Review

Comprehensive Survey of Combinatorial Library Synthesis: 1998

Roland E. Dolle, and Kingsley H. Nelson

J. Comb. Chem., **1999**, 1 (4), 235-282• DOI: 10.1021/cc9900192 • Publication Date (Web): 13 July 1999

JOURNAL OF combinatorial CHEMISTRY

Volume 1, Number 4 July/August 1999

Reviews

Comprehensive Survey of Combinatorial Library Synthesis: 1998

Roland E. Dolle* and Kingsley H. Nelson, Jr.

Department of Chemistry, Pharmacopeia, Inc., CN 5350, Princeton, New Jersey 08543-5350

Received April 29, 1999

The art of solid-phase and solution-phase organic synthesis as applied to the assembly of chemical libraries is widely practiced in many academic and industrial laboratories throughout the world. Introduced in this decade, combinatorial chemistry, in its various formats, is now regarded as an important component of the drug discovery process. It is avidly employed by the biotechnology and pharmaceutical industry for this purpose. A previous comprehensive review provided a historical account of chemical libraries from which biologically active agents were obtained.[1] A total of 86 citations were compiled covering the years 1992 through 1997. In this 1998 annual update, there are 74 new citations,[2−63] nearly equivalent to the cumulative total of published biologically active libraries for the preceding six years. This past year, more so than any other, was marked by the coapplication of library design and synthesis with molecular modeling and structure-based design. The first example of a compound, coming directly from an optimization library (solid-phase parallel synthesis), exhibiting biochemical efficacy and oral bioavailability was described.[58] Traditionally carried out on solid support, the use of solution-phase techniques for library generation is gaining momentum as ca. 30−40% of the 1998 libraries utilized solution-phase protocols. Because many more libraries are published annually without associated biological data and are of equal interest to the combinatorial and medicinal chemical communities, a compilation of these types of constructs is included in this review. In 1998, there were 247 libraries of this genus.[64−257]

* To whom correspondence should be addressed. Tel: 609-452-3739. Fax: 908-422-0156. E-mail: roland@pharmacop.com.

Library Descriptions

In keeping with the format of the previous review,[1] the biologically active libraries are segregated into five principal categories. Tables 1 and 2 list those libraries active against proteolytic and nonproteolytic enzymes, respectively. Table 3 lists libraries yielding agonists and antagonists of G-protein coupled receptors (GPCRs). Tables 4 and 5 delineate libraries active against non-GPCR targets (e.g., integrins, ion channels, domain interactions, nuclear receptors, and transcription factors) and whole-cell oncology and antiinfective targets. The name, generic structure, and affiliation is given for each library. The affiliation indicates whether the library was prepared in industry (company name), academia or another institution (senior author). The size of each library is also indicated, although it should be noted that the reported library size does not necessarily reflect confirmed library size. Each library is accompanied by the name of the molecular target against which it was evaluated and by the structure and potency of the most active library member. Each library is referenced with an entry code, e.g., library 4.11 refers to library entry 11 in Table 4.

In addition to the tabulations of biologically active libraries, an effort has been made to compile a list of libraries with undisclosed biological activity. These libraries, loosely defined as a multistep reaction sequence typically exemplified by >5 examples or members, are divided into five categories composing Tables 6−10. Table 6 entitled "Scaffold Derivatization" lists library constructs in which an existing scaffold or template is derivatized to provide a library. The addition of three nucleophiles to cyanuric chloride or Suzuki coupling of an aryl boronic acid to a resin-

10.1021/cc9900192 CCC: $18.00
Published on Web 07/13/1999

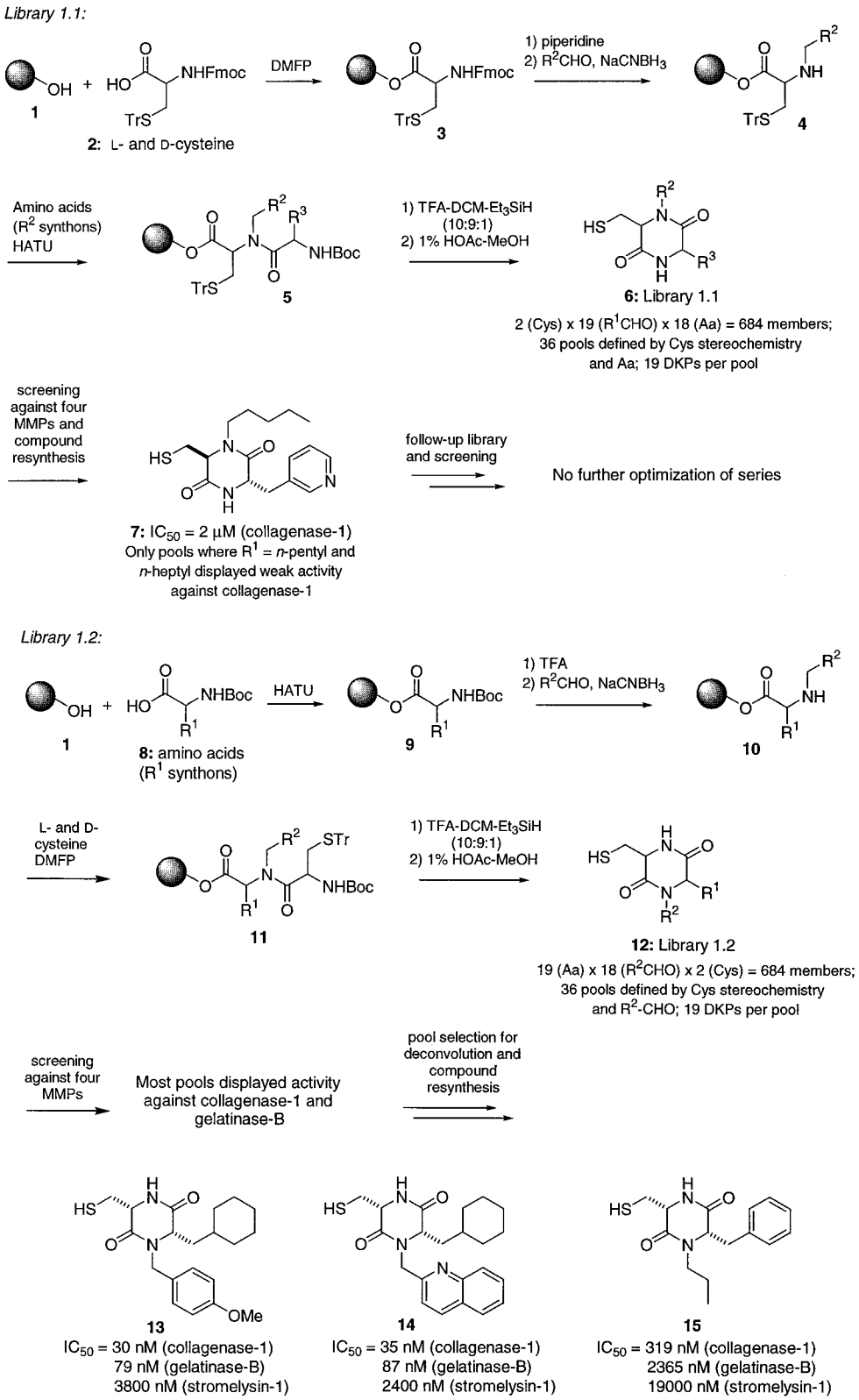


Figure 1. Affymax 3-thiomethyl-2,5-diketopiperazine libraries 1.1 and 1.2 as inhibitors of MMPs.[47]

bound aryl iodide yielding a biaryl are examples of these types of constructs. Table 7 delineates the preparation of acyclic libraries, perhaps via a multicomponent condensation reaction (e.g., Ugi or Passerini reaction). Tables 8−10 include library constructs defined by monocyclic ring synthesis (e.g., Hantzsch thiazole synthesis), bicyclic and spirocyclic ring synthesis (e.g., indole synthesis, Knoevenagel condensation yielding coumarins), and polycyclic (tetrahydro-β-carboline synthesis) and macrocyclic ring synthesis. Each table in turn is further subdivided into solid-phase and solution-phase synthesis. The affiliation, size (given by number of examples and corresponding yield or number of members if yield data was unavailable), and a brief descriptive note are indicated for each library. Single synthetic transformations, polypep-

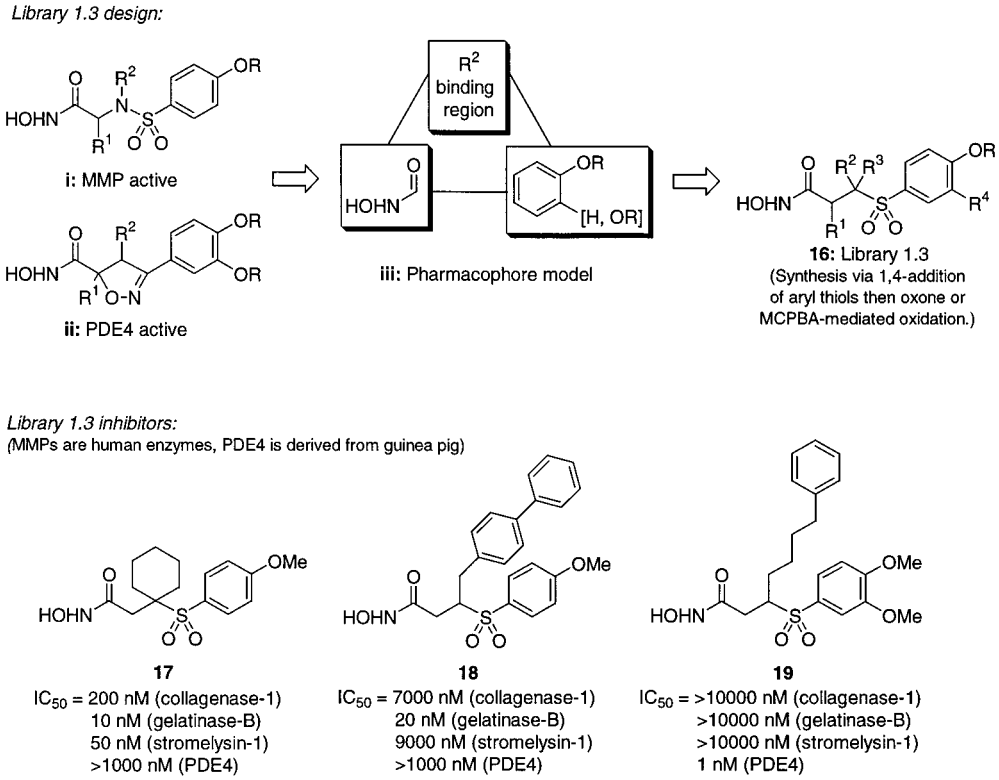


Figure 2. MMP and PDE4 selective inhibitors from the hydroxamate library 1.3.[10]

tide-, polysaccharide-, and oligonucleotide libraries, and libraries for nondrug discovery applications (e.g., catalysts) are generally not included in the tables.

Libraries Yielding Proteolytic Enzyme Inhibitors

Libraries directed toward the inhibition of proteolytic enzymes are listed in Table 1 (libraries 1.1−1.19). A common design strategy centers upon a mechanism-based approach to protease inhibition, i.e., the incorporation of a well-known pharmacophore into a suitable scaffold as a means to elicit potency and selectivity against a particular mechanistic class of protease. Pharmacophores utilized in library design include the following: thiols and hydroxamic acids for the metalloproteases (libraries 1.1−1.3); hydroxyethylamine- and statine-based transition-state isosteres for the aspartic acid proteases (libraries 1.4−1.6); arginine-, lysine-, and amidine-containing ligands and aminimides for the trypsin superfamily of serine proteases (libraries 1.8−1.17); and acyloxymethyl ketones and acyliodides (irreversible inactivators) for cysteine proteases (libraries 1.18 and 1.19).

