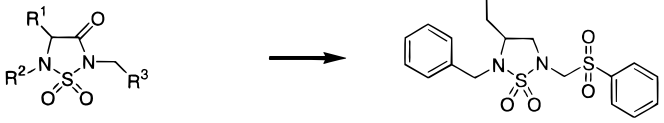
Library: 1.14
Name: Cyclohexanone peptide
Size: 400 members
Affiliation: Seto, C. T.; *et al.* [2]



Enzyme: Plasmin
Activity: K_i = 5 μM

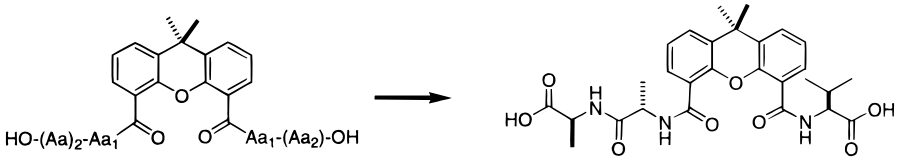
Table 1. (Continued)

Library: 1.15
Name: 1,2,5-Thiadiazolidin-3-one
Size: ca. 12 members
Affiliation: Groutas, W. C.; *et al.* [128]
Note: Solution-phase synthesis.



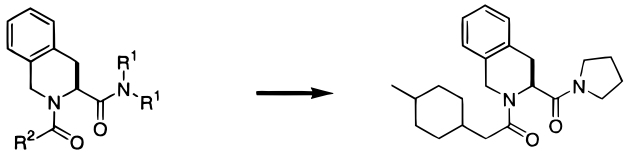
Enzyme: Elastase (human leukocyte)
Activity: k_{inact}/K_i = 95,000 $M^{-1}s^{-1}$

Library: 1.16
Name: Disubstituted xanthenes
Size: ca. 12 members
Affiliation: Pryor, K. E.; *et al.* [186]
Note: Two-phase colorimetry based screen for inhibition.



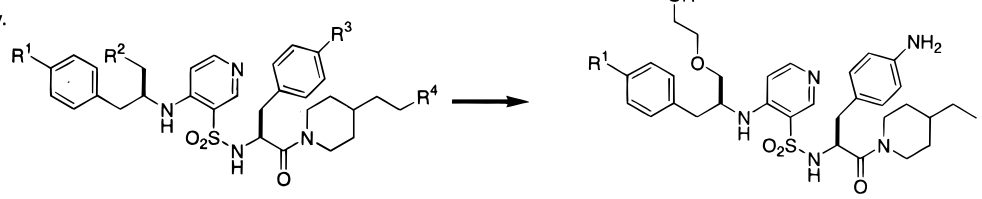
Enzyme: (human leukocyte) Elastase
Activity: K_i = 86 μM

Library: 1.17
Name: Tetrahydroisoquinolin
Size: 2560 members
Affiliation: Sergheraert, C.; *et al.* [232]
Note: Solution-phase synthesis.



Enzyme: Prolyl endopeptidase (*Trypanosoma cruzi*)
Activity: IC_{50} = 9.0 nM

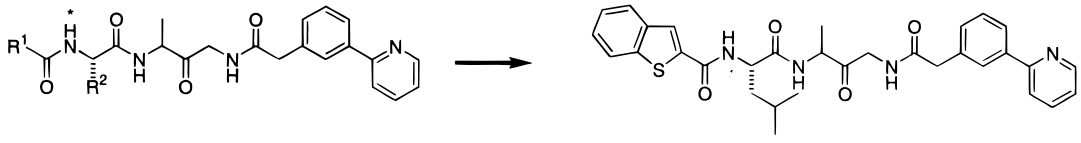
Library: 1.18
Name: Sulfonamides
Size: 198 members
Affiliation: Novartis [252]
Note: Optimization library.



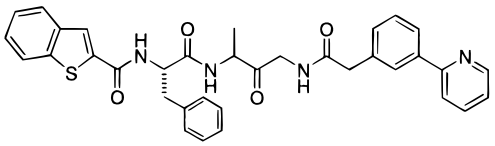
Enzyme: Thrombin
Activity: K_i = 147 nM (55% oral bioavailability (30 mg/kg, p.o.) in rat; $t_{1/2}$ = 120-180 min; C_{max} = 3.36 mg.mL^{-1}

Cysteine proteases

Library: 1.19
Name: Acylaminobutanone
Size: 18 members
Affiliation: SmithKline Beecham [239]
Note: R_f encoding.



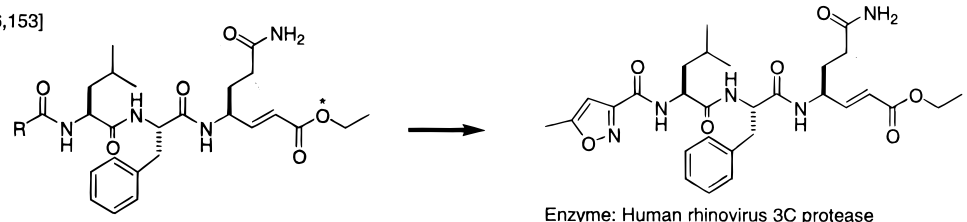
Enzyme: Cathepsin K
Activity: $K_{i,app}$ = 1.3 nM ($K_{i,app}$ = 90 nM, cathepsin L; $K_{i,app}$ = >1000 nM cathepsin B)



Enzyme: Cathepsin L
Activity: $K_{i,app}$ = 18 nM ($K_{i,app}$ = 16 nM cathespin K; $K_{i,app}$ = >1000 nM, cathepsin B)

Table 1. (Continued)

Library: 1.20
Name: Tripeptide Michael acceptor
Size: ca. 500 members
Affiliation: Agouron Pharm. [66,153]



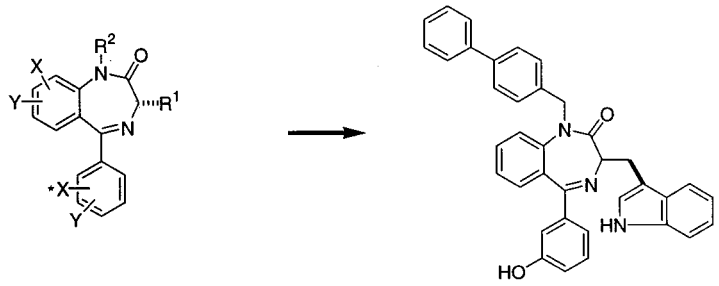
Enzyme: Human rhinovirus 3C protease
Activity: $K_{obs}/I = 260{,}000\ M^{-1}s^{-1}$

[a] Asterisk (*) indicates point of attachment to the resin.

Table 2. Chemical Libraries Targeted for Nonproteolytic Enzymes[a]

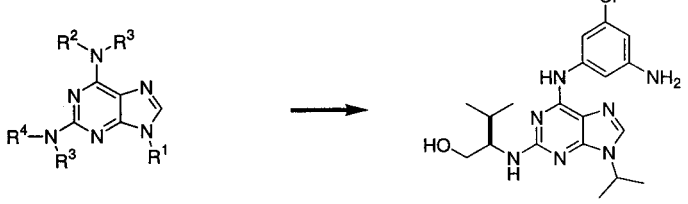
Kinases and phosphatases

Library: 2.1
Name: 1,4-Benzodiazepine
Size: 1680 members
Affiliation: Ramdas, L.; *et al.* [187]



Enzyme: Src protein tyrosine kinase
Activity: $IC_{50} = 35\ \mu M$

Library: 2.2
Name: Substituted purine
Size: Not defined
Affiliation: Chang, Y. T.; *et al.* [44]
Note: Multiple solution- and solid-phase libraries.



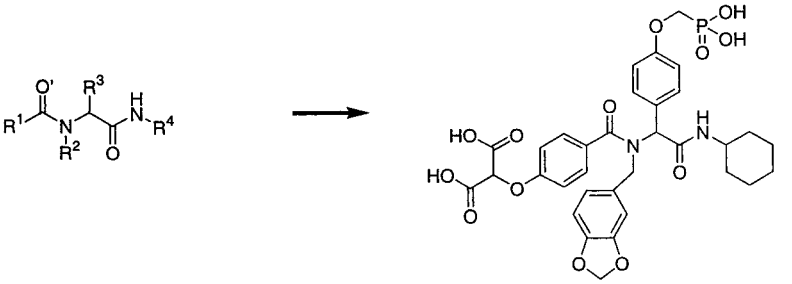
Enzyme: Cyclin-dependent kinase 2 (CDK2)
Activity: $IC_{50} = 33$ nM ($IC_{50} = 28$ nM, CDK1)

Library: 2.3
Name: Octapeptide
Size: ca. 110,000 members
Affiliation: Watterson, D. M.; *et al.* [150]
Note: Positional scanning.

H-Arg-Lys-Lys-Aa_1-Aa_2-Aa_3-Arg-Arg-Lys-$\overset{*}{N}H_2$ → H-Arg-Lys-Lys-Tyr-Lys-Tyr-Arg-Arg-Lys-NH_2

Enzyme: Smooth muscle myosin light chain kinase (chicken)
Activity: $IC_{50} = 50$ nM (>40,000-fold selective versus calmodulin-regulated protein kinase)

Library: 2.4a-c
Name: Amino acid amide
Size: 4320 total members
Affiliation: Mitotix, Inc. [14]
Note: Three libraries based on Ugi reaction with phosphate surrogates.

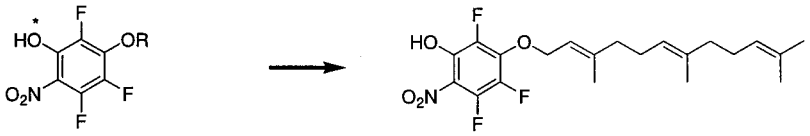


Enzyme: Cdc25 phosphatase
Activity: $IC_{50} = 0.7\ \mu M$
($IC_{50} = 82\ \mu M$, tyrosine phosphatase PTPIB)

Table 2. (Continued)

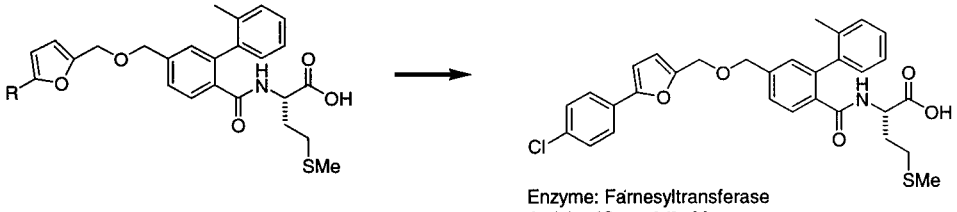
Transferases

Library: 2.5
Name: Trifluoronitrophenol
Size: 12 members
Affiliation: Hardcastle, I. R.; *et al.* [9]



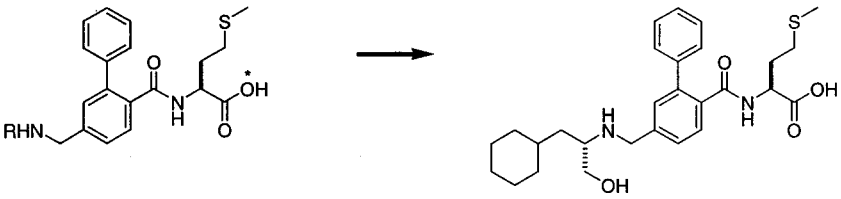
Enzyme: Farnesyltransferase (rat)
Activity: IC_{50} = 6.3 μM
(IC_{50} = 12.5 μM, geranylgeranyl protein transferase-I)

Library: 2.6
Name: Methionine biaryl
Size: 31 members
Affiliation: Abbott [8]
Note: Solution-phase optimization library.



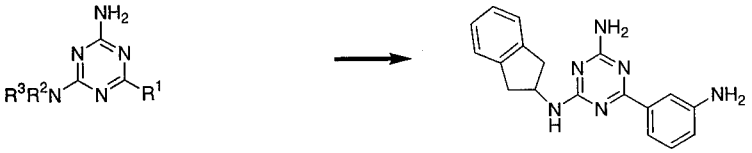
Enzyme: Farnesyltransferase
Activity: IC_{50} = 0.7 nM
(>10,000-fold selective vs. geranylgeranyl protein transferase-1; 21% orally bioavailable, dog)

Library: 2.7
Name: Biphenyl methionine
Size: Not defined
Affiliation: Abbott [101]



Enzyme: Farnesyltransferase (FTase)
Activity: IC_{50} = 8.0 nM

Library: 2.8a,b
Name: Triazine
Size: 643 members
Affiliation: Abbott [89]



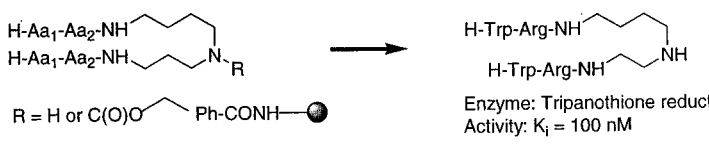
Target: Erm methyltransferase
Activity: IC_{50} = 4 μM

Reductases and dehydratases

Library: 2.9
Name: Dihydrophenyl triazine
Size: 64 members
Affiliation: Chui, W.-K.; *et al.* [139]
Note: Three-component condensation using anilines, ketones, and cyanoguanidine.