Affymax described two novel series of 3-thiomethyl-2,5-diketopiperazines (DKP) as inhibitors of the matrix metalloproteases (MMPs, libraries 1.1 and 1.2; Figure 1).[47] The selection of this heterocyclic scaffold was arrived at by comparative overlap of a number of heterocycles with a pharmacophore model derived from crystal structures of succinyl hydroxamate inhibitor-MMP complexes. The DKP scaffold was hypothesized to orient its thiomethyl group toward the catalytic zinc atom and direct the R^1 and R^2 appendages into the S_1' and S_2' binding subsites. There also existed the potential for hydrogen bond formation between the scaffold's heteroatoms and the active site of the enzyme, an essential feature of the tight-binding succinyl hydroxamate inhibitors. Split-pool synthesis of the DKP inhibitor libraries (36 pools, 19 DKP inhibitors per pool) was straightforward, except that a rather unique coupling reagent, 1,3-dimethyl-2-fluoropyridinium 4-toluenesulfonate (DMFP), was used to minimize epimerization of the optically active cysteine amino acid synthons during the coupling steps.

Inhibition of collagenase-1 was observed in library 1.1 in only a few pools where R^1 = *n*-heptyl and *n*-pentyl, e.g., DKP **7** (IC_{50} = 2 μM). A follow-up library was prepared (details not given) based on the limited structure−activity relationship (SAR) data obtained from the initial screening of the library; however, no further improvement in activity for this series of DKPs was obtained.

In contrast to library 1.1, the regioisomeric DKP library 1.2 displayed broad activity against collagenase-1 and gelatinase-B. The library was essentially devoid of inhibitory activity against stromelysin-1 or matrilysin. Deconvolution of one of the more active pools (library 1.2, R^2 = CH_2-(4-OMe-phenyl) and resynthesis of individual library members provided novel MMP inhibitors, **13**−**15**. Nascent SAR obtained from library screening results and resynthesized compounds indicated a very strict dependence of activity on the thiomethyl and R^1 stereochemistries, limited tolerance for variations at R^1, and rather broad tolerance for functionality at R^2.

Hydroxamic acid library 1.3 was designed and synthesized at Rhone-Poulenc Rorer following in-house observations that *N*-sulfonylamino hydroxamates **i** and dihydroisoxozole hydroxamates **ii** are inhibitors of MMPs and phosphodiesterase-4 (PDE4), respectively (Figure 2).[10] The apparent SAR data suggested that the two mechanistically distinct enzymes may share common pharmacophore elements as depicted in **iii**. Library synthesis of single compounds (>300

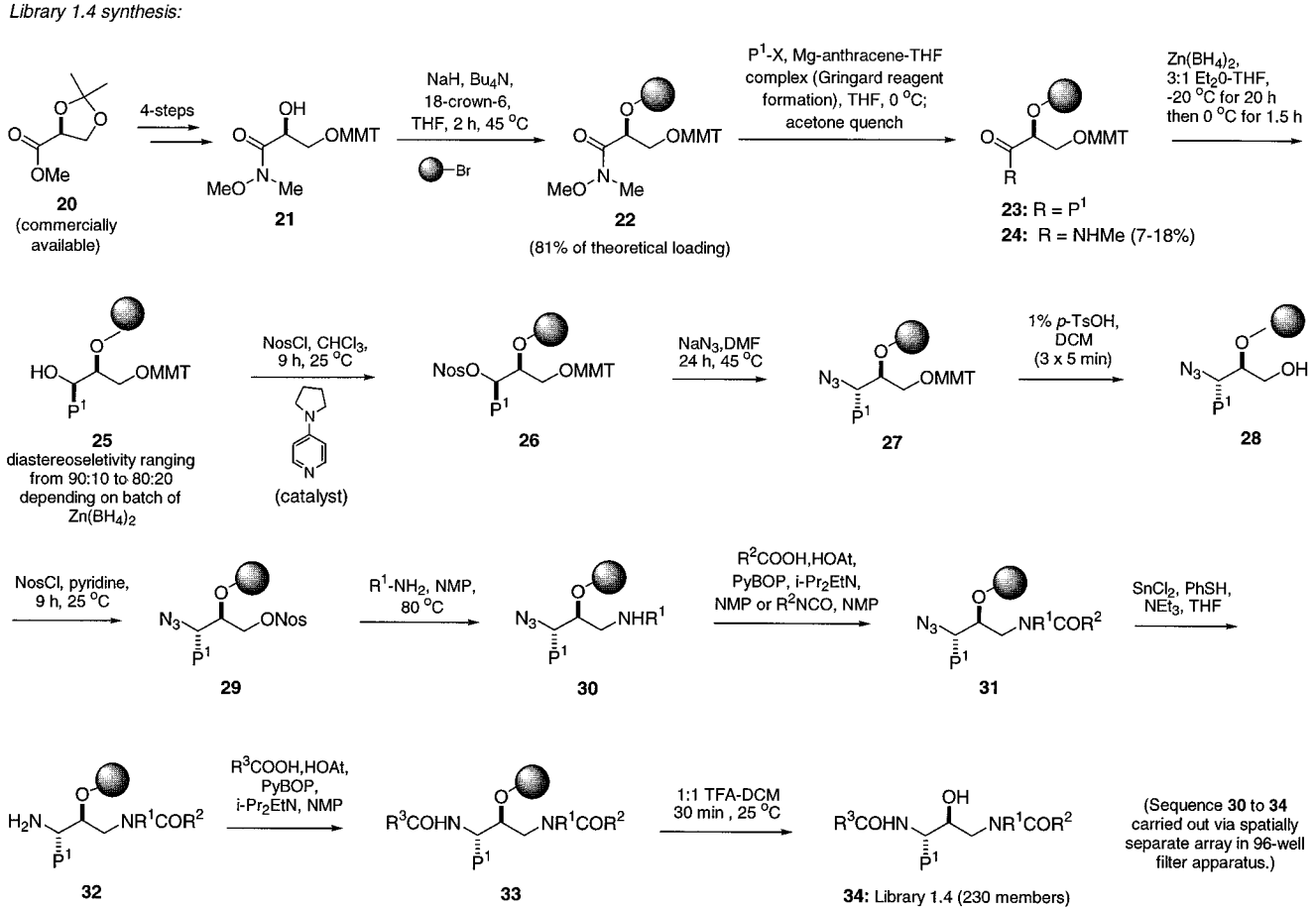


Figure 3. Ellman's library synthesis of mechanism-based inhibitors of aspartic acid proteases.[26]

compounds) was conducted using both solution- and solid-phase methods. Potent and selective inhibitors of each enzyme class were obtained upon in vitro evaluation of the library. Remarkably, there was a striking dependence of target selectivity on the arylsulfonyl moiety; nanomolar potency for either the MMPs or PDE4 could be modulated by a single *m*-methoxy substituent (**17** and **18** versus **19**; hydrophobic R^2R^3 not withstanding). The MMP enzymes were of human origin, while the PDE4 enzyme was obtained from guinea pig. It would be of interest to determine whether a similar SAR trend would be observed among enzymes of the same species.

Ellman published a full paper on the design and synthesis of hydroxyethylamine-based aspartyl protease transition-state isosteres, concluding a multiyear research endeavor.[26] An elegant 12-step synthetic sequence was developed on solid phase which provided full access to diversity at the P^1 side chain (R^1), the terminal amino appendages, and chirality at the secondary hydroxyl and amino groups (Figure 3). This was achieved without the use of amino acids as a source of chirality. The generality of the sequence was demonstrated by the construction of a 230-member library (library 1.4). The library synthesis began with a four-step solution synthesis of Weinreb amide **21** derived from commercially available, optically active isopropylidene glyceric acid methyl ester **20**. The selection of the monomethoxytrityl group for primary hydroxyl group protection in **21** was based upon the ability to remove this protecting group under mild acidic conditions that would not cleave material from the acid-sensitive linker, and its strong UV chromophoric property which made it convenient to monitor spectrophotometrically. Attachment of **21** to the resin was carried out by the reaction of a resin bromide (prepared from Wang resin, Ph_3P, CBr_4 in DCM) with the sodium anion of **21** in THF (**21** → **22**). Resin **22** was reacted with one of 17 Grignard reagents to provide the corresponding ketones **23**. The alkyl Grignard reagents were prepared in the standard way, while the more reactive benzylic-type Grignard reagents were prepared via the addition of the benzylic halide to a solution of magnesium-anthracene-THF complex in THF. A byproduct obtained during the Grignard addition was the *N*-methyl amide **24** (up to 18%), formed by competitive N−O bond cleavage. Chelation-controlled reduction employing $Zn(BH_4)_2$ converted ketone **23** to the alcohol **25** with diastereoselectivities ranging from 90:10 to 80:20, with the ratio apparently independent of the P^1 group but rather dependent upon the batch of freshly prepared $Zn(BH_4)_2$ used for the reduction. Considerable solid-phase reaction optimization was required to convert alcohol **25** to azide **27**. Standard Mitsunobu reactions employing $(PhO)_2P(O)N_3$, HN_3, or $Zn(N_3)_2$-bis pyridine complex were unsuccessful. Ultimately, alcohol **25** was activated as its 4-nitrobenzenesulfonyl ester **26** using 4-pyrrolidinopyridine as the catalyst in chloroform. The choice of catalyst and solvent were critical as the poor conversion was observed with mesyl or tosyl esters in solvents other than chloroform, and DMAP salts readily precipitated into reaction sites on the resin. Displacement of the nosyl group in **26** with NaN_3 (**26** → **27**) was without

complications, (<5% nosyl elimination products). The MMT protecting group in **27** was readily removed and the resulting primary alcohol **28** then converted to its nosyl derivative (**27** → **29**). All scaffolds were cleaved at this stage and characterized. Library synthesis was completed by reaction of **29** with a selection of R^1 amines (**29** → **30**), acylation with R^2 functionality (**30** → **31**), followed by reduction of the azido group, acylation with a series of R^3 carboxylic acids, and TFA-mediated cleavage of the inhibitors from resin (**32** → **34**). The selection of the R^1-R^3 derivatizing reagents was reviewed previously.

Library 1.4 was evaluated against human liver cathepsin D, and resynthesis of the more potent inhibitors was carried out. Several of the inhibitors had a K_i of <5 nM, with structure−activity tracking to the more hydrophobic (arylalkyl) P^1 side chains.

Pharmacopeia described two encoded aspartic acid inhibitor libraries 1.5 and 1.6 exploiting the statine pharmacophore in library design.[11,12] The libraries were prepared and evaluated against plasmepsin II, one of two aspartyl proteolytic isozymes required for hemoglobin metabolism in the malarial parasite. An encoded mixture of 21 Boc-protected statine amides **40** (derived from 7(R^1) amines × 3(R^2) Boc-statines) served as a common encoded intermediate for the libraries (Figure 4). For library 1.5,[12] encoded intermediate **40** was deprotected and apportioned into 31 lots, and then each lot was coupled with one of 31 Fmoc-protected amine amino acids (R^3 synthons corresponding to the P^2 residue; **40** → **41**). The resin lots were encoded with molecular tags and combined. The combined resin was treated with piperidine to remove the Fmoc protecting group, and then the resin was divided into 20 lots. Each lot was reacted with one of 20 N-derivatizing reagents (R^4 synthons), yielding **42** (library 1.5) as 20 sublibraries containing 651 compounds per sublibrary for a total of 13 020 members (**41** → **42**). Library 1.5 was evaluated (off-bead, solution screening (**43**) against plasmepsin II). The results of the assay revealed that 10 of the 20 sublibraries displayed inhibitory activity against the enzyme. A total of some 60 beads were decoded across the 10 sublibraries, revealing the preference for hydrophobic synthons at R^1 and R^4 and for hydrophobic P^1 statines (leucine or phenylalanine statine) at R^2. The more basic R^1 amines and alanine statine were not observed in the decoded structures. Interestingly, *only two* amino acids, isoleucine and valine, out of the potential 31 amino acids were seen at R^3. This result may argue for β-branched amino acids as P^2 specificity determinants for the enzyme. A counter screen was conducted against cathepsin D, a human lysosomal aspartyl protease. Similar R^1, R^2, and R^4 preferences were observed for this enzyme in addition to a much broader frequency of R^3 (P^2) amino acid residues. A total of 18 compounds were resynthesized, and inhibition constants (K_i) were determined against each enzyme. Inhibition constants ranged from 50 nM to >30 μM, with inhibitors **44**−**47** representative of the more active and selective agents. Inhibitor **45** was also active in malaria cell culture at ca. 10 μM.

Library 1.6 employed cyclic diamino acids as R^3 synthons in place of the R^3 amino acids used in library 1.5 (Figure 4).[11] A selection of heterocyclic peptidomimetics were docked into the active site of plasmepsin, and it was determined that piperazine carboxylic acids **48** and **49** and, possibly, 4-aminoproline **50** were potential surrogates for the P^2 amino acid residue. Encoded intermediate **40** was deprotected and apportioned into three resin lots. Each lot was coupled to one of three orthogonally protected diamino carboxylic acids (**40** → **51**). After an encoding step, the resins were combined, the Boc group was removed, and the corresponding amino resin was divided into 15 lots. Each lot was either acylated with one of six carboxylic acids or reductively aminated with one of nine aldehydes (15 R^4 synthons in total; **51** → **52**). Following a fourth encoding step, the resins were once again combined, the Alloc group was removed, and the resin was reapportioned into 20 lots. These lots were derivatized with one of 20 carboxylic acids yielding **53** (library 1.6) as 20 sublibraries with 945 compounds per sublibrary for a total of 18 900 members. Evaluation of library 1.6 (off-bead assay, **53** → **54**) against malarial plasmepsin II and the counter screen, human cathepsin D, followed by decoding of some 100 active beads, revealed preferences for hydrophobic R^1 and R^2 synthons analogous to library 1.5. Of the three diamino acid scaffolds (R^3 synthon), there was a high frequency found for the piperazine carboxylic acids **48** and **49** in the decoded structures. Inhibition constants (K_i) for four resynthesized compounds were reported, with inhibitors **55** and **56** representative of the screening results.

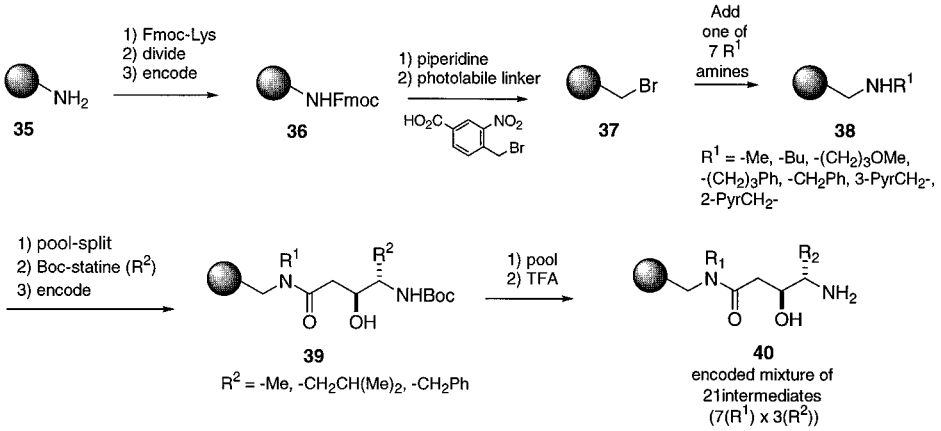
Three libraries 1.8−1.10 were reported to display activity against factor Xa.[20,31,39] Two of the libraries utilized heterocyclic cores in their design: a triazine core (library 1.8)[20] and the 3,5-difluoro-4-trifluoromethylpyridine core (library 1.9).[31] Each library was prepared from their respective halogenated templates. The third library 1.10 was a collection of L-octapeptides.[39]

Library 1.9 is a focused library based on the previously known bisamidine **57** (K_i = 13 nM, Figure 5).[31] Its purpose was to identify a replacement for one of the benzamidine groups in **57** so as to enhance the overall drug-like characteristics of the series. Library 1.9 was moderately successful in its task. Modest inhibitors **59** (K_i = 560 nM) and **60** (K_i = 495 nM) were obtained. Structurally related compounds **61** and **62** were inactive against the enzyme.

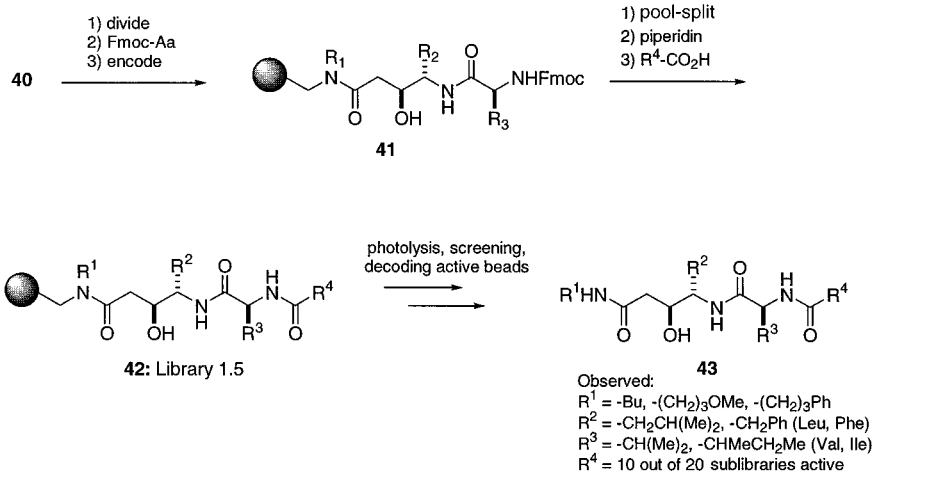
Selectide Corporation conducted an on-bead screening assay for factor Xa inhibition using a large L-octapeptide library (Figure 6).[39] Active beads (colored) were manually retrieved from the assay, and the structures of the associated peptides were determined via Edman degradation. Among the active beads, the sequence -L-Tyr-L-Ile-L-Arg- was highly conserved at or near the N-terminus. Interestingly, this same sequence is known as a minimal inhibitory sequence for factor Xa. Resynthesis of actives revealed a family of octapeptides with micromolar inhibitory activity against factor Xa (K_i = 4−15 μM, e.g., **63**). Further modification of the series led to the pentapeptide **64** (K_i = 3 nM) as a potent and selective inhibitor of factor Xa.

Serine proteases typically bind their pseudo-substrates and inhibitors as an extended antiparallel β-strand. By comparative analysis of enzyme inhibitor crystal structures, with

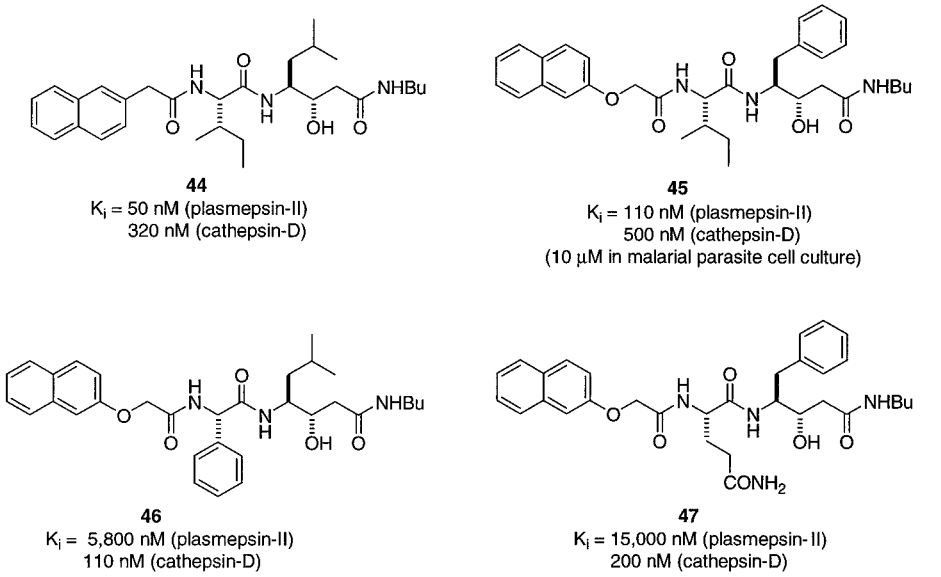
*Synthesis of encoded intermediate **40** common to both libraries:*



Library 1.5 synthesis:



Library 1.5 actives:



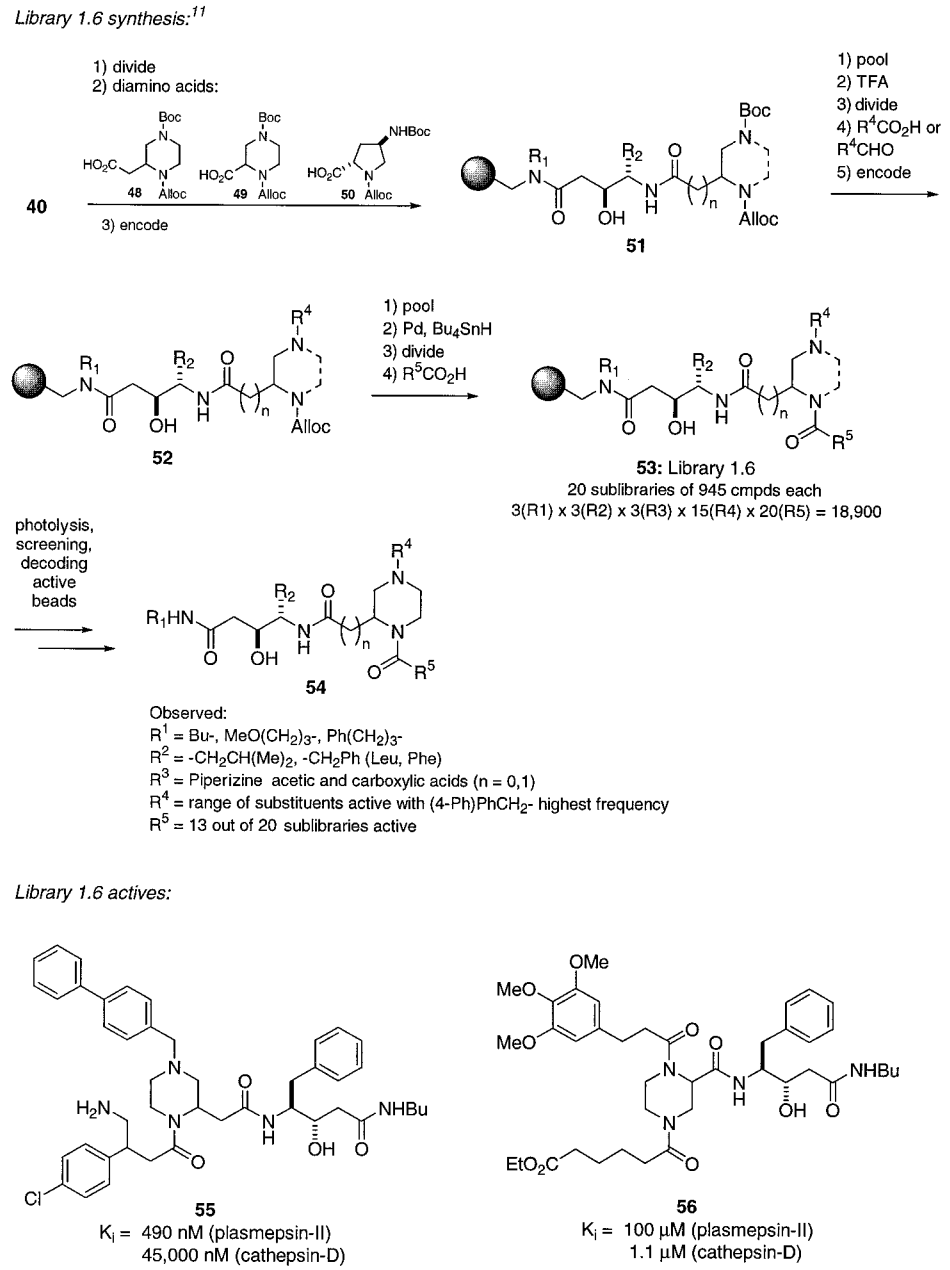


Figure 4. Pharmacopeia's encoded statine-based aspartyl protease inhibitor libraries 1.5 and 1.6.[11,12]

conformational searches carried out on potential β-strand mimetics, libraries 1.11 and 1.12 containing putative bicyclic β-strand mimetics were conceived.[38] The libraries were prepared via the Diels−Alder reaction between resin-bound diene **65** and dienophiles **66** and **70** followed by oxidation to install an α-keto amide function (**65** → **67**; **65** → **71**; Figure 7). The bicyclic template was thought to form three critical hydrogen bonds found at the active site of serine proteases, while the reactive carbonyl (α-keto amide) was designed to engage the active site serine hydroxyl group. Evaluation of the two libraries against thrombin revealed three subnanomolar inhibitors **68**, **72**, and **73**, and related inhibitor **69**.