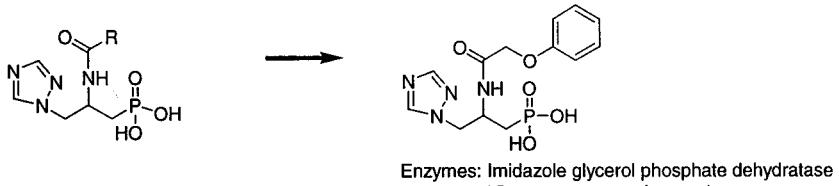
Enzyme: Dihydrofolate reductase
Activity: IC_{50} = 6.0 nM; K_i = 200 μM

Library: 2.10
Name: Polyamine peptide conjugate
Size: 576 members
Affiliation: Bradley, M.; *et al.* [209]
Note: Three identical libraries produced in solution on PEGA resin, and on Tentagel to compare success of solution- versus on-bead assays.



Enzyme: Tripanothione reductase
Activity: K_i = 100 nM

Library: 2.11
Name: β-Carboxamido phosphonate
Size: 15 members
Affiliation: Monsanto Co. [202]
Note: Solution-phase synthesis using solid-phase capture reagents.



Enzymes: Imidazole glycerol phosphate dehydratase (*Cryptococcus neoformans*)
Activity: K_i = 80 nM

Library: 2.12
Name: Amide
Size: 768 members
Affiliation: Du Pont Agricul. [113]
Note: Solution-phase synthesis.

Enzymes: Scytalone dehydratase
Activity: K_i = 0.05 nM

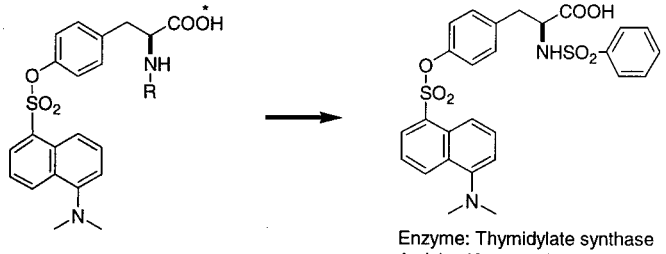
Table 2. (Continued)

Other enzymes

Library: 2.13
Name: 1,3-Dioxane-4,6-dione carboxamide
Size: ca. 113 members
Affiliation: Gelb, M. H.; *et al.* [33]
Note: Solution-phase synthesis.

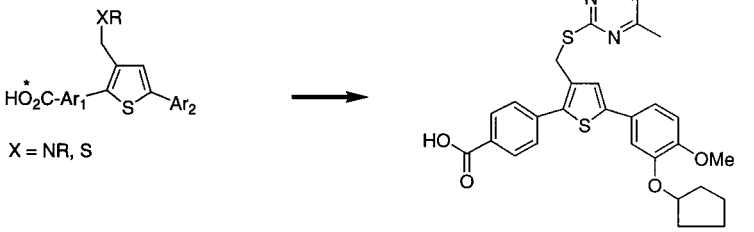
Enzyme: Phospholipase A_2 (human group IIA)
Activity: X_I (50) = 0.022

Library: 2.14
Name: Dansyltyrosine
Size: 34 members
Affiliation: Tondi, D.; *et al.* [225]



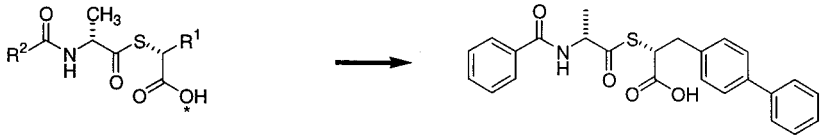
Enzyme: Thymidylate synthase
Activity: K_i = 1.5 μM

Library: 2.15
Name: Substituted thiophene
Size: ca. 100 members
Affiliation: Merck Frosst [93]



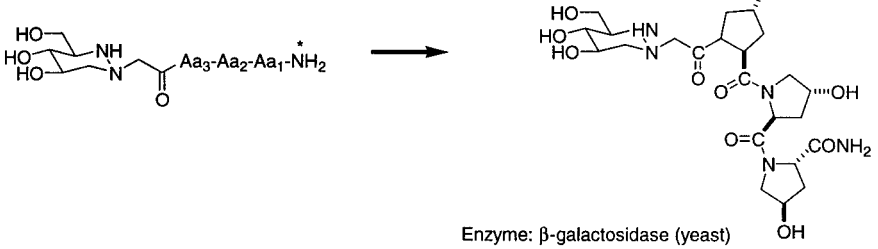
Enzyme: Phosphodiesterase-4 (PDE-4)
Activity: IC_{50} = 8.0 nM

Library: 2.16
Name: Thiodepsipeptide
Size: 38 members
Affiliation: Merck [84]



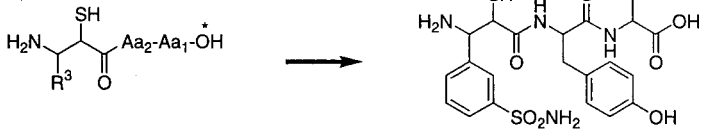
Enzyme: IMP-1 metallo-β-lactamase
Activity: IC_{50} = 0.4 nM (IC_{50} = 180 nM, CcrA metallo-β-lactamase)

Library: 2.17
Name: 1-Azafagomine peptide
Size: 125 members
Affiliation: Bols, M.; *et al.* [148], [149]



Enzyme: β-galactosidase (yeast)
Activity: K_i = 20 μM

Library: 2.18
Name: β-Aminothiol peptide
Size: ca. 600 members
Affiliation: Roques, B. P.; *et al.* [151]



Enzyme: Bacterial protein tetanus toxin (TeNt)
Activity: K_i = 5.0 μM

Library: 2.19
Name: Tetrahydro-β–carboline
Size: 48 members
Affiliation: Jung, G.; *et al.* [250]

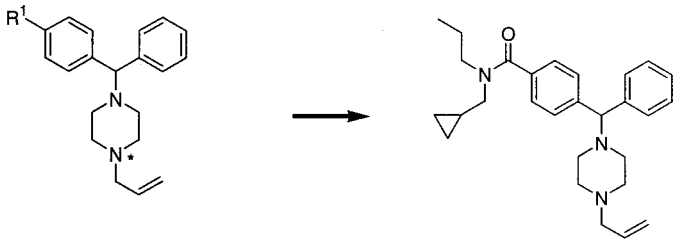
Enzyme: DNA gyrase
Activity: IC_{50} = 10 μM

[a] Asterisk (*) indicates point of attachment to the resin.

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

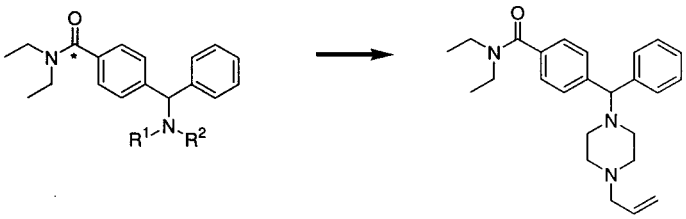
Opioid receptors

Library: 3.1a,b
Name: *N*-Diarylmethylpiperazine
Size: ca. 125 members
Affiliation: Organon Labs. [55]
Note: Solid-phase synthesis using REM resin.



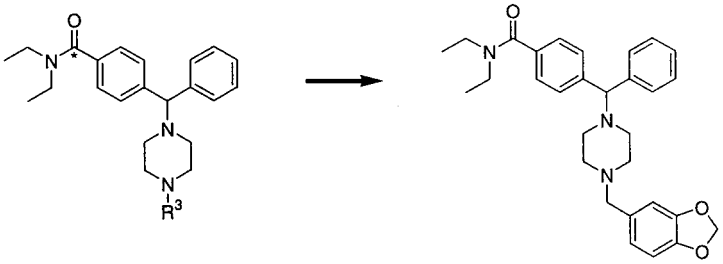
Target: δ opioid (human)
Activity: IC_{50} = 3.0 nM
(IC_{50} = >10,000 nM, μ (rat))

Library: 3.2
Name: Diarylmethylamine
Size: 20 members
Affiliation: Organon Labs. [11]
Note: $AlCl_3$-mediated diethylaminolysis of Wang esters.
See library 3.3.



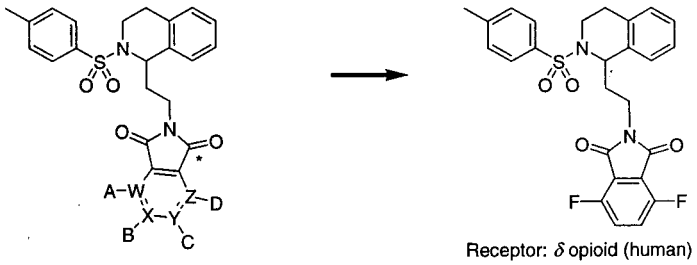
Receptor: δ opioid (human)
Activity: IC_{50} = 8 nM

Library: 3.3
Name: *N*-Diarylmethylpiperazine
Size: 46 members
Affiliation: Organon Labs. [11]
Note: $AlCl_3$-mediated diethylaminolysis of Wang esters.
See library 3.2.



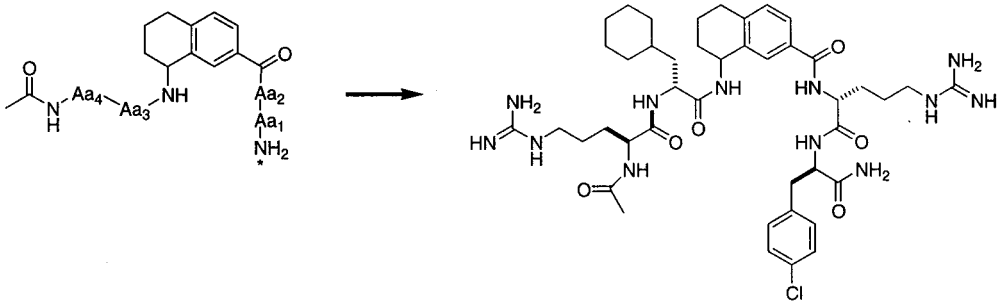
Receptor: δ opioid (human)
Activity: IC_{50} = 1.4 nM
(IC_{50} = >10,000 nM, μ (rat);
IC_{50} = 3900 nM, κ (guinea pig))

Library: 3.4
Name: Cyclic imide
Size: 30 members
Affiliation: Organon Labs. [12]



Receptor: *δ* opioid (human)
Activity: IC_{50} = 16 nM

Library: 3.5
Name: Pseudopentapeptide
Size: 20,000,000 members
Affiliation: Simonin, F.; *et al.* [13]
Note: Positional scanning at Aa_4.

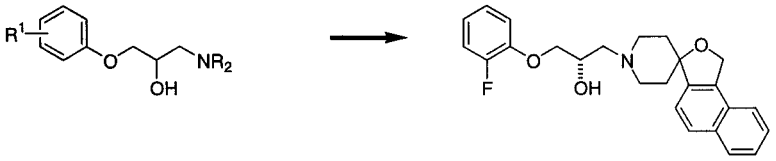


Receptor: Opioid receptor-like 1 (ORL-1, human)
Activity: K_i = 517 nM (K_i = 114 nM, κ-opioid;
K_i = 1300 nM, μ-opioid; K_i = 11000 nM, δ–opioid)

Table 3. (Continued)

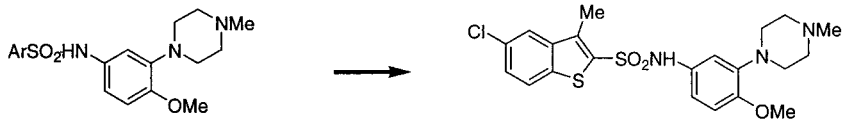
Serotonin receptors

Library: 3.6
Name: Aryloxy-2-propanolamine
Size: Not defined (large)
Affiliation: Merck [229]
Note: Solution-phase parallel synthesis.



Receptor: 5-HT_{1A} (human receptors in HeLa cells)
Activity: K_i = 1.0 nM

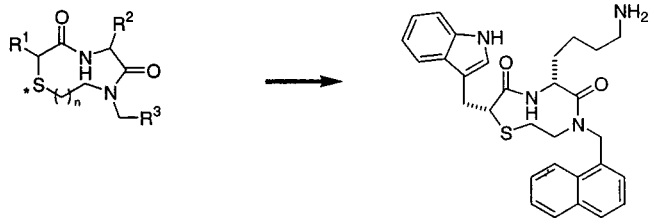
Library: 3.7
Name: Bisaryl sulfonamide
Size: >12 members
Affiliation: SmithKline Beecham [30]
Note: Solution-phase optimization library.



Receptor: 5-HT_6 (human cloned receptors in HeLa cells)
Activity: pK_i = 9.2 (selective vs.13 subtypes and other receptors); pK_b 8.5 (5-HT simulated adenylyl cyclase; antagonist)

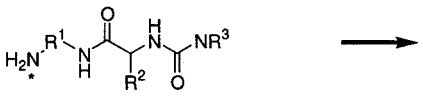
Somatostatin receptors

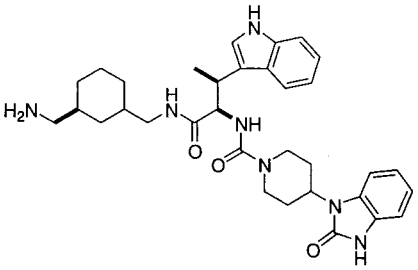
Library: 3.8
Name: β-Turn mimetic
Size: 172 members
Affiliation: Ellman, J. A.; *et al.* [213]



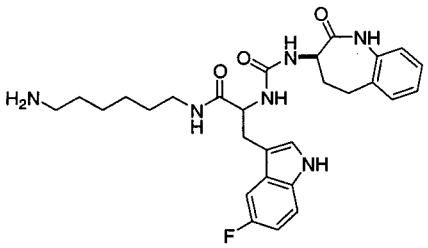
Receptor: Somatostatin-5 ($hsstr_5$, human)
Activity: IC_{50} = 87 nM (ca. 5-fold selective vs. $hsstr_1$; >10-fold selective vs. $hsstr_{2-4}$)

Library: 3.9
Name: Amino acid amides
Size: 131,670
Affiliation: Merck [158]

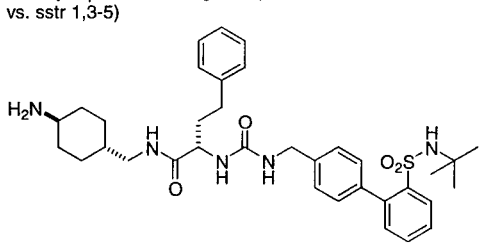




Receptor: Somatostatin-2 (sstr 2; human)
Activity: K_i = 0.04 nM, agonist (>1000x selective vs. sstr 1,3-5)



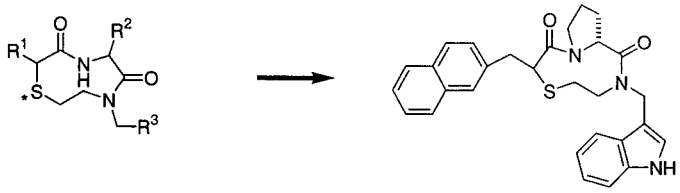
Receptor: Somatostatin-5 (sstr 5; human)
Activity: K_i = 170 nM, agonist (>23x selective vs. sstr 2; >1000x selective vs. sstr 1,3,4)



Receptor: Somatostatin-1 (sstr I; human)
Activity: K_i = 64 nM agonist (>23x selective vs. sstr 2-5)

Other receptors

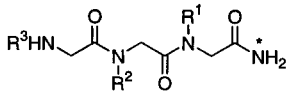
Library: 3.10
Name: β-Turn mimetic
Size: 951 members
Affiliation: Ellman, J. A.; *et al.* [96]
Note: 951 compounds selected from a library of 5544 compounds.

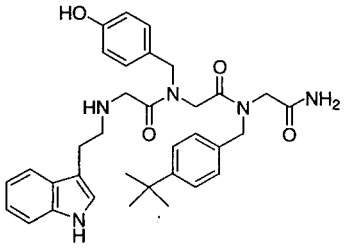


Target: Melanocortin-1
Activity: EC_{50} = 42.5 μM (agonist)

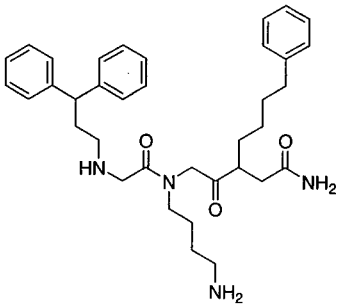
Table 3. (Continued)

Library: 3.11
Name: Tripeptoid
Size: 328,509 members
Affiliation: Eberle, A. N.; *et al.* [99]



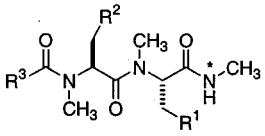


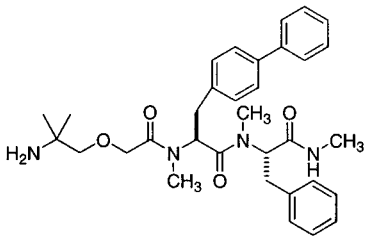
Receptor: GRP/bombesin
Activity: K_D = 3.40 μM



Receptor: Melanocortin-1 (human)
Activity: K_D = 1.58 μM

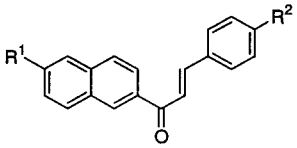
Library: 3.12
Name: Dipeptide
Size: 96 members
Affiliation: Novo Nordisk [5]
Note: Optimization library based on ipamiorelin.

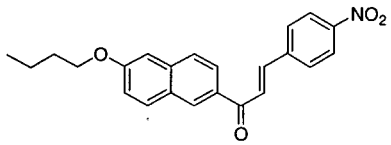




Receptor: Growth hormone segretagogue (rat pituitary cell assay)
Activity: EC_{50} = 1 nM (agonist)

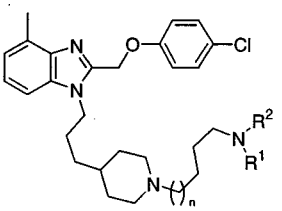
Library: 3.13
Name: Chalcone
Size: ca. 40 members
Affiliation: Natu, A. A.; *et al.* [63]
Note: Solution-phase synthesis of two sets of nine combinatorial mixtures.

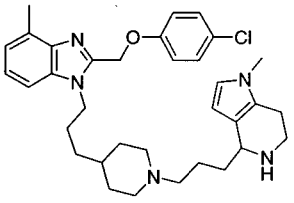




Receptor: Leukotriene B_4 (human whole blood)
Activity: IC_{50} = 18.5 μM (inhibition of LTB_4 formation)

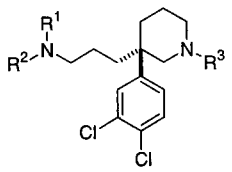
Library: 3.14
Name: Benzimidazole diamine
Size: 84 members
Affiliation: Lilly [205]
Note: Optimization library based on LY344090. Most active compound derived from unexpected Pictet-Spengler cyclization.

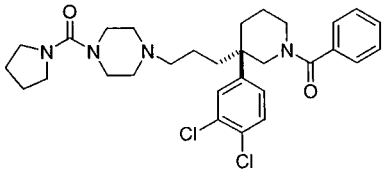




Receptor: Neuropeptide Y-1 (NPY-1; human)
Activity: K_i = 13 nM (antagonist)

Library: 3.15
Name: Dichlorophenyl-3-propylpiperidine
Size: 49 members
Affiliation: SmithKline Beecham [188]
Note: Solution-phase synthesis. Focused library based on Sanofi lead structure.





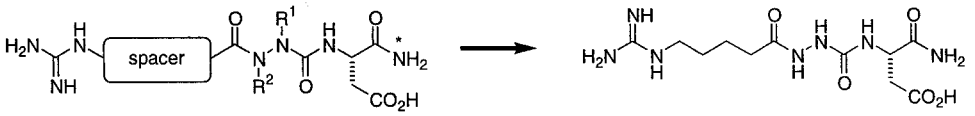
Receptor: Neurokinin-3 (human)
Activity: K_i = 35 nM (antagonist)

[a] Asterisk (*) indicates point of attachment to the resin.

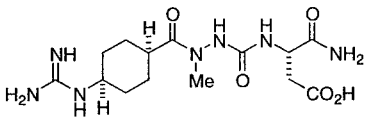
Table 4. Chemical Libraries Targeted for Non-G-Protein Coupled Receptors (non-GPCRs)[a]

Integrins

Library: 4.1
Name: Azapeptoid
Size: 6 members
Affiliation: Kessler, H.; *et al.* [77]

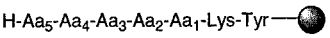


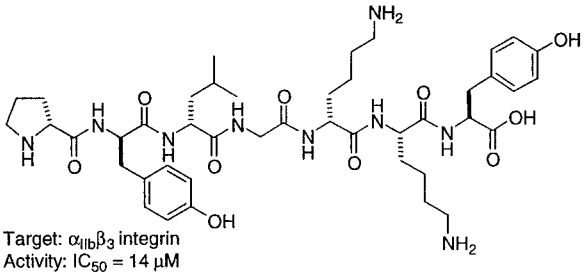
Target: $\alpha_v\beta_3$ integrin
Activity: IC_{50} = 6.8 μM (IC_{50} >100 μM, αIIbβ3)



Target: $\alpha_{IIb}\beta_3$
Activity: IC_{50} = 2.7 μM (IC_{50} >100 μM, αvβ3)

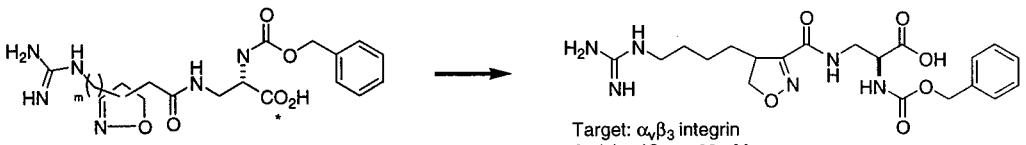
Library: 4.2
Name: Pentapetide
Size: Large
Affiliation: Selectide Corp. [223]
Note: L- and D-amino acids was in split-pool synthesis. On-bead screening.





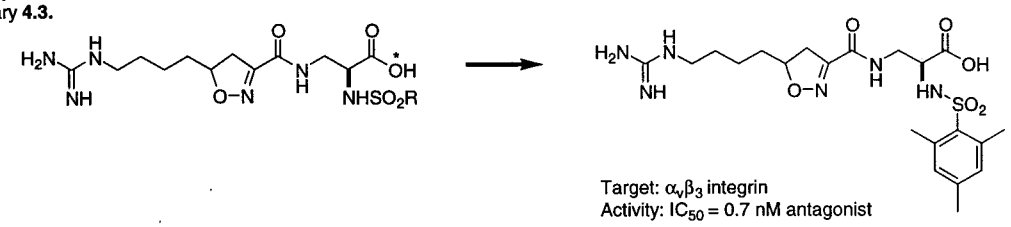
Target: $\alpha_{IIb}\beta_3$ integrin
Activity: IC_{50} = 14 μM

Library: 4.3
Name: Isoxazolinyl guanidine
Size: Not defined
Affiliation: DuPont Pharm. [190]



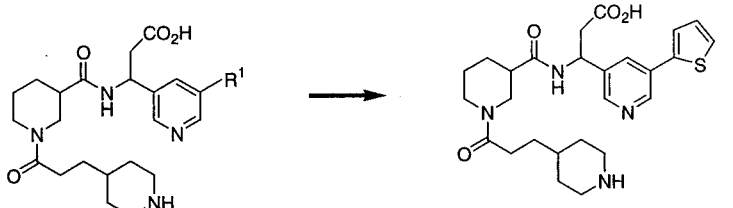
Target: $\alpha_v\beta_3$ integrin
Activity: IC_{50} = 23 nM

Library: 4.4
Name: Isoxazolinyl guanidine
Size: Not defined
Affiliation: DuPont Pharm. [190]
Note: Optimization library based on lead identified in library **4.3.**



Target: $\alpha_v\beta_3$ integrin
Activity: IC_{50} = 0.7 nM antagonist

Library: 4.5
Name: 5-Substituted pyridine
Size: 15 members
Affiliation: R. W. Johnson Pharm. [104]
Note: Optimization library.

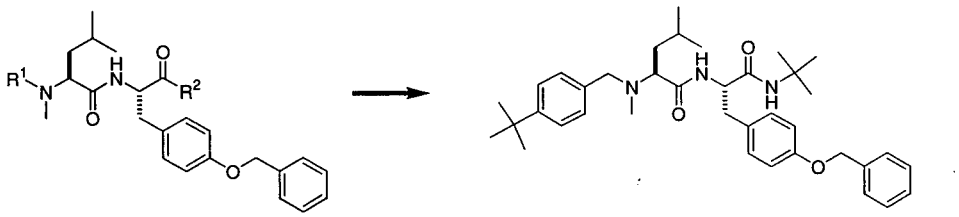


Target: GPIIb/IIIa integrin
Activity: IC_{50} = 1.5 nM (antagonist)

Table 4. (Continued)

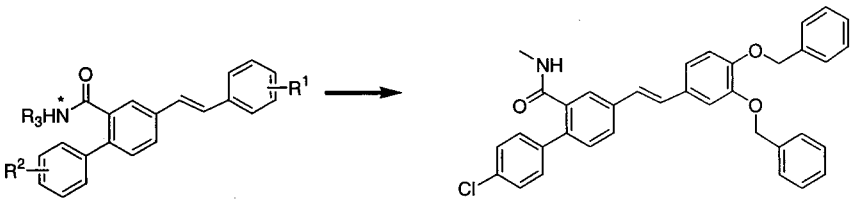
Ion channels and transporters

Library: 4.6
Name: *N*,*N*-Dialkyldipeptidylamine
Size: 30 members
Affiliation: Parke-Davis [195]
Note: Solution-phase synthesis.