The Merck proline amide libraries 1.14 and 1.15 represent interesting case studies for successful lead optimization through solid-phase synthesis (Figure 8). Inhibitors **74** and **75** were peptidomimetic leads identified in a thrombin inhibitor discovery program. Although potent and selective, neither inhibitor displayed significant blood levels upon oral administration to rats and dogs. In an effort to identify analogues with improved pharmacokinetic properties, leads **74** and **75** were subjected to optimization via a parallel solid-phase synthesis. Library 1.15[28] was designed to identify less basic thrombin inhibitors. A small series of analogues (18 proline amides) were prepared in which the cyclohexylamine moiety in **75** was exchanged for neutral, lipophilic species. Evaluation of library 1.15 revealed inhibitors **77** (K_i = 40 nM) and **78** (K_i = 3 nM) possessing the lipophilic 2,5-dimethyl and 2,5-dichlorobenzyl amido groups.

Complementary to library 1.15, library 1.14 explored SAR in the region of the acylated proline nitrogen. In this optimization library, 200 new analogues of inhibitor **74** were synthesized. The N-acylating reagents were carefully selected from a combined commercial and in-house collection of over 2 200 carboxylic acids. Substructure features of particular interest included aromatic or hydrophobic moieties, con-

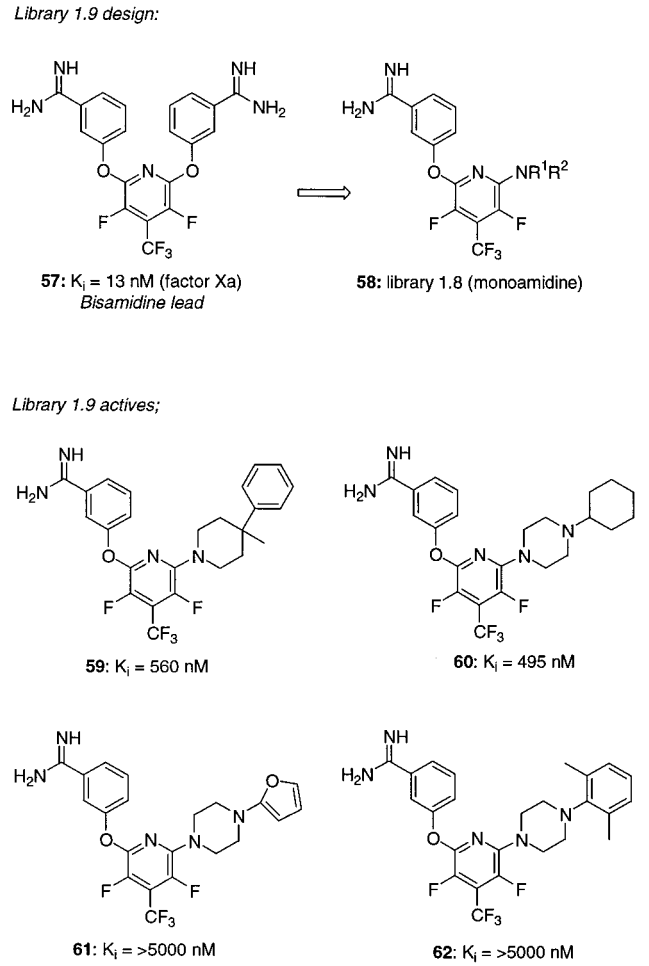


Figure 5. Amidinopyridines as factor Xa inhibitors.[31]

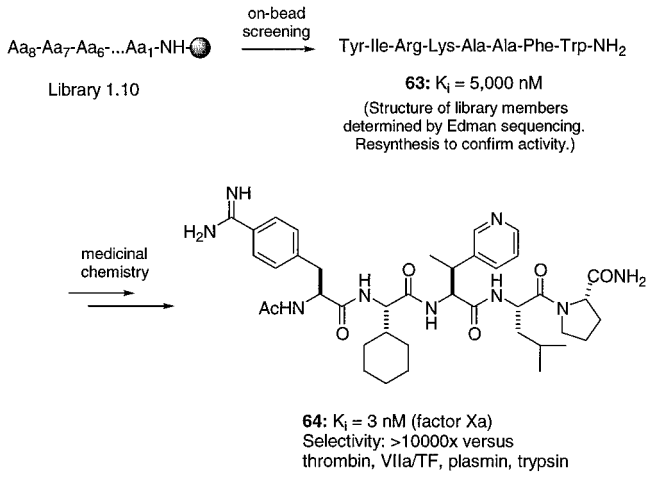


Figure 6. Selectide's factor Xa inhibitor library 1.10.[39]

straints or conformational reinforcements affording directional diversity, heteroatoms to access potential H-bonding, and achirality to structurally simplify the lead. A number of structurally novel inhibitors were identified upon bioassay. Compound **76** proved to be a highly potent and selective inhibitor and fully efficacious in a rat model of $FeCl_3$-induced arterial thrombosis. The oral absorption of **76** was excellent in the dog (74% at 5 mg/kg, C_{max} = 4.6 μM at 40 min, i.v. plasma half-life ca. 2 h) and cynomologus monkey (39%, C_{max} = 1.77 μM at 113 min, i.v. plasma half-life ca. 4 h). The unique, putative binding interactions of **76** with enzyme were also determined via a molecular model of **76** created using the X-ray coordinates of thrombin-**74** complex. This is the first reported, successful example of improving a lead's pharmacokinetic parameters via analogue synthesis on solid support.

A solution-phase synthesis of aspartic acid-based acyloxymethyl ketones was reported by a Parke-Davis group (library 1.18; Figure 9).[52] The two-step reaction sequence (**79** → **82**) was optimized in 3−4 days via a nonlinear array where over 200 different reaction conditions were evaluated. Some 82 different reaction conditions alone were carried out to optimize the displacement of the bromide in Z-Asp(O-*t*-Bu)CH_2Br with naphthyl acetic acid. Excess bromomethyl ketone was removed from the reaction mixture using a thiourea scavenging resin. Optimal deprotection of the β-*tert*-butyl ester Asp side chain to provide the free β-carboxyl group was examined via 40 reaction conditions. Classical TFA-mediated deprotection in CH_2Cl_2 was found inferior to 1 M HCl in EtOAc. The optimized reaction conditions were then applied to library synthesis **83** → **86**. Compounds of this class are known interleukin-1β converting enzyme (ICE) inhibitors, and IC_{50}/K_i values for five resynthesized compounds were reported.

Libraries Yielding Nonproteolytic Enzyme Inhibitors

Table 2 lists 13 libraries (2.1−2.13) targeted for nonproteolytic enzymes. These are subdivided into kinases (library 2.1 (tyrphostin analogues), library 2.2 (phosphonates), and library 2.3 (purines)) and phosphatases (library 2.4 (α,α-difluorophosphonates) and miscellaneous mammalian and nonmammalian enzymes. The mammalian enzyme entries include the following: cyclooxygenase-1 and -2 (COX-1/2; library 2.5), dihydroorotate dehydrogenase (library 2.5), and phosphodiesterase-4 (PDE4, library 2.7). The nonmammalian enzyme targets include the following: phosphomannose isomerase (PMI, libraries 2.8 and 2.9), glucosyltransferase-1 (GFT-1, library 2.10), β-galactosidase (library 2.11), HIV-1 reverse transcriptase (library 2.12), and flu A sialidase (library 2.13).

A novel class of 10-substituted phenothiazines as selective COX-2 inhibitors was identified through a combination of computational 3-D database searching and combinatorial library synthesis (Figure 10).[45] Tricyclic **87** (melitracene) was selected as a putative COX-1/2 inhibitor upon executing a DOCK search against the sheep COX-1 crystal structure. Although melitracene **87** was not available for biological evaluation, it was hypothesized that other tricyclic ring systems may adopt a binding orientation similar to that predicted for **87**. In this regard, N-substituted phenothiazines were tested and found to inhibit COX-1/2 with modest selectivity, e.g., **88**−**90**. A small parallel library **91** (library 2.5) of *N*-(3-amidopropyl)phenothiazines yielded **92** (IC_{50} = 21 μM, COX-2) and **93** (IC_{50} = 1.3 μM, COX-2) as selective COX-2 inhibitors (**92** and **93**: IC_{50} > 50 μM, COX-1).

Library 2.8 is a 1 296-member collection of acylated dipeptides with 2-aminoindane-2-carboxylic acid as a conserved central building block (**97**: Figure 11).[6] The impetus for creating library 2.8 was the result of information obtained

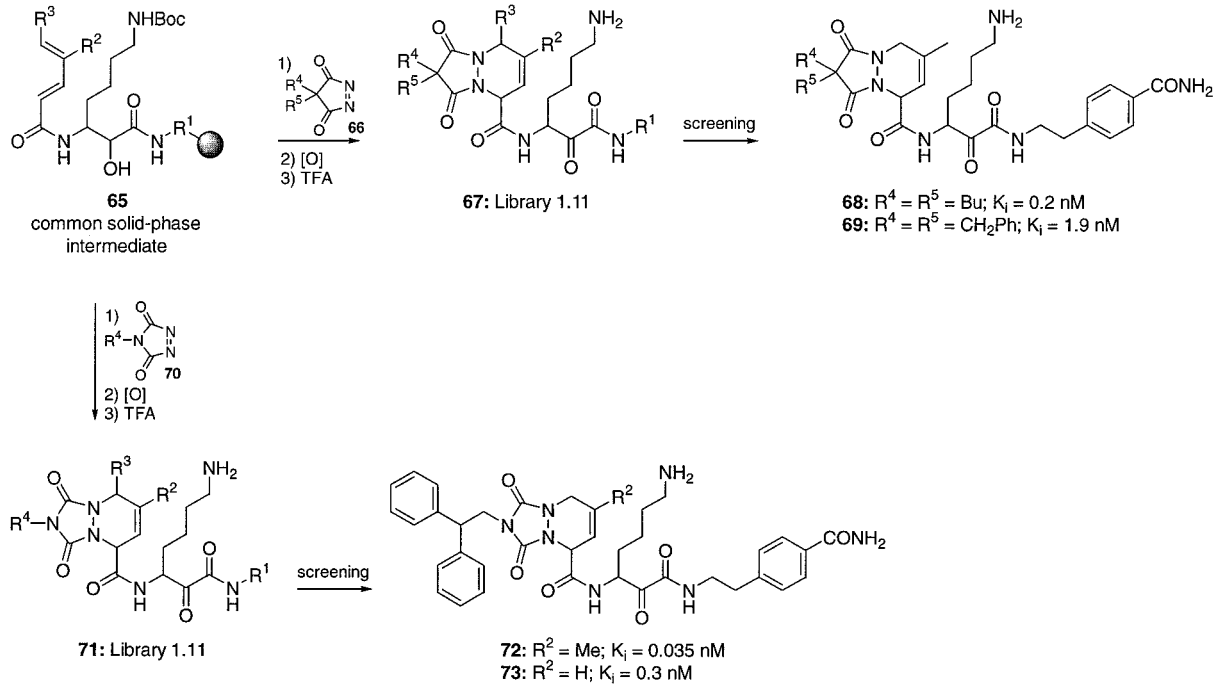


Figure 7. β-Strand mimetics as thrombin inhibitors (libraries 1.11 and 1.12).[38]

from the screening of many combinatorial libraries (>300 000 total compounds). A single library of acylated dipeptides **94**, containing the 2-aminoindane-2-carboxylic acid, was the only library which possessed any appreciable activity against phosphomannose isomerase (PMI), an essential enzyme in fungal cell wall biosynthesis. Some 36 compounds from library 2.8 were selected for resynthesis following evaluation against PMI. There were two R^1 amino acid residues, 3-pyridylalanine and citrulline (e.g., **99**−**100**), that were associated with activity; however, the data was puzzling in that there was no direct correlation of activity with the synthons. An identical impurity, however, was observed in all of the HPLC traces of the crude resynthesized compounds. The structure of the impurity was deduced through mass spectrometry and shown to be N-acylated indane-2-carboxamide **101** ($K_i = 27\ \mu$M). This material was a deletion adduct arising from incomplete coupling of the first amino acid to the photolabile amine resin. Library 2.8 was followed up with a series of optimization libraries (library 2.9) to furnish analogue **103** ($K_i = 4\ \mu$M).