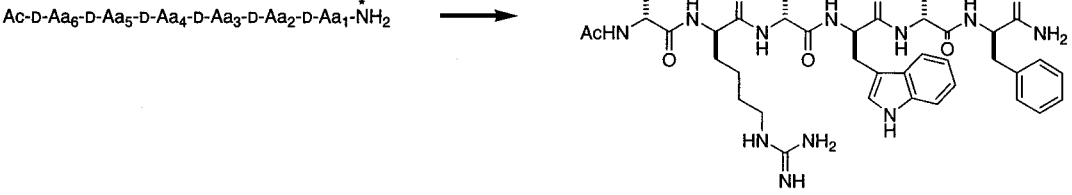
Target: N-Type voltage sensitive calcium channel (in IMR-32 cells)
Activity: IC_{50} = 40 nM

Library: 4.7
Name: Substituted phenyl stilbene
Size: ca. 400 members
Affiliation: Chamberlin, A. R.; *et al.* [145]
Note: Kenner's safety-catch linker used.



Target: KV1.3 potassium channel
Activity: IC_{50} = 2.9 μM (^{125}I-ChTx binding assay)

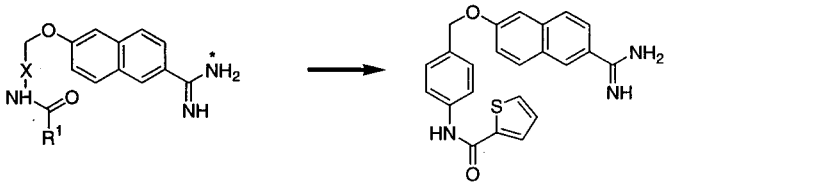
Library: 4.8
Name: D-Hexapeptide
Size: ca. 400 members
Affiliation: Rothman, R. B.; *et al.* [192]
Note: Kenner's safety-catch linker used.



Target: Dopamine transporter
Activity: IC_{50} = 1.8 μM

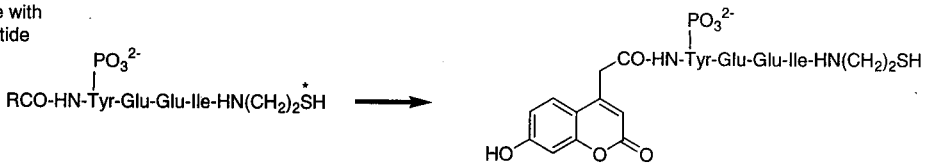
Other non-GPCR

Library: 4.9
Name: Amidinonaphthyl ether
Size: ca. 145 members
Affiliation: Bradley, M.; *et al.* [194]



Target: Tissue factor/factor VIIa complex (human)
Activity: IC_{50} = 4.1 μM

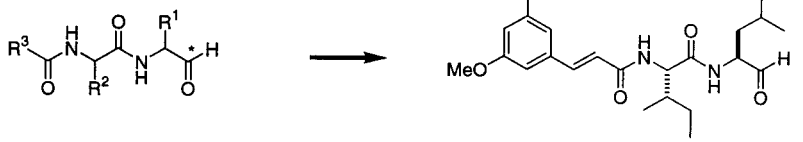
Library: 4.10
Name: Phosphopeptide
Size: 900 members
Affiliation: Lawrence, D. S.; *et al.* [143]
Note: Disulfide link to resin. Cleavage with dithiothreitol in Tris buffer to give peptide conjugates in assay-ready solution.



Target: Src SH2 domain of Lck
Activity: K_D = 35 nM (K_D = 150 nM, Fyn)

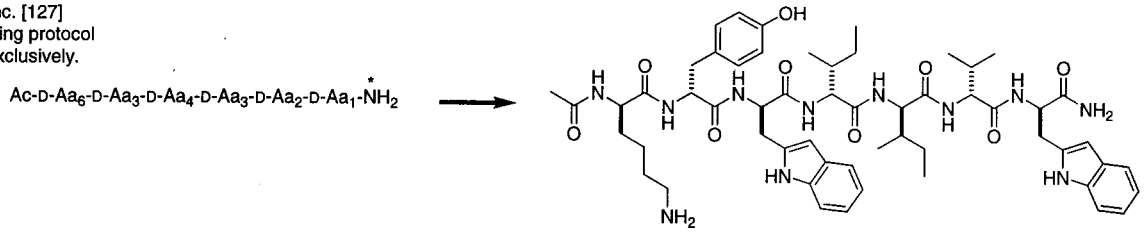
Table 4. (Continued)

Library: 4.11
Name: Dipeptide aldehyde
Size: 100 members
Affiliation: Scios Inc. [102]



Target: β-Amyloid production
Activity: IC_{50} = 9.6 μM

Library: 4.12
Name: D-Hexapeptides
Size: 47,000,000 members
Affiliation: Centocor, Inc. [127]
Note: Positional scanning protocol using D-amino acids exclusively.



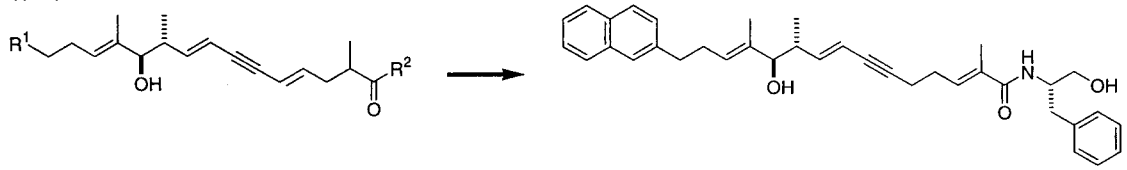
Target: TNFα
Activity: IC_{50} = 0.33 μM (antagonist effect due to binding of hexapeptide to TNF-α not its receptor)

[a] Asterisk (*) indicates point of attachment to the resin.

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

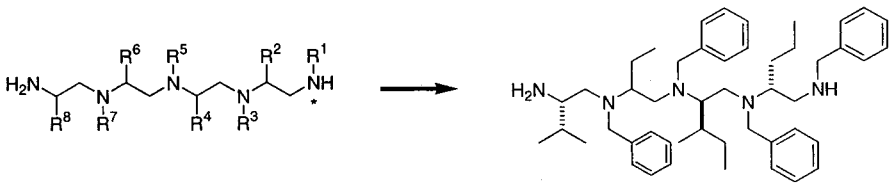
Cytotoxic agents

Library: 5.1
Name: Polyene
Size: 42 members
Affiliation: Amdris, M. B.; *et al.* [4]
Note: Solution-phase indexed combinatorial library based on MDR reversing polyene (-)-stipiamide.



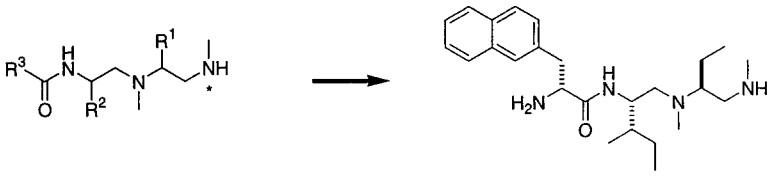
Target: McF7 - adriamycin resistant cells expressing P-glycoprotein (multidrug resistant pump)
Activity: IC_{50} = 1.45 μM

Library: 5.2
Name: Pentamine
Size: ca. 7,311,616 members
Affiliation: Appel, J. R.; *et al.* [7]



Target: 60 different cell lines
Activity: $MGIC_{50}$ = 2.02 μM (mean growth inhibition)

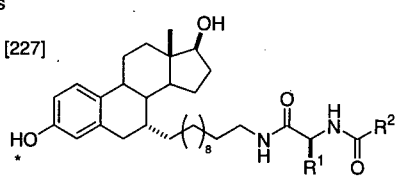
Library: 5.3
Name: *N*-Acylated triamine
Size: 454,272 members
Affiliation: Appel, J. R.; *et al.* [7]

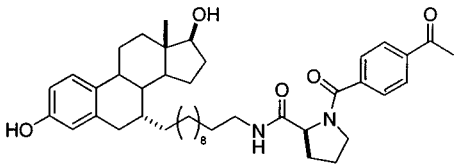


Target: 60 different cell lines
Activity: $MGIC_{50}$ = 0.69 μM
(mean growth inhibition)

Table 5. (Continued)

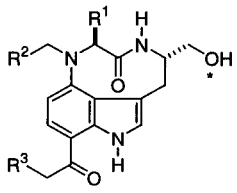
Library: 5.4
Name: Estradiol derivatives
Size: 20 members
Affiliation: Poirier, D.; *et al.* [227]





Target: T-47D (human breast cancer cell)
Activity: 95% antiproliferative activity at 0.1 μM

Library: 5.5
Name: Indole lactams
Size: 31 members
Affiliation: Waldmann, H.; *et al.* [156]
Note: Library based on known PKC activator, (-)-indolactam V.

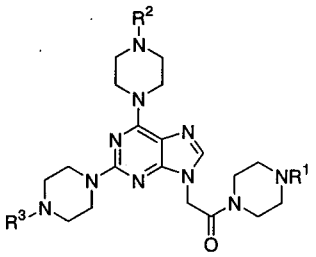


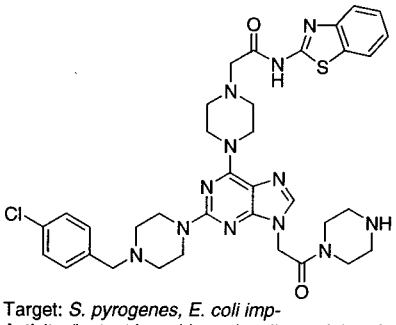
No single compound identified

Target: PKC activation in Swiss 3T3 cells
Activity: 3-5 fold increase in MARKS translocation at 200 nM; less efficient than (-)-indolactam V.

Antiinfective agents

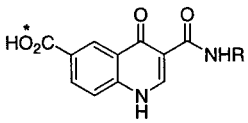
Library: 5.6
Name: Substituted purine
Size: 2725 members
Affiliation: Isis Pharm. [71]
Note: Solution-phase simultaneous addition of functionalities.

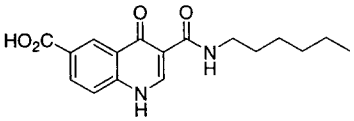




Target: *S. pyrogenes, E. coli imp-*
Activity: "potent broad-based antibacterial profile"

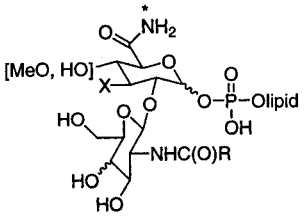
Library: 5.7
Name: Quinolone
Size: 5 members
Affiliation: Chauhan, P. M. S.; *et al.* [215]



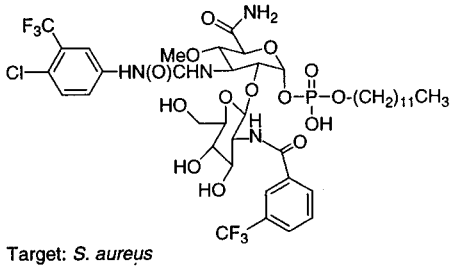


Target: *B. Malayi*
Activity: EC_{100} = 100 μM

Library: 5.8
Name: Disaccharide
Size: 1300 members
Affiliation: Intercardia Inc. [212]
Note: IRORI R_f tags.

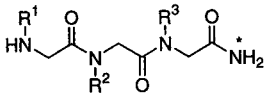


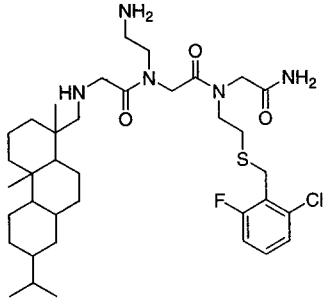
X = R^2HN(O)CO-
X = R^2HN(O)CHN-



Target: *S. aureus*
Activity: MIC = 6.25 μg/mL

Library: 5.9
Name: Peptoid
Size: 845 members
Affiliation: Chiron Corp. [81,165]
Note: Optimization library.

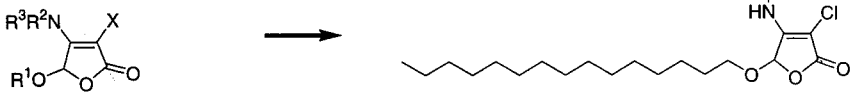




Target: *E. faecium*
Activity: MIC = 5 μg/mL; broad spectrum

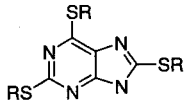
Table 5. (Continued)

Library: 5.10
Name: Butenolide
Size: 288 members
Affiliation: Lattmann, E.; *et al.* [134, 135]
Note: Solution-phase synthesis from commercially available halogenated mucochloric acids.



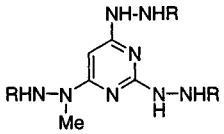
Target: *S. aureus (MRSA 96-7778)*
Activity: MIC = 8-16 μg/mL

Library: 5.11
Name: Substituted purine
Size: Not defined
Affiliation: Isis Pharm. [119]
Note: Solution-phase simultaneous addition of functionalities.



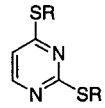
Target: Bacteria
Activity: Not defined

Library: 5.12
Name: Substituted pyrimidine
Size: Not defined
Affiliation: Isis Pharm. [119]
Note: Solution-phase simultaneous addition of functionality.



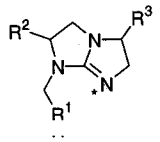
Target: Bacteria
Activity: Not defined

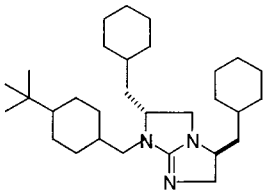
Library: 5.13
Name: Substituted pyrimidine
Size: Not defined
Affiliation: Isis Pharm. [119]
Note: Solution-phase simultaneous addition of functionality.



Target: Bacteria
Activity: Not defined

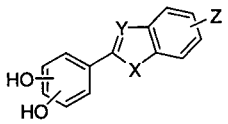
Library: 5.14
Name: Bicyclic guanidine
Size: ca. 100,000 members
Affiliation: Blondelle, S.E.; *et al.* [19]
Note: Positional scanning protocol.

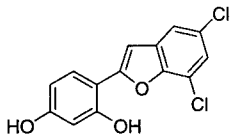




Target: *C. albicans*
Activity: MIC = 3-4 μg/mL

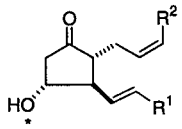
Library: 5.15
Name: Kramerixin analog
Size: ca. 120 members
Affiliation: Fecik, R. A. *et al.* [68]

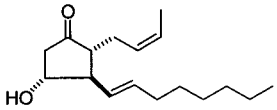




Target: *C. albicans*
Activity: MIC = 1.25 μg/mL

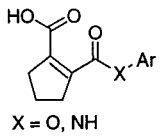
Library: 5.16
Name: Prostanoid
Size: ca. 64 members
Affiliation: Janda, K. D.; *et al.* [141]
Note: Library created on soluble support.



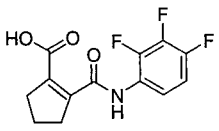


Target: Cytomegalovirus (CMV)
Activity: 98% reduction in viral titer (control titer: 6.8×10^3 PFU/mL (plague forming units))

Library: 5.17
Name: Cyclopentene-1,2-dicarboxylic acid derivative
Size: 600 virtual members
Affiliation: de Julian-Ortiz, J. V.; *et al.* [60]
Note: Compounds identified through process of virtual library synthesis and computational screening.



X = O, NH

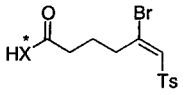


Target: HSV-1 (plaque inhibition assay)
Activity: IC_{50} = 0.9 μM

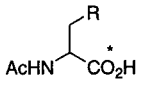
[a] Asterisk (*) indicates point of attachment to the resin.

Table 6. Scaffold Derivatization: (a) Solid Phase, (b) Solution Phase[a]

(a) Solid phase

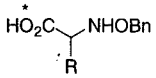


- Glaxo Wellcome [36]
- 5 ex; 24-95%
- addition of TsBr to resin-bound alkyne and alkenes; X = NR, O



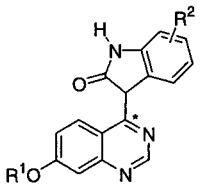
- Yim, A.-M. [242]
- 3 ex; 49-60%
- radical addition of organomercury chlorides to dehydroalanine

- RPR [197]
- 22 ex; 0-54%
- reductive cleavage of resin-bound Weinreb type amides

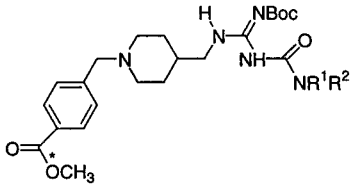


- Kobe Pharm. [158]
- 7 ex; 24-83%
- triethylborane-mediated radical addition of alkyls to glyoxylic oxime ethers

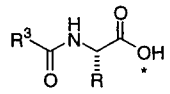
- Waldermann, H. [217]
- 7 ex; 50-95%
- traceless linker based on acyl hydrazines



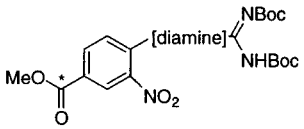
- Zeneca [100]
- 13 ex; 0-72%
- nucleophilic displacement of resin-bound quinazolines with oxindols



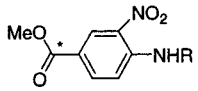
- Sun, C.-M. [218]
- 10 ex; 75-92%
- aminolysis of bis-Boc guanidines then acylation; liquid phase synthesis



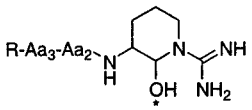
- Petillo, P. A. [51]
- 7 ex; high purity
- $MeSiCl_3$-mediated conversion of Fmoc-amino acid to isocyanate, then addition of amines



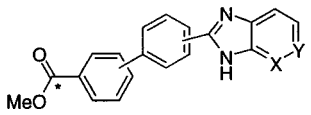
- Sun, C.-M. [103]
- 3 ex; ca. 84%
- from soluble polymer-bound 4-fluoro-3-nitro benzoic acid



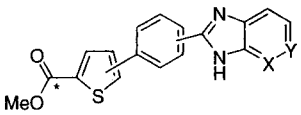
- Sun, C.-M. [175]
- 8 ex; 99%
- amine displacement of soluble-polymer supported 4-fluoro-3-nitrobenzoic acid



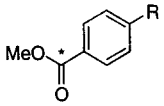
- Corvas [206]
- 20 ex; 17-83%
- from resin-bound argininal equivalent



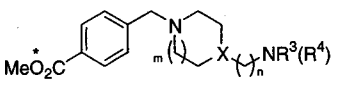
- Schotten, T. [17]
- 19 ex; 33-60%
- liquid-phase Suzuki coupling



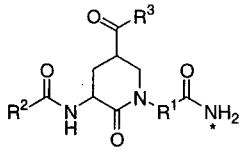
- Schotten, T. [17]
- 6 ex; 54-93%
- liquid-phase Suzuki coupling



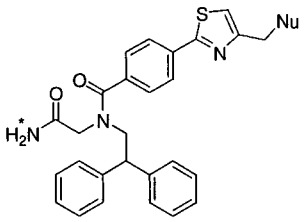
- Kondo, Y. [126]
- ca. 5 ex;
- immobilized organometallic reagents; R = electrophile, Ph



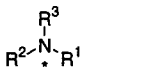
- Sun, C.-M. [203]
- 15 ex; 80-95%
- from resin-bound 4-chloromethylbenzoic acid; liquid-phase synthesis; X = CH, N; n = 0, 1; m = 1, 2



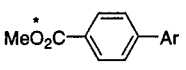
- Glaxo Wellcome [147]
- size not defined
- ^{1}NH alkylation of 3-amino-5-carbomethoxy-1H-pyridin-2-one to resin-bound halo acids, then N-acylation and amination



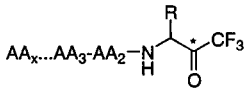
- Woski, A. [41]
- displacement of Cl in resin-bound chloromethylthiazole



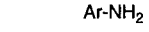
- Brase, S. [28]
- ca. 9 ex; good yield
- triazene linker



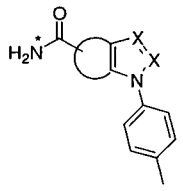
- Finn, M. G. [29]
- 7 ex; 0-95%
- Stille coupling with resin-bound aryl stannanes



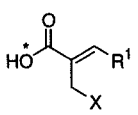
- Boehringer Ingel. [183]
- 100 members
- derivatization of Boc-protected trifluoromethyl ketones attached to resin via semicarbazone linkage



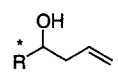
- Morishima, H. [220]
- 9 ex; 90->95%
- Curtius rearrangement and trapping intermediate isocyanate with Wang resin, then hydrolysis



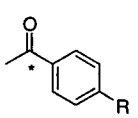
- Du Pont [54]
- 4 ex; 55-64%
- C-N cross-coupling X = CH, N



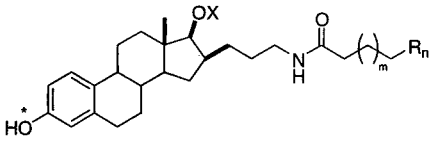
- Jung, G. [189]
- 5 ex; >65%
- from Baylis-Hillman intermediate; X = OAr, NR^2R^3



- Pharmacopeia [39]
- 10 ex; ca. 70%
- addition of allylindium or allylboronate to resin-bound aldehyde



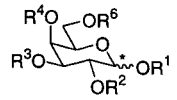
- Schering AG [111]
- 7 ex; 28-59%
- Suzuki coupling of resin-bound 4-bromobenzophenone dithioketal



- Poirier, D. [226]
- 2 ex; 20-30%
- from resin-bound 16-β-(azidopropyl)estradiol; X = H, COR

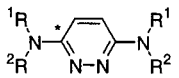
- Hanessian, S. [94]
- 3 ex; 94-98%
- from 2-pyridylthiocarbonate resin, ROH, AgOTf, then TFA.

Table 6. (Continued)

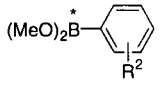


- Kunz, H. [115]
- 14 ex; 6-69%
- from resin-bound orthogonal protected galactose

- Abell, C. [224]
- 10 ex; 58-96%
- esters and amides from novel safety-catch linker involving formation of N-arylindoles on resin; X = OR, NRR

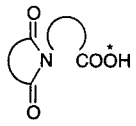


- Hilbert, M. [177]
- 8 ex; 50-100%
- functionalization of 3,6-dichloropyridazines

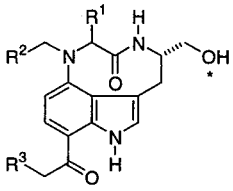


- Carboni, B. [38]
- 6 ex; 54-67%
- functionalization of resin-bound boronic acids, then transesterification

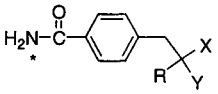
- Carboni, B. [38]
- 3 ex; 63-74%
- oxidative cleavage of resin-bound aryl boronic acids



- Chandrasekhar, S. [42]
- 6 ex; 58-72%
- reaction of resin-bound amino acids with anhydrides

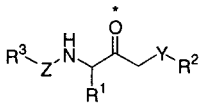


- Waldmann, H. [156]
- 31 ex; 10-65 ex
- derivatives of (-)-indolactam V; THP linker

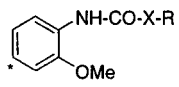


- PE Biosystems [45]
- 5 members
- C-C bond formation via Mitsunobu reaction of resin-bound alcohols and active methylene compounds

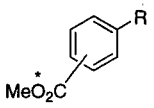
- Taddei, M. [152]
- 15 ex; 58-87%
- activation of carboxylic acid via resin-bound 2,4-dichlorotriazine



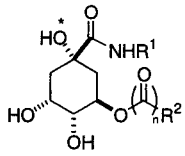
- Ellman, J. A. [138]
- 8 ex; 40-100%
- acylhydrazone linkage strategy; Z = CO, SO_2, Aa; Y = O, S, NH, NR



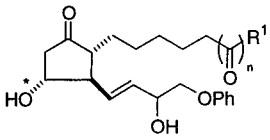
- Langlois, M. [58]
- 11 ex; 53-90%
- use of traceless silicone linker; BOC deprotection with β-catecholborane



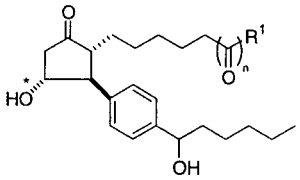
- Janda, K. D. [204]
- 15 ex; 69-99%
- Stille coupling on soluble polymer



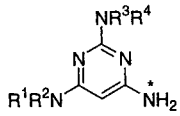
- Abell, C., W. [182]
- 12 ex; 62-92%
- derived from D-(-)-quinic acid; n = O, 1



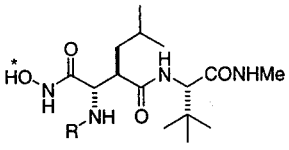
- Ellman, J. A. [65]
- 13 ex; 18-47%
- Side chains introduced via Suzuki and Michael reactions



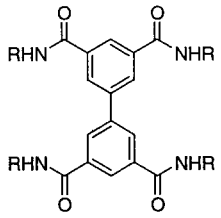
- Ellman, J. A. [65]
- 13 ex; 18-47%
- Side chains introduced via Suzuki and Michael reactions



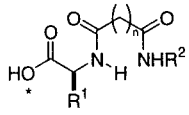
- Bradley, M. [85]
- ca, 17 ex; 11-52%
- attachment of 4,6-dichloro-2-thiomethylpyrimidine to Rink resin and sequential amination