Libraries Yielding G-Protein Coupled Receptor Agonists and Antagonists

Table 3 delineates libraries active against GPCR targets including opioid receptors (libraries 3.1−3.4), somatostatin receptors (libraries 3.5−3.7), and the benzodiazepine receptor (library 3.8).

Dooley and co-workers, in their continuing interest in peptide libraries now spanning some five years, reported the synthesis of a 6 250 000-member tetrapeptide library (Table 3).[17] Library 3.1 employed L-, and D-natural and unnatural amino acids as diversity elements. Using a mixture-based positional scanning format, library 3.1 was assayed against the μ, δ, and κ opiate receptors. Potent and selective agonists were identified for each receptor subtype. There was notable similarity between the peptides with μ and δ agonist activity. Conservative changes in amino acids moderated μ and δ binding affinity. This result suggests that perhaps the two receptor subtypes may share a common topography with one another. This is reminiscent of topographies shared by other receptors, namely somatostatin with NK-1 receptors.[258] The κ agonist series was structurally distinct from either of the μ or δ peptide series, favoring D-amino acids in all four positions. It should be noted too that the μ and δ binding assays were derived from the rat, while the κ receptors were obtained from the guinea pig. There may be species differences accounting for the distinct peptide motifs found for the κ versus μ/δ agonists.

A search of selective κ opioid receptor antagonists was initiated due to the potential of κ selective antagonists to be effective in treating substance abuse.[48] For a number of years, N-substituted derivatives of 3,4-dimethyl-(3-hydroxyphenyl)-piperidine were known for their pure opioid receptor antagonist activity but were lacking in subtype (μ, δ, κ) selectivity. A more recent finding that **104** possesses a measure of μ selectivity prompted the synthesis of library 3.2 in an effort to find κ receptor subtype selective agents (Figure 12). Library synthesis was carried out in solution starting with optically active **105**. Derivatization of **105** with 11 different Boc-protected amino acids followed by diborane reduction and TFA-mediated removal of the Boc protecting group gave diamines **106**. These in turn were acylated with substituted benzoic, phenylacetic, phenyl cinnamic, and 3-phenylpropionic acids to give a 288-member library (**107**). Screening the library at 100 nM against a κ selective ligand revealed **108**−**110** as potent and selective inhibitors. From the percent inhibition data it was observed that the stereochemistry of the *i*-Pr (R^1) group was critical for binding affinity as was the 3-(4-hydroxyphenyl)-propionyl group with R^2 = H. A purified sample of **108** possessed a $K_i = 7$ nM against the κ receptor. The μ/κ and δ/κ selectivity was 57 and >824, respectively. Examination of **108** in a functional

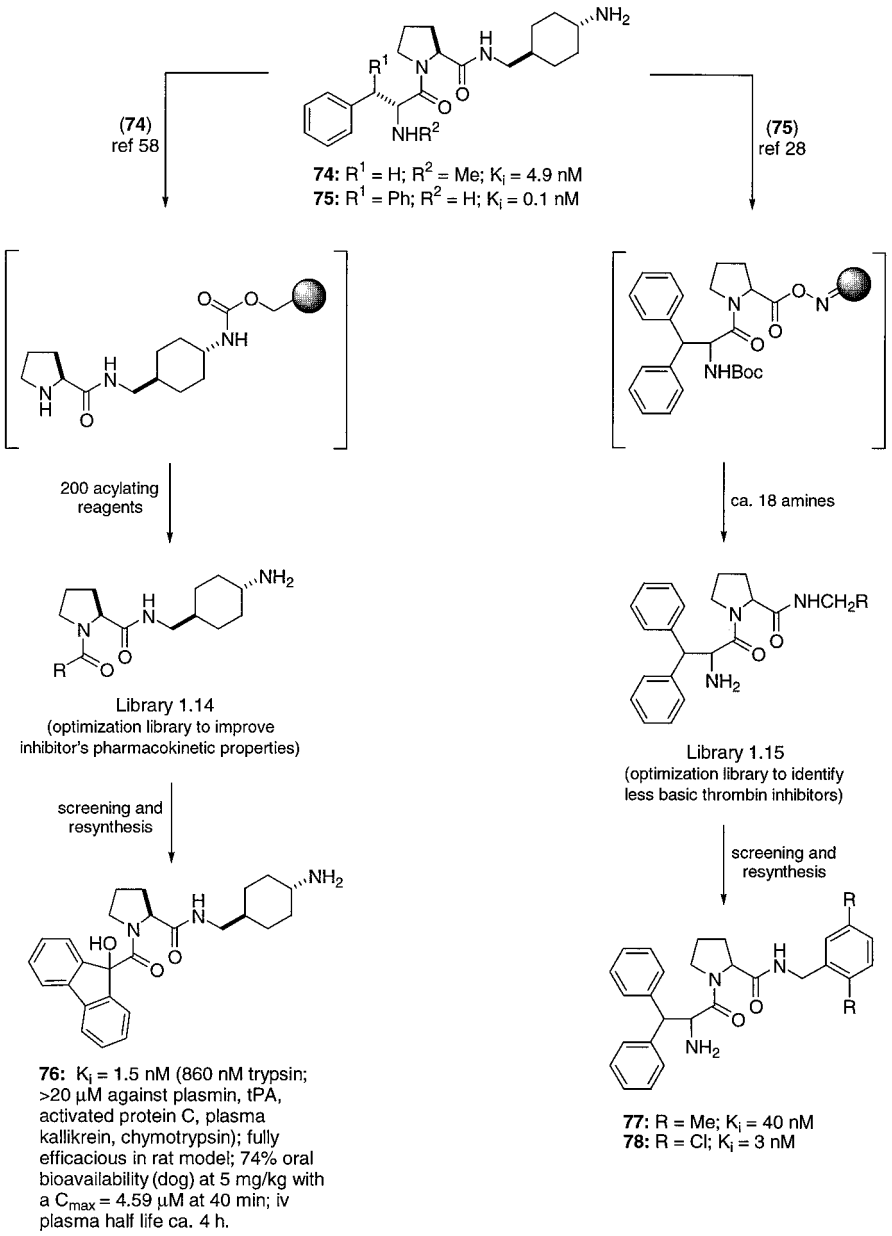


Figure 8. Merck's thrombin inhibitors (libraries 1.14 and 1.15).[28,58]

assay revealed it to be an antagonist of the κ receptor, although the selectivity against μ and δ was not as great as observed in the radioligand binding assay.

Other non-peptide libraries active against the opiate receptors include Houghten's dialkylated hydantoin library 3.3 and bicyclic guanidine library 3.4.[33] The synthesis of library 3.3 is illustrated in Figure 13. The library of 38 000 hydantoins was examined in a σ opiate radio receptor binding assay. The IC_{50} values of 12 resynthesized compounds ranged from 62 to 4615 nM. A basic residue (L- or D-Lys) at R^3 and *N*-benzyl groups at R^2 and R^4 and small hydrophobic groups at R^1 were found in the more potent δ binders, e.g., **117**−**119**. No selectivity data against μ, δ, or κ was given, nor any indication of whether **117** was a functional agonist or antagonist.

The bicyclic guanidine library 3.4 was derived from the condensation of resin-bound triamines with thiocarbonyldiimidazole (TCDI). The triamines in turn were prepared via the borane-mediated reduction of a library of tripeptides.[33] Library 3.4 possessed selective κ opiate receptor activity. The most active compound had an $IC_{50} = 37$ nM, although the actual structure was not disclosed.

Subtype selective agonists for each of the human somatostatin receptors (sstr1 through sstr5) were discovered at Merck via the synthesis and evaluation of libraries 3.5a−d based on lead **121** (Figure 14).[41] The initial lead **121** (K_i = 100 nM, sstr2) was the most potent of 75 compounds extracted from an internal 200 000 member compound file collection, following a 3-D pharmacophore search using cyclic hexapeptide somatostatin agonist **120** as the probe.

Retro-combinatorial analysis dissects **121** into three fragments: 1,4-butylenediamine, tryptophan (Aa), and a spiroarylpiperidine unit. Further translation of this analysis into the design of lead optimization libraries suggested C-/N-terminal derivatized amino acids **122** as a generic library construct. This amino acid amide theme (**122**) served as the basis for the synthesis of libraries 3.5a−c; library 3.5d was an unrelated collection of arylindoles.

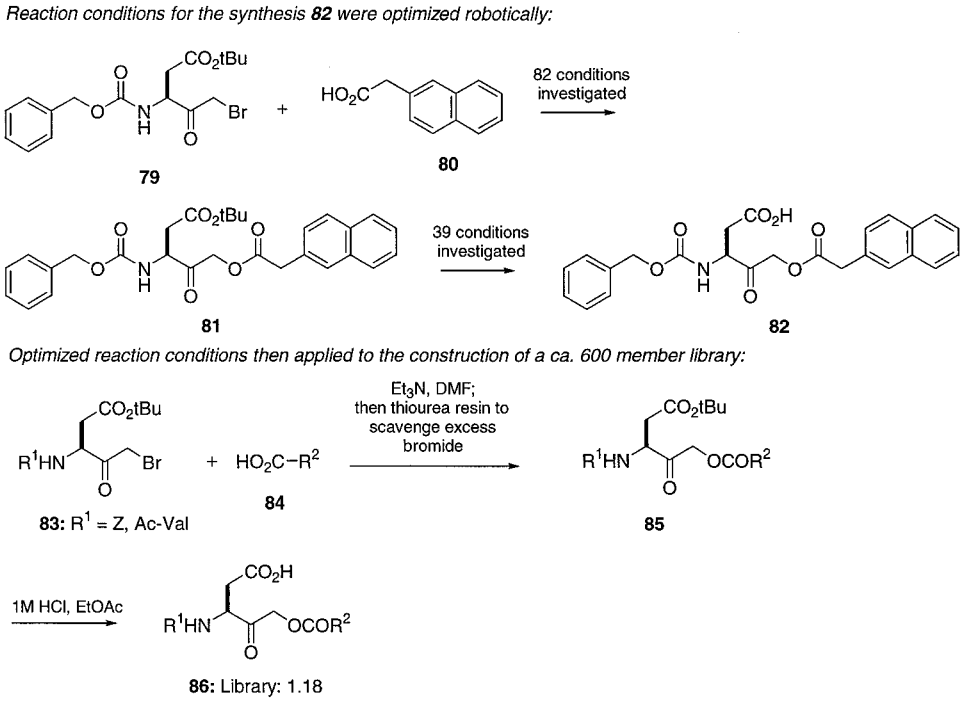


Figure 9. Solution-phase synthesis of ICE inhibitors (library 1.18).[52]