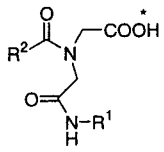
- Zeneca [10]
- ca. 30 ex; 43-100%
- attachment of dipeptide acid (R = Fmoc) to sasrin-ONH_2, deprotection and N-derivatization; R = RCO, RCO_2, RCH_2



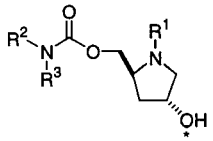
- Boger, D. L. [20]
- ca. 15 ex; 75-95%
- Coupling using 10% Pd/C, Et_3N, DMF, 100 °C, 16 h



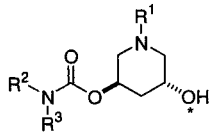
- Biochem. Pharm. [234]
- 576 members
- Pre-activation of symmetric dicarboxylic acids with BOP, then additon to resin-bound amino acid



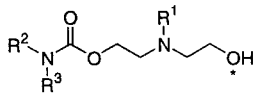
- CombiChem [48]
- 46 ex; 13-73%
- derived from iminodiacetic acid; use of soluble polymer



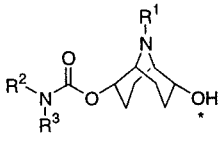
- Ibis Ther. [251]
- part of a 17,000 member library



- Ibis Ther. [251]
- part of a 17,000 member library



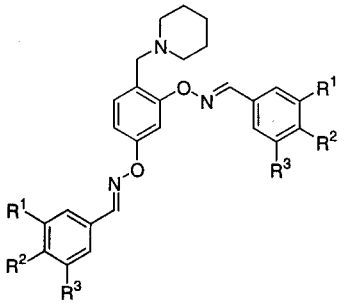
- Ibis Ther. [251]
- part of a 17,000 member library



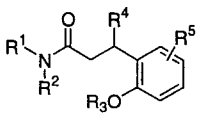
- Ibis Ther. [251]
- part of a 17,000 member library

Table 6. (Continued)

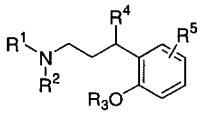
(b) Solution phase



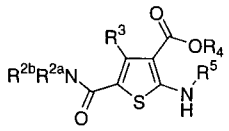
- Eliseev, A. V. [161]
- 220 members
- pair-wise condensation of ArCHO with 2,4-diaminoxyaryl



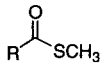
- R. W. Johnson [35]
- 300 members
- aminolysis of dihydrocoumarins



- R. W. Johnson [35]
- 5 ex; 51-84%
- aminolysis of dihydrocoumarin, then borane reduction



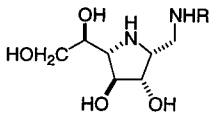
- Cadus [154]
- 3000 member library
- thiophene template derived from three-component condensation; R^3 = Me or CH_2OMe



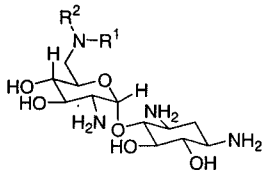
- Vulfson, E. N. [120]
- 11 ex; high purity
- from carboxylic acids, methyl chlorothiolformate and catalytic DMAP

Ar-OTf (ONf)

- Zhu, J. [23]
- 20 ex; 65-100%
- Perfluoroalkanesulfonyl transfer with polymer supported base



- Fleet, G. W. J. [142]
- 3 ex; ca. 35-50%
- derived from amino lactone

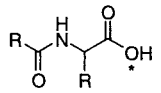


- Berrisford, D. J. [167]
- 15 ex; 26-60%
- from neamine

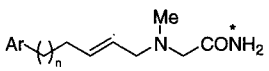
[a] Asterisk (*) indicates point of attachment to the resin.

Table 7. Acyclic Synthesis: (a) Solid Phase, (b) Solution Phase[a]

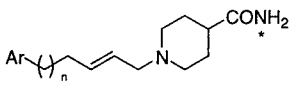
(a) Solid phase



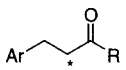
- O'Donnell, M. J. [168,169]
- 14 ex; 51-99%
- reaction of resin-bound Schiff base with organo boranes



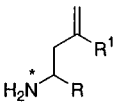
- Hoffmann-La Roche [236]
- 2 ex; 84-87%
- Pd-catalyzed three-component coupling



- Hoffmann-La Roche [236]
- 13 ex; 70-95%
- Pd-catalyzed three-component coupling

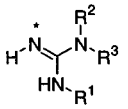


- Ganesan, A. [131]
- 26 ex; 0-49%
- sequential Baylis-Hillman and Heck reactions of resin-bound acrylic acids, then decarboxylation

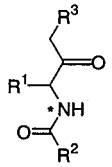


- Hiemstra, H. [155]
- ca. 40 members
- three-component condensation of resin-bound carbamate, RCHO and allylsilanes

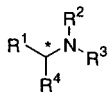
- Kobayashi, S. [6]
- 16 ex; 41-93%
- reductive alkylation of BOBA resin then acylation



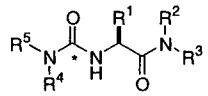
- P&G Pharm. [238]
- 8 ex; 38-74%
- use of a novel traceless linker: acyl isothiocyanate resin



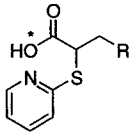
- Nielsen, J. [105]
- 18 members
- microwave assisted Ugi four-component condensation



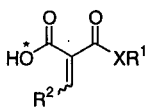
- Katritzky, A. R. [117]
- 5 ex; good yields
- from polymer-bound 1*H*-benzotriazole



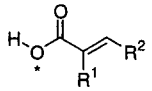
- Du Pont [92]
- 10 ex; 45-100%
- phoxime resin



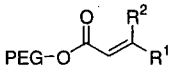
- Ganesan, A. [249]
- 5 ex; 32-94%
- intermolecular alkyl radical conjugate addition of resin-bound acrylate



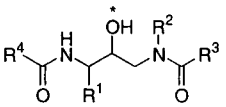
- Monsanto [91]
- 96 members
- from resin-bound malonic acid



- RPR [196]
- 48 ex; 62->95%
- Horner-Emmons olefination with resin-bound phosphonate esters

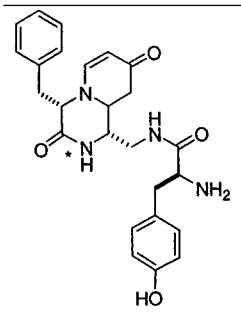


- Blettner, C. G. [18]
- 14 ex; 88-98%
- liquid-phase Horner-Emmons olefination with polymer-bound ketophosphonate and RCHO, then Heck reaction with R^2-I



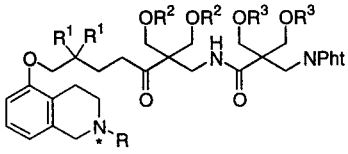
- CombiChem [248]
- 92 members
- THP linker

Table 7. (Continued)

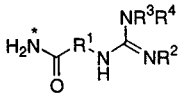


- Goodman, M. [57]
- 1 ex; 45%

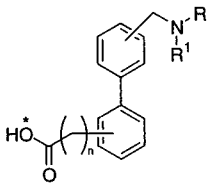
[4+2] cyclocondensation of resin-bound imine with Danishefsky diene, then intracyclative cleavage



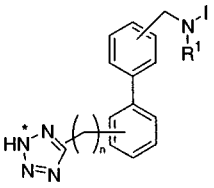
- Heinonen, P. [98]
- 96 member library
- coupling of α,α-disubstituted β-alanine units to resin-bound tetrahydroisoquinoline



- Merck [43]
- 48 ex; 11-77%
- synthesis carried out on multivarient soluble support

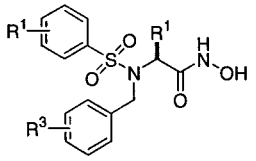


- Tripos [56]
- >150 members
- R_f tags

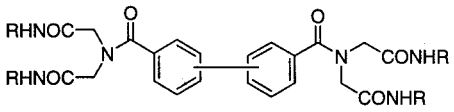


- Tripos [56]
- >100 members
- R_f tags

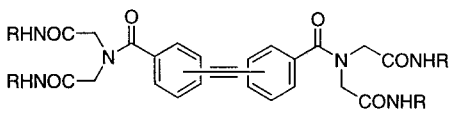
(b) Solution phase



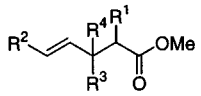
- Ley, S. V. [37]
- 27 ex; ca. 50%
- polymer-supported reagents and scavenger resins



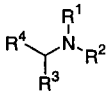
- Boger, D. L. [21]
- 64,980 members
- from N-Boc iminodiacetic acid anhydride



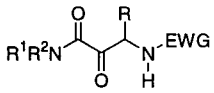
- Boger, D. L. [21]
- 64,980 members
- from N-Boc iminodiacetic acid anhydride



- Argonaut [107]
- 5 ex; 0-60%
- ester enolate Claisen rearrangement using polymer-supported silyl triflate



- Schowalter, H. D. H. [199]
- 12 ex; 20-77%
- amines from Mannich adducts of polymer-supported benzotriazole



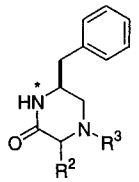
- Chiron [121]
- 10 ex; 61-85%
- ring opening of 3,3-di-OMe-N-sulfonyl and carbamoyl azetidin-2-ones, then ketal hydrolysis

- Glaxo Wellcome [173]
- ca. 21 ex; 20-50%
- resin-bound from benzotriazoles, aldehydes, and amines and alcohols; X = OR^3; NR^3R^4

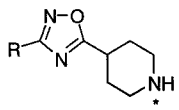
[a] Asterisk (*) indicates point of attachment to the resin.

Table 8. Monocyclic Synthesis: (a) Solid Phase, (b) Solution Phase[a]

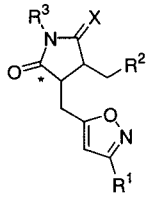
(a) Solid phase



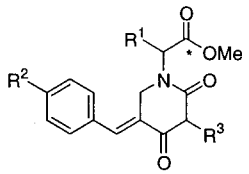
- Ibis [132]
- 4 ex; 61-90%
- ring formation via intramolecular Mitsunobu reaction of resin-bound phenylalaninol



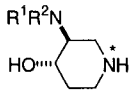
- Merck [146]
- 7 ex; 75-99%
- base-catalyzed condensation-cyclization of resin-bound esters and amidoximes



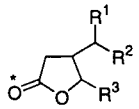
- Kurth, M. J. [176]
- 18 ex; 20-39%
- dipolar cycloaddition on resin; intracyclative cleavage; X = O, S



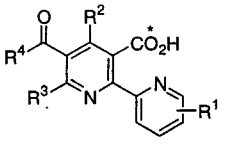
- R. W. Johnson [40]
- 5 ex; 60-72%
- Dieckmann condensation



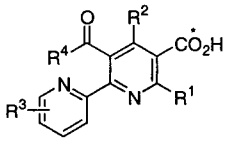
- Hoffman-La Roche [191]
- 4 ex; 53-78%
- aminolysis of resin-bound epoxide; plus regioisomer



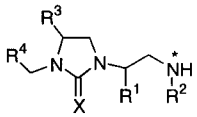
- Toru, T. [237]
- 12 ex; 47-93%
- Bu_3SnH-mediated intramolecular cyclization of resin-bound β-bromoethylacetals, then Jones oxidation



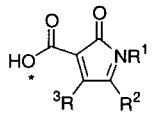
- Affymax [222]
- 7 ex; ca. 30%
- Knoevenagel-Hantzsch reaction sequence



- Affymax [222]
- 4 ex; ca. 30%
- Knoevenagel-Hantzsch reaction sequence

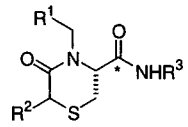


- Houghten, R. A. [164]
- 4 libraries of 118,400 members each
- $CXIm_2$-mediated ring formation from resin-bound polyamine; X = O, S

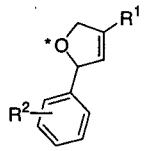


- Monsanto [157]
- 11 ex; 43-80%
- from resin-bound malonic acid and amino acid alcohols

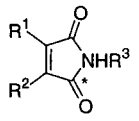
Table 8. (Continued)



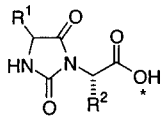
- Affymax [160]
- 7 ex; 17-65%
- intramolecular cyclization of cysteine SH and 2-bromoamide carboxylic acids, then post cleavage amidation



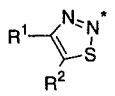
- Knochel, P. [193]
- 20 ex; 55-95%
- formation of resin-bound Grignard, addition of ArCHO, then intracyclative cleavage



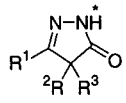
- Organon [12]
- 2 ex; 24-57%
- intracyclative cleavage of resin-bound 1,2-dicarboxylic acids