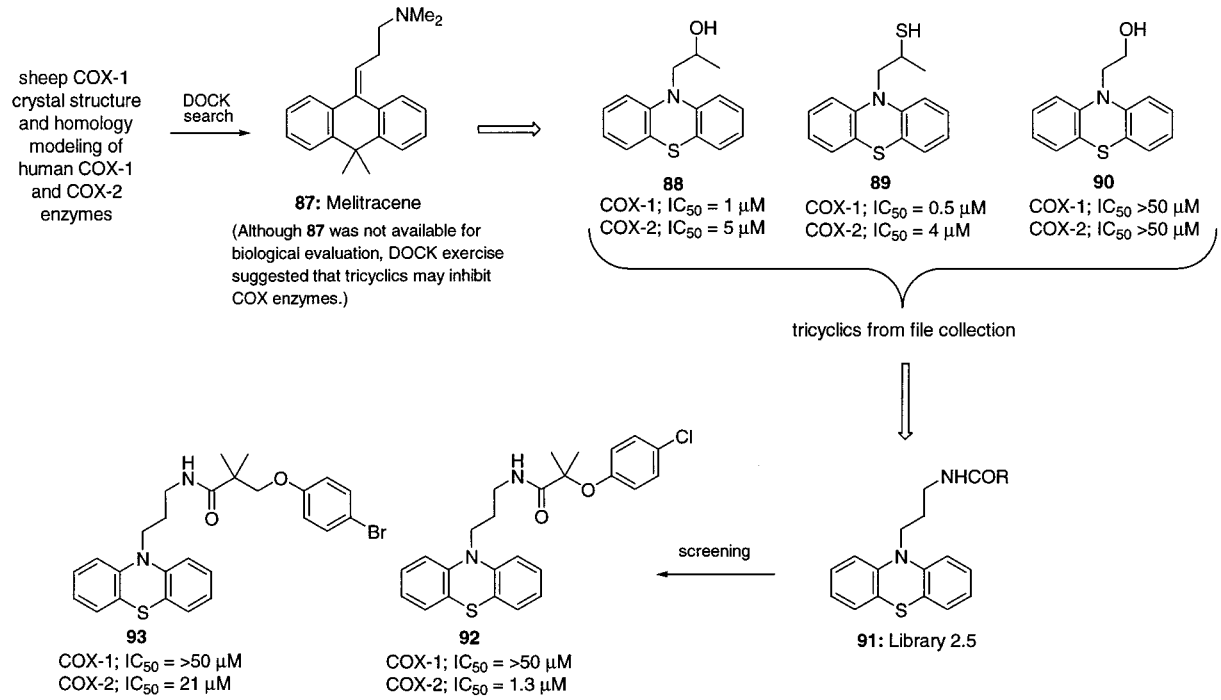


Figure 10. Phenothiazine-based COX-2 selective inhibitors (library 2.5).[45]

Library 3.5a may be considered a "tryptophan amide library", composed of 20 diamines (R^1), 20 tryptophan surrogates (Aa), and 79 spiroarylpiperidine replacements (R^3). This gave a library of 20 × 20 × 79 = 31 600 compounds; however, taking into consideration that racemic synthons were used, the approximate library size was estimated to be 130 000 members. The details of the actual library synthesis were not given, but multiple pools of compound mixtures were prepared. The library was evaluated against all five sst receptors. Two pools active against sst were identified. The first pool of 1 330 spiroindane analogues **123**, including lead **111**, was not deconvoluted as potent sstr2 agonists for this class were already known. The second active pool of 1 330 benzimidazolones **124** was of interest and subjected to further deconvolution. In a first round of deconvolution, where the R^3 benzimidazolone moiety was kept constant, 20 pools of 20 compounds each were prepared. Each pool was defined by a single amino acid (Aa) and all possible combinations of the diamines (R^1). Screening indicated the pool with β-methyltryptophan **115** possessed the greatest activity (sstr2). Subjecting **125** to a second round of deconvolution (R^3 and Aa constant, varying the 20 R^1

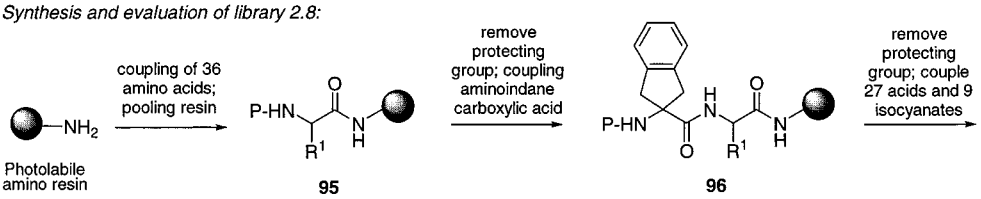
Initial lead discovery:

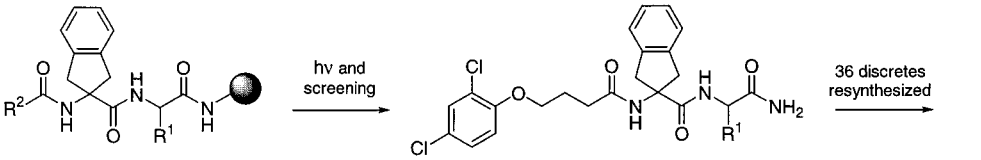
HTS of multiple combinatorial libraries against PMI; totaling >300,000 compounds

94

(**94** was the only library that had activity against PMI. It was characterized by 2-aminoindane-2-carboxylic acid as a central core.)

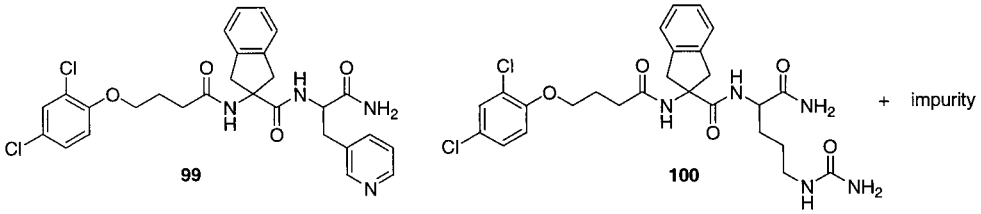
Synthesis and evaluation of library 2.8:





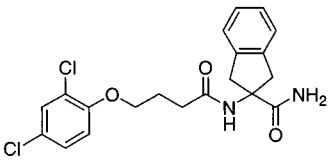
97: library 2.8
36(R^1) x 1 x 27(R^2) = 1296 members

98: one pool found active



Activity associated with two unrelated amino acid building blocks: 3-pyridylalanine and citrulline; HPLC reveals identical impurity in all resynthesized samples.

identification of impurity

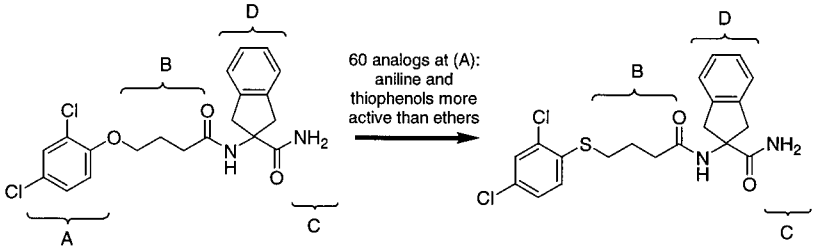


101: K_i = 27 μM
(slow binding, irreversible inhibition)

Deletion adduct from incomplete coupling of 3-pyridylalanine and citrulline building blocks in step one of the synthesis.

*Optimization of lead **101**:*

101



102: library 2.9
(a series of optimization libraries)

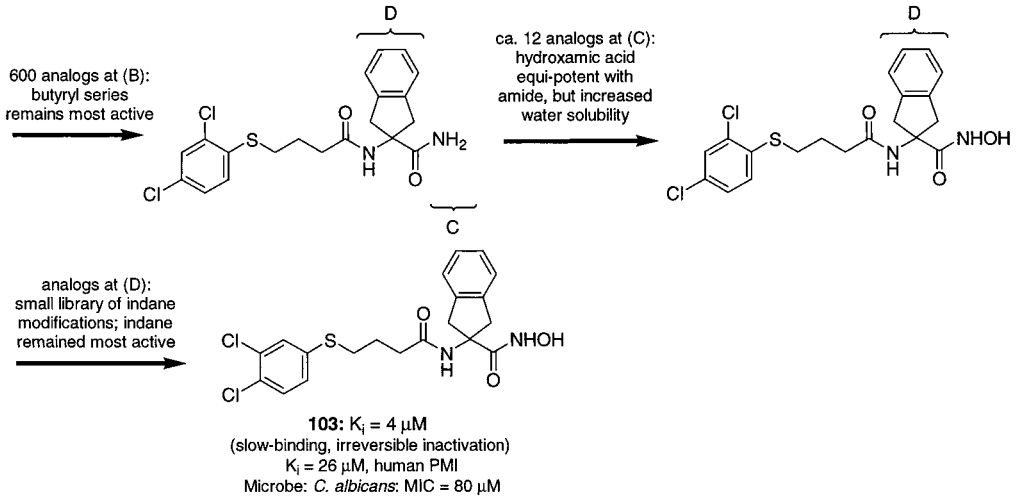


Figure 11. Deletion adduct from library 2.8 as an inhibitor of fungal phosphomannose isomerase (PMI).[6]

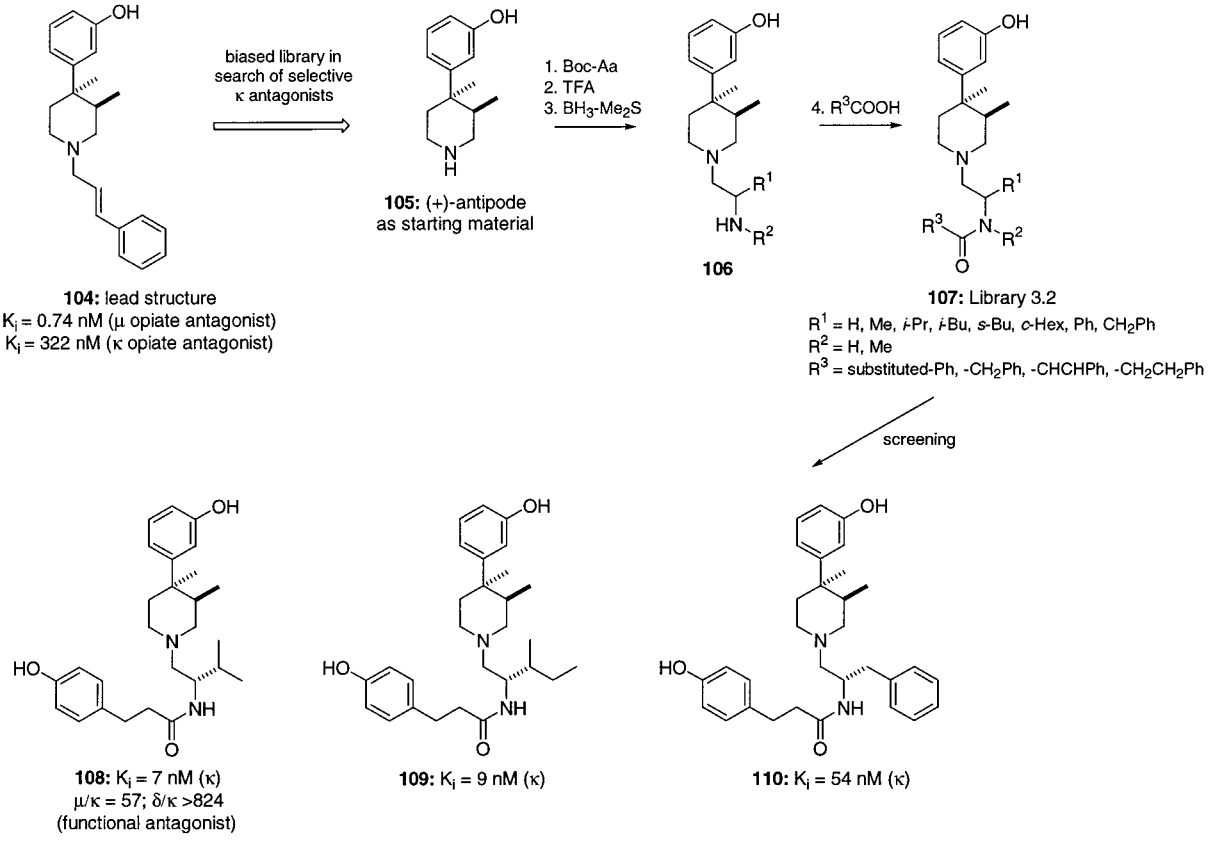


Figure 12. Solution-phase synthesis of biased library 3.2.[48]

diamines) led to the identification of **126** as a potent sstr2 agonist (6000-fold selective versus sstr1,3−5).