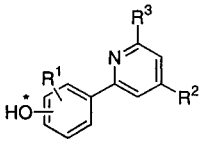
- Petillo, P. A. [58]
- 7 ex; good purity
- direct cyclization of Fmoc-dipeptides via treatment with Et_3N/TMSCl and heating



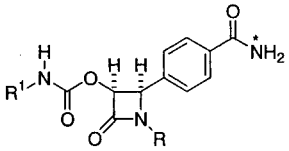
- Argonaut [106]
- 6 ex; 48-98%
- $SOCl_2$-mediated cyclative cleavage of resin-bound sulfonyl-hydrazones



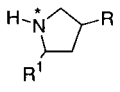
- Kobayashi, S. [125]
- 16 ex; 38-88%
- $Sc(OTf)_3$-mediated Mannich type reaction of resin-bound acylhydrazones and ketene silyl acetals, then NaOMe-mediated cyclative cleavage



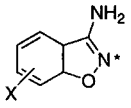
- Wyeth-Ayerst [50]
- 10 ex; 19-62%
- from resin-bound hydroxyacetophenones



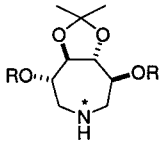
- Chiron [207]
- 12 ex; 78-89%
- Staudinger reaction using resin-bound arylimines



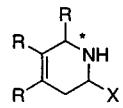
- Hiemstra, H. [231]
- 6 ex; 36-98%
- N-acyliminium ion cyclization



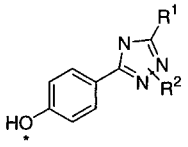
- Eli Lilly [144]
- 12 ex; 55-86%
- reaction of 2-fluoro-benzonitriles with oxime resin cleavage followed by intracyclative cleavage



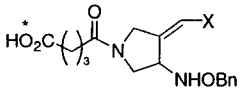
- Merrer, Y. L. [76]
- 7 ex; 53-90%
- alkylation of Rink resin with L-iditol bis-epoxide then OH-derivatization; R = H, COR, CONHR, $COCH_2NHFmoc$



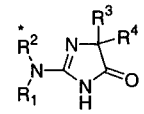
- Wang, G. [246]
- 8 ex; 52-96%
- Yb (OTf), -catalyzed aza Diels-Alder reaction with resin-bound imines; cleavage using ACE chloride; X = H, CO_2Et,



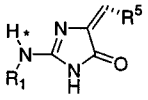
- Katritzky, A. R. [118]
- 13 ex; >95%
- reaction of resin-bound acylhydrazine with amidines, then optionally N-alkylation



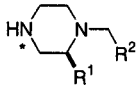
- Kobe Pharm. [159]
- 3 ex; 64-77%
- Et_3B-mediated intramolecular radical cyclization of oxime ethers



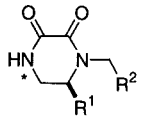
- Tularik [72]
- 8 ex; 66-97%
- reaction of resin-bound S-methyl isothioureas with Fmoc-amino acids



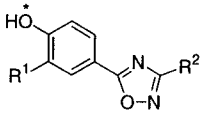
- Tularik [72]
- 5 ex; 46-91%
- reaction of resin-bound S-methyl isothioureas with oxazolones



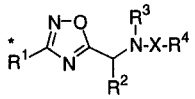
- Houghten, R. A. [162]
- 12 ex; >80%
- reduction of 1,2-diketo-piperazines derived from reduced N-acylated amino acids



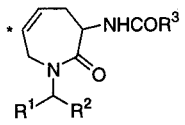
- Houghten, R. A. [162]
- 12 ex; >80%
- from resin-bound reduced N-acylated amino acids



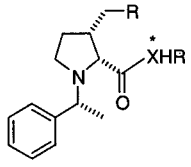
- Novo Nordisk [198]
- 16 ex; 24-40%
- cyclization of resin-bound acylated N-hydroxyamidines



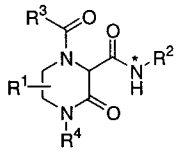
- Trega [97]
- size & yields not given
- conversion of resin-bound nitriles to amide oximes and cyclization to oxadiazoles using N-protected amino acid anhydrides; X = CO, SO_2



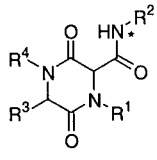
- Amgen [183]
- ca. 15 ex; 15-60%
- ring closing metathesis



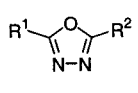
- Perrotta, E. [116]
- ca. 5 ex; high yield
- amino-zinc-enolate cyclization then derivatization



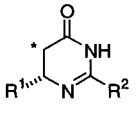
- RPR [109]
- 6 ex; 31-100%
- Ugi three-component condensation with ethyl-glyoxalate



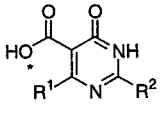
- RPR [109]
- 3 ex; 70-100%
- Ugi three-component condensation with ethyl-glyoxalate



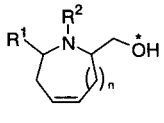
- Novartis [26]
- 16 ex; 75-98%
- dehydration of 1,2-diacylhydrazines using polymer-supported Burgess reagent



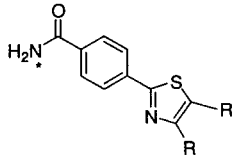
- Monsanto [90]
- 7 ex; 0-21%
- Knoevenagel condensation of resin-bound malonic ester, condensation with amidines then decarboxylation



- Monsanto [90]
- 10 ex; 49-99%
- Knoevenagel condensation of resin-bound malonic ester, condensation with amidines then oxidation with CAN

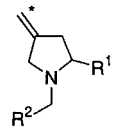


- Blechert, S. [181]
- 4 ex; > 70%
- ring formation via olefin metathesis

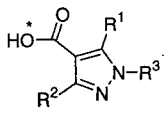


- Chiron [78]
- 4 ex; 54-97%
- Hantzch thiazole synthesis; on-resin conversion of ArCN to thioamides

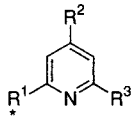
Table 8. (Continued)



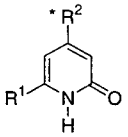
• Brown, R. C. D. [32]
• ca. 7 ex; 16-95%
• imino-Sakurai and Pd-catalyzed intra-cyclative cleavage



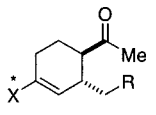
• Jung, G. [83]
• 13 ex; 41-61%
• from alkylidene-and arylidene-β-oxo esters



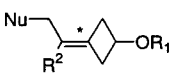
• Jung, G. [83]
• 9 ex; 72-85%
• condensation of resin-bound enones and 1-(methoxycarbonylmethyl) pyridinium bromide



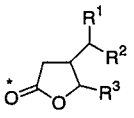
• Jung, G. [83]
• 6 ex; 71-75%
• condensation of resin-bound enones with 1-(methoxycarbonylmethyl) pyridinium bromide



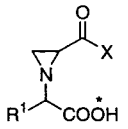
• Blechert, S. [200]
• 5 ex; 26-55%
• yne-ene cross metathesis and Diels-Alder cycloaddition then intracyclative cleavage



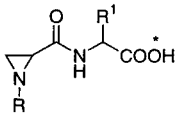
• Kurth, M. J. [49]
• 8 ex; 30-38%
• derived from resin-bound allyl sulfones



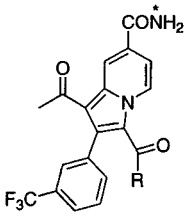
• Toru, T. [237]
• 6 ex; 47-93%
• radical cyclization of resin-bound β-bromo-ethylacetals



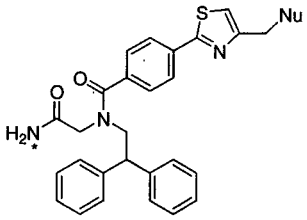
• Taddei, M. [70]
• ca. 10 ex; good yields
• Gabriel-Cromwell synthesis from resin-bound amino acid



• Taddei, M. [70]
• ca. 20 ex; good yields
• Gabriel-Cromwell synthesis from resin-bound α-bromoacrylamide

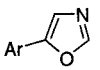


• Chiron [79]
• 9 ex; ca. 50%
• from resin-bound isonicotinic acid



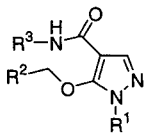
• Chiron [78]
• 8 ex; 58-95%
• Hantzch thiazole synthesis; on-resin conversion of ArCN to thioamides

(b) Solution phase

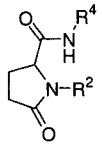


• Ganesan, A. [130]
• 10 ex; 25-50%
• reaction of polymer-supported TosMIC with ArCHO

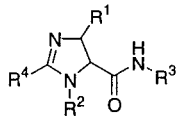
• Ganesan, A. [130]
• 13 ex; 54-85%
• condensation of TosMIC and ArCHO catalyzed by ion exchange resin



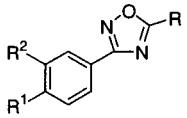
• SKB [31]
• 960 members
• from 5 unique pyrazo-linone carboxylic acids



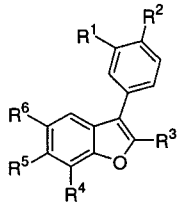
• RepliGen [245]
• 13 ex; 85-100%
• Ugi three-component condensation



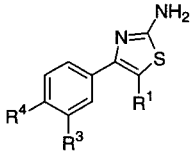
• RPR [110]
• 10,members
• Ugi four-component condensation with Boc-amino acid aldehydes, then TFA-mediated cyclization



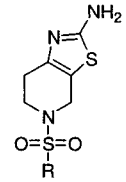
• Argonaut [61]
• 20 ex; 50-69%
• CDI-mediated formation and cyclodehydration of *O*-acylbenzamidoximes



• Ley, S. V. [88]
• 27 ex; 30-95%
• from acetophenones; use of polymer supported reagents



• Ley, S. V. [87]
• 4 ex; 47-95%
• use of scavenger reagent to mediate cyclization of α-bromoketones and thiourea

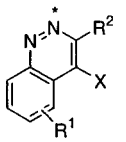


• Ley, S. V. [87]
• 4 ex; 73-95%
• use of scavenger reagent to mediate cyclization of α-bromoketones and thiourea

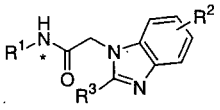
[a] Asterisk (*) indicates point of attachment to the resin.

Table 9. Bicyclic and Spirocyclic Synthesis: (a) Solid Phase, (b) Solution Phase[a]

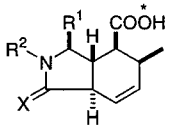
(a) Solid phase



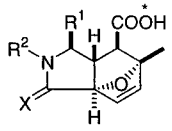
- Brase, S. [27]
- 5 ex; 47-95%
- Pd-catalyzed alkynylation of triazene bound *o*-halo arenes, HX-mediated cleavage and cyclization



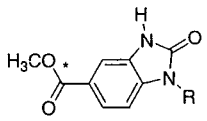
- Affymax [228]
- 12 ex; 43-80%
- nitroarylation of resin-bound glycine, nitro reduction and cyclization with R^3CHO



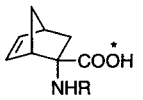
- R. W. Johnson [219]
- 5 ex; 32-55%
- intramolecular Diels-Alder reaction; X = O, 2H



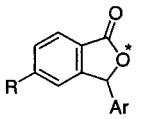
- R. W. Johnson [219]
- 5 ex; 32-55%
- intramolecular Diels-Alder reaction; X = O, 2H



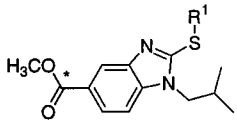
- Sun, C.-M. [174]
- 5 ex; 75-96%
- from resin-bound 4-fluoro-3-nitrobenzoic acid



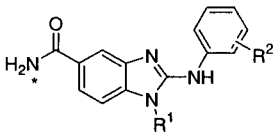
- Burkett, B. A. [34]
- 4 ex; 72-81%
- Diels-Alder reaction between resin-bound dihydroalanine and cyclopentadiene



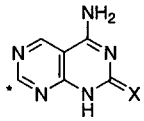
- Novo Nordisk [75]
- 8 ex; 66-81%
- resin-bound benzamide ortho-lithiation then reaction with ArCHO and intracyclative cleavage



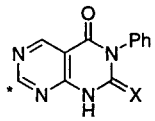
- Sun, C.-M. [240]
- 12 ex; 72-99%
- liquid-phase synthesis from immobilized 4-fluoro-3-nitrobenzoic acid



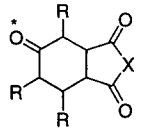
- SIDDCO [210]
- 96 ex; ca. 77%
- from resin-bound 4-fluoro-3-nitrobenzoic acid



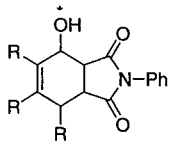
- Chauhan, P. M. S. [214]
- 2 ex; 76-80%
- from resin-bound 2-(alkylthio)-4-aminopyrimidine-5-carbonitrile; resin cleavage with Ni/H_2; X = O, S



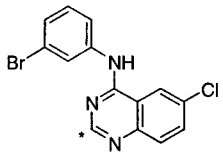
- Chauhan, P. M. S. [214]
- 2 ex; ca. 75%
- from resin-bound 2-(alkylthio)-4-aminopyrimidine-5-carboxamide; resin cleavage with Ni/H_2; X = O, S



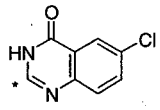
- Du Pont [208]
- 8 ex; 18-99%
- Diels-Alder reaction of resin-bound silyloxydienes derived from polymer-supported silyl triflate and unsaturated ketone; X = O, NPh



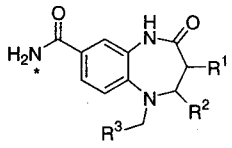
- Du Pont [208]
- 4 ex; 31-97%
- Diels-Alder reactions of resin-bound silyloxydienes derived from polymer-supported silyl triflate and unsaturated aldehyde



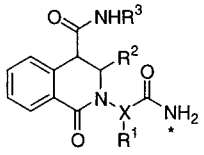
- Abell, C. [53]
- 1 ex; 69%
- reaction of 3-bromoaniline and resin-bound 4-chloroquinazolone-2-carboxylic acid, then cleavage via decarboxylation



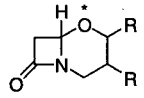
- Abell, C. [53]
- 1 ex; 64%
- condensation of resin-bound ethyl oxalate and 2-amino benzamide, then cleavage via decarboxylation



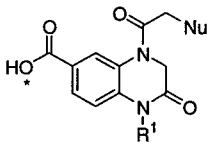
- R. W. Johnson [140]
- 35 ex; 46-98%
- from 4-fluoro-3-nitrobenzoic acid and β-amino esters



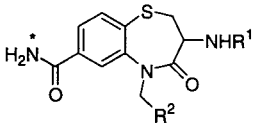
- Spyder [136]
- 380 members
- centrifuge based liquid removal



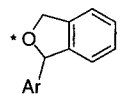
- Chmielewski, M. [73, 74]
- 2 ex; 26-30%
- intracyclative cationic cleavage



- Novo Nordisk [244]
- 6 ex; 26-43%
- from resin-bound 4-fluoro-3-nitrobenzoic acid

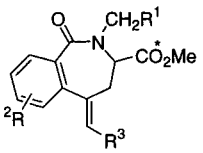


- Affymax [201]
- ca. 50 ex; ca. 50%
- S_NAr addition of cysteine to resin-bound 4-fluoro-3-nitrobenzoic acid

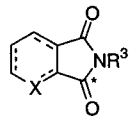


- Knochel, P. [193]
- 10 ex; 69-98%
- formation of resin-bound Grignard, addition of ArCHO, then intracyclative cleavage

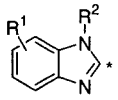
Table 9. (Continued)



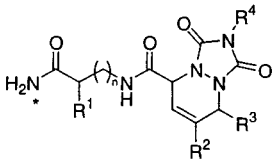
- Parke-Davis [25]
- ca. 8 ex; 34-73%
- ring formation via intramolecular Heck reaction



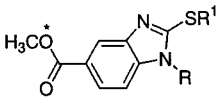
- Organon [12]
- 7 ex; 20-80%
- intracyclative cleavage of resin-bound 1,2-dicarboxylic acids



- COR Ther. [108]
- 9 ex; 85-90%
- TMOF/TFA-mediated cyclization of resin-bound anilino carbamates

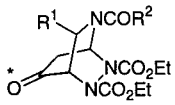


- Axys Pharm. [24]
- 10 ex; 24-82%
- [4+2] cycloaddition of resin-bound diene and urazine, then Mitsunobu to introduce R^4

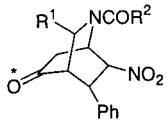


- Sun, C.-M. [241]
- 12 ex; 64-92%
- from resin-bound 4-fluoro-3-nitrobenzoic acid; soluble support

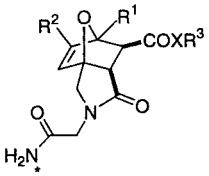
- SIBIA [46]
- 13 ex; 0-83%
- Diels-Alder reaction of resin-bound enol ether derived from N-acyl-2-substituted-dihydro-4-pyridone



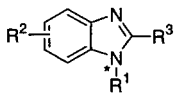
- SIBIA [46]
- 2 ex; 41-83%
- Diels-Alder reaction of resin-bound enol ether derived from N-acyl-2-substituted-dihydro-4-pyridine



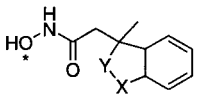
- SIBIA [46]
- 2 ex; 15%
- Diels-Alder reaction of resin-bound enol ether derived from N-acyl-2-substituted-dihydro-4-pyridine



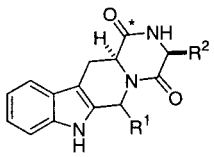
- Affymax [179]
- 14 ex; 83-98%
- intramolecular Diels-Alder reaction of resin-bound furans; X = O, NH



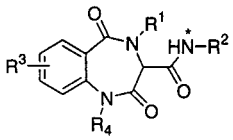
- SIDDCO [211]
- 10 ex; 30-74%
- reductive amination of resin-bound aldehyde, then N-arylation with *o*-fluoronitroaryls, NO_2 reduction, acylation, intracyclative cleavage



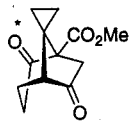
- Grigg, R. [82]
- 5 ex; 20-40%
- Pd-catalyzed intermolecular cascade reaction with aryl-iodides, CO, and resin-bound hydroxylamine



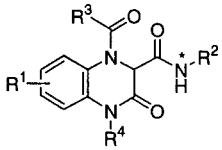
- Ganesan, A. [235]
- ca. 17 ex; 39-88%
- Pictet-Spengler condensation of N-acyliminium species prepared from resin-bound tryptophan, Fmoc-amino acid chlorides and RCHO, then Fmoc removal and intracyclative cleavage



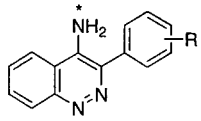
- RPR [109]
- 5 ex; 39-82%
- Ugi three-component condensation with ethyl-glyoxalate



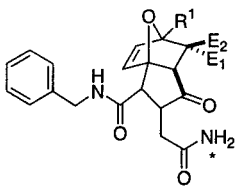
- Spitzner, D. [86]
- 1 ex; 79%
- resin-bound anionically-induced domino reactions; three derivatives also prepared



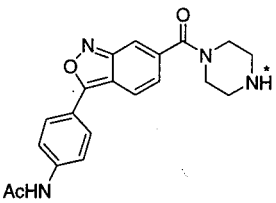
- RPR [109]
- 5 ex; 20-100%
- Ugi three-component condensation with ethyl-glyoxalate



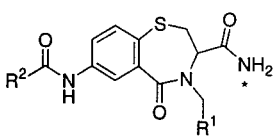
- Amgen [122]
- size and yield not given
- novel condensation from *o*-trifluorophenyl hydrazones



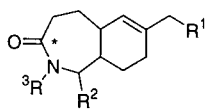
- Affymax [178]
- 6 ex; 88-95%
- tandem four-component condensation/intramolecular Diels-Alder reaction



- Novo Nordisk [216]
- 1 ex; 66%
- S_NAr displacement of 4-fluoro-3-nitrobenzoic acid amide with arylacetonitrile, then nitro reduction and cyclization

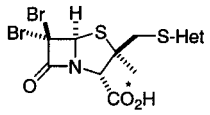


- Houghten, R. A. [163]
- ca. 4560 members
- from resin-bound cysteine and 2-fluoro-5-nitrobenzene carboxylic acid

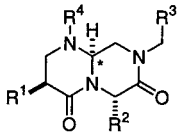


- Blechert, S. [200]
- 9 ex; 14-28%
- yne-ene cross metathesis and Diels-Alder cycloaddition then intracyclative cleavage

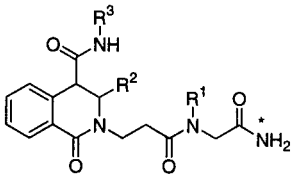
Table 9. (Continued)



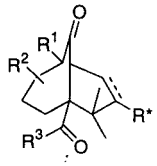
• Mata, E. G [62]
• 4 ex; 45-55%
• thermal rearrangement of penicillin sulfoxide



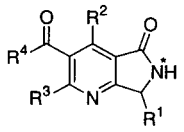
• Molecumetics [67]
• 11 ex; 22-71%
• acyliminium cyclization



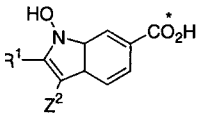
• Spyder [137]
• 30,816 members
• from resin-bound imine and homophthalic anhydride



• Nicolaou, K. C. [166]
• ca. 15 ex; 21-98%
• Se-mediated cyclization using polymer-supported reagent

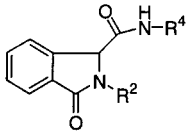


• Affymax [16]
• 4800 members
• sequential Hantzch condensation and intracyclative cleavage

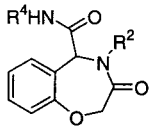


• Novo Nordisk [216]
• 3 ex; 39-74%
• S_NAr displacement of resin-bound 4-fluoro-3-nitrobenzoic acid with 1,3-dicarbonyls or acetonitriles, then nitro reduction and cyclization

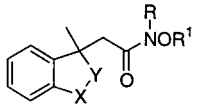
(b) Solution phase



• RepliGen [245]
• 13 ex; 75-100%
• Ugi three-component condensation



• RepliGen [245]
• 13 ex; 56-91%
• Ugi three-component condensation

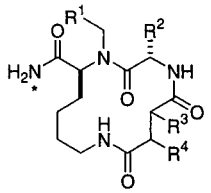


• Grigg, R. [82]
• 10 ex; 21-89%
• Pd-catalyzed intramolecular cascade reaction with *o*-iodo aryl ethers, CO, and protected hydroxylamines

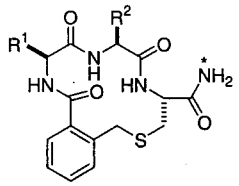
[a] Asterisk (*) indicates point of attachment to the resin.

Table 10. Polycyclic and Macrocyclic Synthesis: (a) Solid Phase, (b) Solution Phase[a]

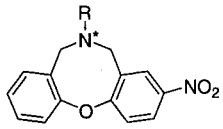
(a) Solid phase



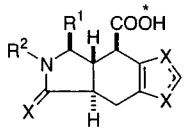
• SKB [133]
• 11 ex; 68-99%
• macrocyclization of lysine ε-NH_2 and succinamide carboxylic acid



• Burgess K. [69]
• 13 ex; 15-44%
• intramolecular cyclization of cysteine and benzylbromide

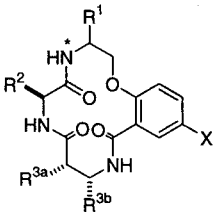


• Amgen [171]
• 5 ex; 38-53%
• reductive alkylation of resin-bound β-alanine with 2-fluoro-5-nitrobenzaldehyde and 2-hydroxybenzaldehyde, then intramolecular cyclization, cleavage, and N-alkylation

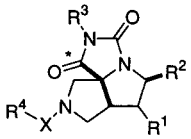


• R. W. Johnson [219]
• 2 ex; 36-37%
• intramolecular Diels-Alder reaction; X = CH, O; Y = O, 2H

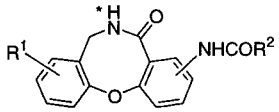
Table 10. (Continued)



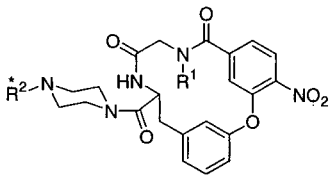
• Ibis Ther. [112]
• 26 ex; good purity
• intramolecular ether formation via nucleophilic aromatic substitution; X = NO_2, NHR^4



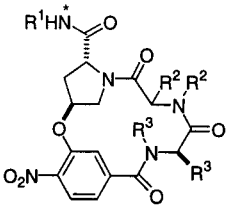
• Affymax [180]
• 12 ex; 14-34%
• intramolecular azomethine ylide cycloaddition and intracyclative cleavage



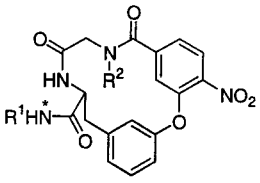
• Amgen [170, 172]
• 15 ex; 55-87%
• S_NAr cyclization from resin-bound phenols and 2-fluoro-5-nitrobenzoic acid



• Amgen [123]
• 20 ex; 52-68%
• S_NAr reaction

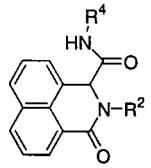


• Amgen [80]
• 18 ex; 55-78%
• S_NAr intramolecular cyclization of 4-OH-Pro

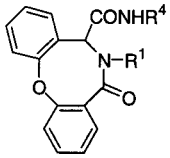


• Amgen [124]
• 30 members
• S_NAr cyclization

(b) Solution phase



• RepliGen [245]
• 13 ex; 38-64%
• Ugi three-component condensation



• RepliGen [245]
• 13 ex; 19-42%
• Ugi three-component condensation

[a] Asterisk (*) indicates point of attachment to the resin.

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