Amino acid amide library 3.5b is an expanded version of library 3.5a and is composed (21 (R^1) × 22 (Aa) x 147 (R^3)) of approximately 350 000 compounds, again considering the use of racemic synthons. Two pools were selected for deconvolution (details not disclosed), resulting in the identification of **127** and **128** as potent, selective sstr1 and sstr3 agonists.

In a third extension of library 3.5a (details not disclosed), the sstr5 ligand **129** was obtained. Ligand **129** was highly selective (7100-fold) for the sst2−4 receptor subtypes but possessed modest selectivity (8-fold) for the sst1 receptor.

The fourth library, library 3.5d (**130**), is a library unrelated to the amino acid amide libraries 3.5a−c, but rather an "arylindole library of limited complexity" (details not disclosed). From library 3.5d, the highly potent and selective sstr4 ligand **131** (K_i = 0.7 nM, sstr4) was obtained.

Functional activity for the selective ligands **126**−**129** and **131** was also investigated. The chart of Figure 14 summarizes the functional data for the ligands against cAMP accumulations (CHO K1), GH release, glucagon release, and insulin release. Clearly, compounds of this type are useful in unraveling the biological roles of the individual receptors. Fundamentally, the study represents a landmark prototypical model of how combinatorial chemistry may be used to

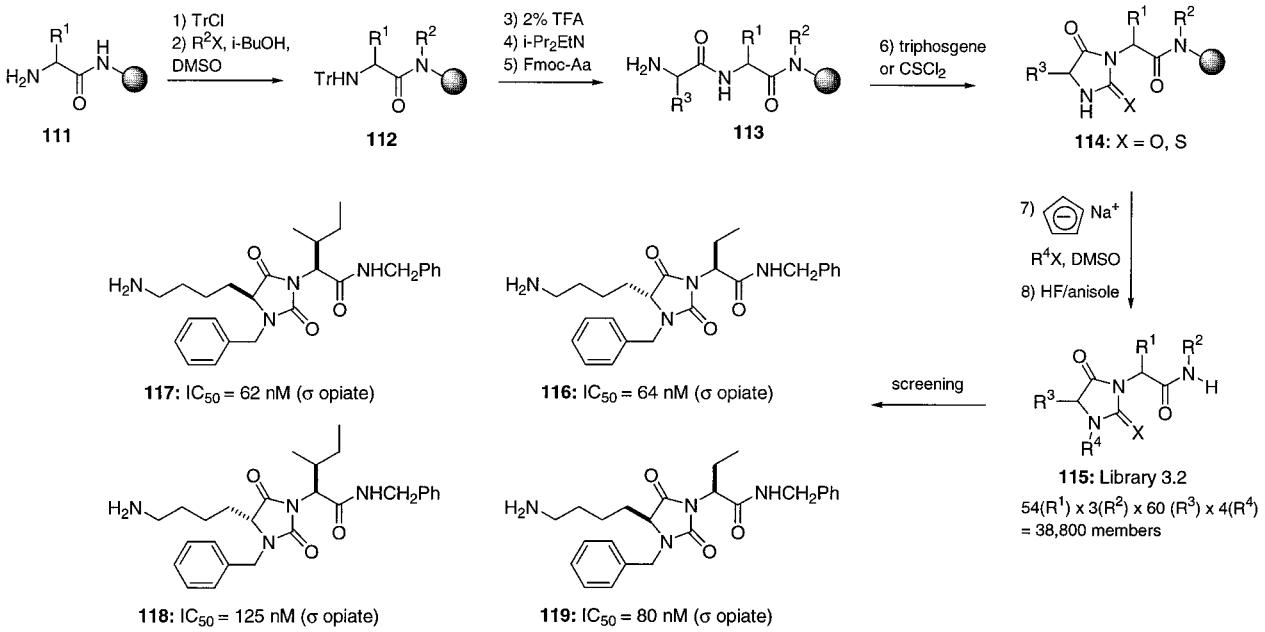


Figure 13. Hydantoin library 3.3 processing σ opiate binding affinity.[33]

rapidly identify selective ligands to assess the functional significance of a given receptor. No doubt it is this type of exercise that will be repeated many times over in the future to unveil the roles of new proteins as they are characterized from genomic research.

In addition to Merck's libraries of subtype selective somatostatin agonists, Glaxo Wellcome described sstr5 selective agonists (library 3.6; Figure 15).[42] The substituted thiazolidinone **132**, a potent and selective sstr5 agonist (pIC_{50} = 5.85, human recombinant sst5 receptors), discovered from an Affymax screening library, served as a lead compound. Because complex stereochemical mixtures are produced during thiazolidinone synthesis and the fact that a large library of compounds of this class had already been screened against the sst receptors, a heterocyclic surrogate for the thiazolidinone was sought. The hydantoin motif **133** was selected on the basis that substituents could be displayed analogous to the array found in **132** with stereochemical control and it was more amenable to solid-phase synthesis. The hydantoin library 3.6 was synthesized using Fukuyama−Mitsunobu chemistry to ensure diversity (alkyl and aralkyl) at the R^2 position. Library members were tested for their ability to inhibit [^{125}I] Thr^{11}-SRIF membrane binding (0.03 nM) in CHO Kl cells expressing human recombinant sst2 and sst5 receptors. None of the hydantoins exhibited appreciable activity against sst2, but they were active against the sstr5. Preliminary SAR studies suggested that larger chain aralkyls (four-carbon tether, e.g., **134**) at R^1 and R^2 were preferred over short chain (<3 carbons) aralky substituents.

The discovery of a *somatostatin antagonist* was also described (library 3.7, Table 3).[56] The D-hexapeptide, Ac-his-phe-ile-arg-trp-phe-NH_2, identified from a 64-million-member library, was found to be active in vivo (i.v. administration). The D-hexapeptide bound to sstr2 with a K_i = 172 nM, blocked somatostatin inhibition of adenylate cyclase in vitro (IC_{50} = 5.1), and induced growth hormone release when given alone to anesthetized rats with or without pretreatment with a long-active somatostatin agonist.

Libraries Targeted for Non-GPCRs

Table 4 delineates those libraries active in non-GPCR receptor targets: integrin receptors (libraries 4.1−4.5), selectins (libraries 4.6−4.7), ion channels and re-uptake mechanisms (libraries 4.8−4.10), domain interactions (libraries 4.11−4.14), nuclear receptors (library 4.15), transcription factors (library 4.16), and MHC-complex class I (library 4.16).

The -Arg-Gly-Asp- (RGD) is a well-known integrin binding motif for both the β_3 and β_1 classes of integrin families. Through the past decade, numerous peptidomimetic scaffolds have been described which display the salient positive and negative charged Arg and Asp side chains or their equivalents. These agents have been useful in the discovery of non-peptide integrin antagonists with potential application in treating thrombosis (β_3 class), unstable angina (β_3 class), restenosis (β_3 class), osteoporosis (β_3 class), tumor metastasis (β_3 class), and T-cell-mediated immune responses (β_1 class). Three new scaffolds displaying these charged side chains were incorporated into combinatorial libraries. These include the cyclic and acyclic oligocarbamates by Schultz[13] (β_3 class; 20 000- to 530 000-member libraries, 4−13 nM antagonists), a biaryl scaffold reported by Schering-Plough[34] (β_3 class; 275 000 members, 34 μM antagonist), and a cyclic turn mimetic scaffold synthesized in the Ellman laboratories[44] (β_1 class; 2304 members, 5 μM antagonist).

Schreiber described selective binders of the Src SH3 and Hck SH3 domains.[21] These were obtained from structure-based, encoded hexapeptide and nonapeptide libraries in which mono- and bicyclic peptidiomimetics were attached to the N- or C-terminus, respectively (libraries 4.11 and 4.12). In this way non-peptide elements were thought to be directed toward the Leu-Pro specificity pockets of the SH3 domains. The libraries were useful in the identification of agents selective for one domain versus another and in further understanding of the domain−ligand binding interactions.

Troglitazone **135** is a marketed drug for the treatment of type 2 diabetes. Troglitazone **135** and structurally related thiazolidinediones act as agonists at the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), as demonstrated via the correlation between the PPARγ binding affinity and the in vivo antihyperglycemic potency (Figure 16). During the course of an antidiabetic program at Glaxo Wellcome, a novel class of tyrosine-based nonthiazolidinedione PPARγ agonists (**136**) were discovered.[14] In an effort to improve binding affinity, functional activity, selectivity, and aqueous solubility for the series, an optimization program was initiated using a 2-fold strategy. Solution-phase synthesis (traditional medicinal analogue preparation) focused on modifying the oxazole moiety, introducing water-solubilizing groups in that region of the molecule. Complementary to this effort was the construction of library 4.15 (**138**: ca. 75 members), wherein a much broader exploration of the phenyl alkyl ether was undertaken. Although more potent oxazole surrogates were found through the solution-phase analogue synthesis, they were not significantly more soluble than **136**. Conversely, the more water soluble agents such as **137** (phenyl to pyridyl exchange) were not as potent as the original lead **136**. The solid-phase work did generate a number of potent and selective PPARγ agonists (e.g., **139**), but again these agents did not possess binding affinity as high as **136**. Collectively, the SAR in conjunction with X-ray crystallographic studies have led to an detailed understanding of the binding interactions of these agents with PPARγ (details to be published).

Nuclear factor-κ binding (NF-κB) and activator protein-1 (AP-1) regulate the expression of a variety of proinflammatory cytokines and proteins. In chronic inflammatory disease states, where there is a continual overproduction of these proinflammatory cytokines, inhibition of NF-κB and AP-1 transcriptional activation may lead to suppression of cytokine levels and subsequent modulation of the inflammatory response. Researchers at Signal Pharmaceuticals recently identified pyrimidine carboxamide **140** ($IC_{50} = 0.5\ \mu M$) as an agent inhibiting both NF-kB and AP-1 transcriptional activation in stably transfected human Jurkat T-cells (Figure 17).[46] Pyrimidine **140** displayed similar inhibitory action on the production of IL-2 and IL-8 levels in stimulated cells and was active in an animal model of inflammation. Through a traditional medicinal chemical approach, it was established that the 2-chloro group was important for activity (Cl → H, OH, OR, NRR; inactive) as was the amino NH group (NH→ NMe, NBz; loss of activity). Consequently, the solution-phase parallel synthesis of library 4.16 (**141**) was carried out to discern an SAR for the carboxamide moiety of **140**. A library of some 160 compounds was synthesized by the reaction of the corresponding acid chloride of **140** with commercially available alkylamines, anilines, and heterocyclic amines. Operationally, this was performed by sonicating EtOAc solutions of a slight excess of the acid chloride and amine in the presence of Amberlyst A-21, quenching with water, and then further sonicating. The library of discrete compounds was tested, and 3,5-disubstituted arylamines were found to retain or enhance potency (**142**−**144**). In particular, pyrimidine carboxamide **144** showed a 10-fold improvement over the original lead **140**. Pyrimidine **144** blocked the production of IL-2 and IL-8 in Jurkat T-cells ($IC_{50} = 30$ nM). Curiously, this latter activity was specific to T-cells as the compound was inactive in monocytes, epithelial cells, fibroblasts, osteoblasts, or endothelial cells. Pyrimidine **144** was cell penetrant and active in several models of inflammation and immunosuppression.

Libraries Displaying Cytotoxic and Antimicrobial Activity

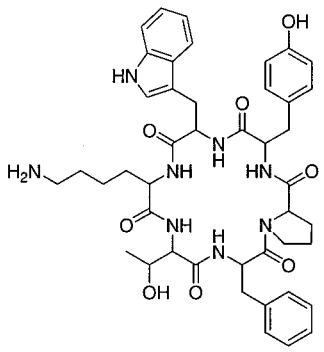
Chemical libraries of cytotoxic agents (libraries 5.1−5.3) and antiinfectives (libraries 5.4−5.15) are presented in Table 5.

Two contributions from the Scripps Research Institute describe the synthesis of libraries of cytotoxic agents (libraries 5.1 and 5.2). The first of these is from the Boger laboratories in which a vast number of polyamides were prepared using iminodiacetic acid **145** as a core template (Figure 18).[8] The synthetic strategy utilized a solution-phase convergent approach to library synthesis allowing facile multiplication of diversity. This is in contrast to linear, divergent solid-phase synthesis (oligomer or template libraries) in which diversity elements are introduced sequentially. Using solution-phase methodology, libraries of dimers, trimers, and tetramers based on the template were synthesized. These are perhaps the largest collections of compounds yet to be prepared by solution-based methods. Polyamides of this type are thought to be useful in modulating protein−protein interactions, in particular as agonists or antagonists of receptor activation via dimerization. The specific biological activity of a 20 200 member library of iminodiacetic acid diamides **148** was disclosed with several agents displaying cytotoxic activity in L-1210 cells.

The second contribution from Scripps is from the laboratories of K. C. Nicolaou.[35] In recent years, Nicolaou has successfully tackled the total synthesis of several natural products with potent antitumor activity. These include Taxol, epothilone A and B, eleutherobin, **151**, eleuthosides A (**152**) and B (**153**), and the sarcodictyines A (**154**) and B (**155**; Figure 19). One of the distinguishing characteristics of his efforts is a potential paradigm shift toward the simultaneous development of solution- and solid-phase methodologies for natural product total synthesis and subsequent generation of analogue libraries. This is in contrast to the traditional approach to total synthesis in which the natural product construction is an end to itself. Case in point is the total synthesis of sarcodictyin A (**154**) and B (**155**) and the solid-phase synthesis of library 5.3 (Figure 19).

Intermediate **156**, generated during the total synthesis of sarcodictyins A (**154**) and B (**155**), was attached to solid support in a four-step sequence (**156** → **158**), taking advantage of the facile transketalization chemistry of **156**. Resin-bound intermediate **158** was deacetylated (**158** → **159**), reacted with a series of alcohol derivatizing agents (yielding esters and a carbamate), and subjected to desilylation to give resin-bound intermediates **160**. These intermediates in turn were subjected to a series of transformations which generated

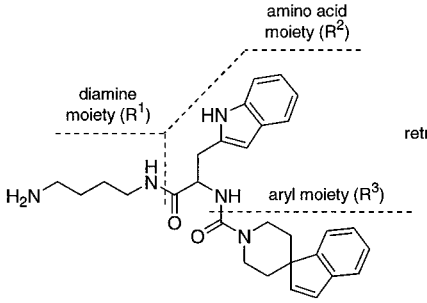
Overall library design:



120

Known cyclic hexapeptide agonist active against all five somatostatin receptor subtypes (ssrt1-5).

molecular modeling and database search with emphasis on Tyr-Trp-Lys pharmacophore



121: K_i = 100 nM (sstr2)

Most potent agonist of 75 compounds extracted from an internal 200,000 compound file collection. Serves as the basis for libraries 3.5a-c.

retro-combinatorial analysis

$R^1NHCO\text{-}Aa\text{-}NHR^2$

122: Libraries 3.5a-c

Essentially C-/N-derivatized amino acid libraries

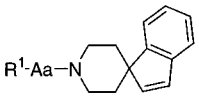
Library 3.5a:

$R^1NHCO\text{-}Aa\text{-}NHR^3$

122

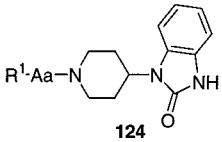
20 (R^1) x 20 (Aa) x 79 (R^3) = 130,000 members (including stereoisomers) Aa in this case were largely tryptophan analogs. Library synthesis generated multiple sublibraries.

screening



123

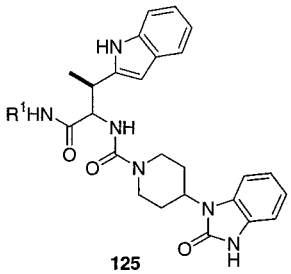
Sublibrary of 1330 members active against sstr2. This was a well studied class and was not followed up further.



124

Sublibrary of 1330 members active against sstr2. Selected for deconvolution.

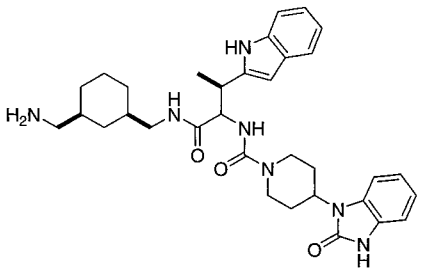
1st round of deconvolution



125

20 mixtures examined, each mixture with a defined Aa and 20 R^1 (essentially positional scanning at Aa). Pool with β-methyl tryptophan possessed greatest potency and was subjected to further deconvolution.

2nd round of deconvolution



126: K_i = 50 nM (sstr2 selective)

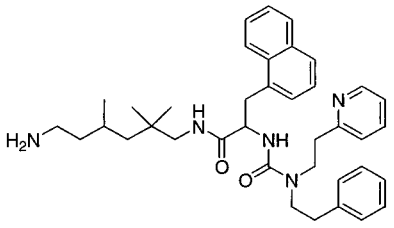
Library 3.5b:

$R^1NHCO\text{-}Aa\text{-}NHR^3$

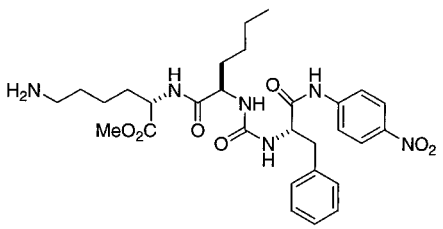
122

21 (R^1) x 22 (Aa) x 147 (R^3) = ca. 350,000 members including stereoisomers. Aa in this case expanded beyond tryptophan analogs. Library synthesis generated multiple sublibraries.

2 sublibraries with activity against sstr1 and sstr3 selected for deconvolution

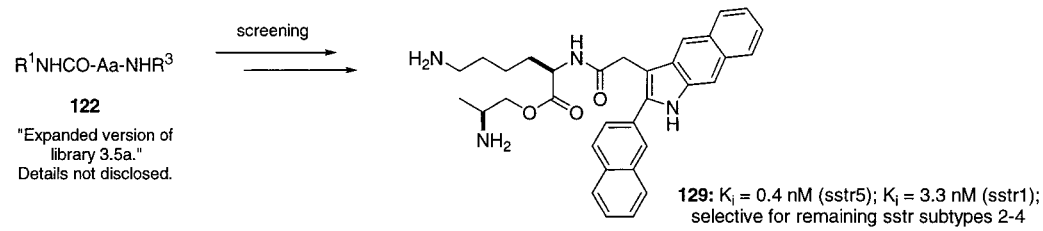


127: K_i = 1.4 nM (sstr1 selective)



128: K_i = 24 nM (sstr3 selective)

Library 3.5c:

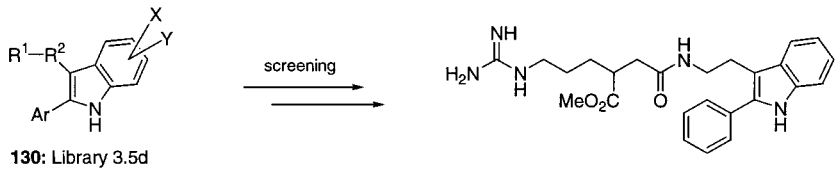


122

"Expanded version of library 3.5a." Details not disclosed.

129: K_i = 0.4 nM (sstr5); K_i = 3.3 nM (sstr1); selective for remaining sstr subtypes 2-4

Library 3.5d:



130: Library 3.5d "Arylindole library of limited complexity." Unrelated to **122**; size and synthons not disclosed.

131: K_i = 0.7 nM (sstr4 selective)

Activity chart for selective sstr agonists obtained from libraries 3.5a-d.[a]

Agonist	sstr1	sstr2	sstr3	sstr4	sstr5	cAMP accum.[c]	GH release assay	Glucagon release	Insulin release
ss-14[b]	●	●	●	●	●	—	●	●	●
120	—	●	—	—	—	—	—	—	—
126	●	○	○	○	○	●	○	○	○
127	○	●	○	○	○	●	●	●	○
128	○	○	●	○	○	●	○	○	○
131	○	○	○	●	○	●	○	○	○
129	d	○	○	○	●	d	●	○	●

[a]Black dot indicates activity. White dot indicates inactivity. Dash indicates no data available. [b]ss-14: naturally occurring somatostatin tetradecapeptide. [c]cAMP accumulation in CHO K1 or appropriate cell line. [d]Weak activity also seen against sstr1 and cAMP accumulation for **129** (sstr5/ssrt1 8:1)

Figure 14. Subtype selective somatostatin receptor agonists as reported by Merck.[41]

three spurs **161**−**163** of library 5.3 and some 60 new sarcodictyin analogues (radio frequency encoding). In addition to the solid-phase synthesis, other analogues at R^1 were prepared in solution. Because of the structural resemblance of **161** and **162** to **151** and **153**, the combinatorial libraries may also be considered analogue libraries of eleutherobin and eleuthosides A and B. Evaluation of the library gave new agents with comparable or superior activity to the sarcodictyins and provided important SAR insights into this class of antitumor natural products.

With regard to antimicrobial agent discovery, Isis continued to publish on the synthesis and biological activities of their unique polyazapyridinocyclophanes,[4a,5b] pyridinopolyamines,[3] and the novel, structurally related polyazadipyridinocyclophanes,[4b] oxytriamines,[24] and aminoethylpiperazine[25] classes of antibacterial agents (libraries 5.4−5.9). For several of the reported libraries, biological data is given for active sublibraries containing multiple compounds, without subsequent deconvolution to identify specific active compounds. In a few instances, certain sublibraries also acted to disrupt the HIV-1 tat/TAR protein-RNA binding.[4,5]

Library Statistics and Summary

As compiled here, a total of 321 library constructs were reported in 1998. There were 74 biologically active libraries reported that year with approximately 60% of the contributions coming from industry. There were nearly twice the number of solid-phase versus solution-phase library syntheses from industry, while nearly equal numbers of solid- and solution-phase syntheses reported from academia. Of the 247 libraries with undisclosed biological activity, 66% of these

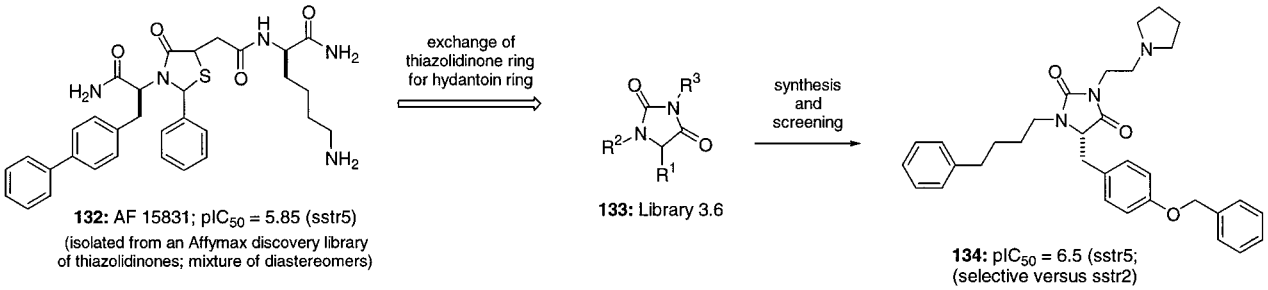


Figure 15. Glaxo Wellcome's hydantoin library 3.6 yielding selective sst5 receptor agonists.[42]

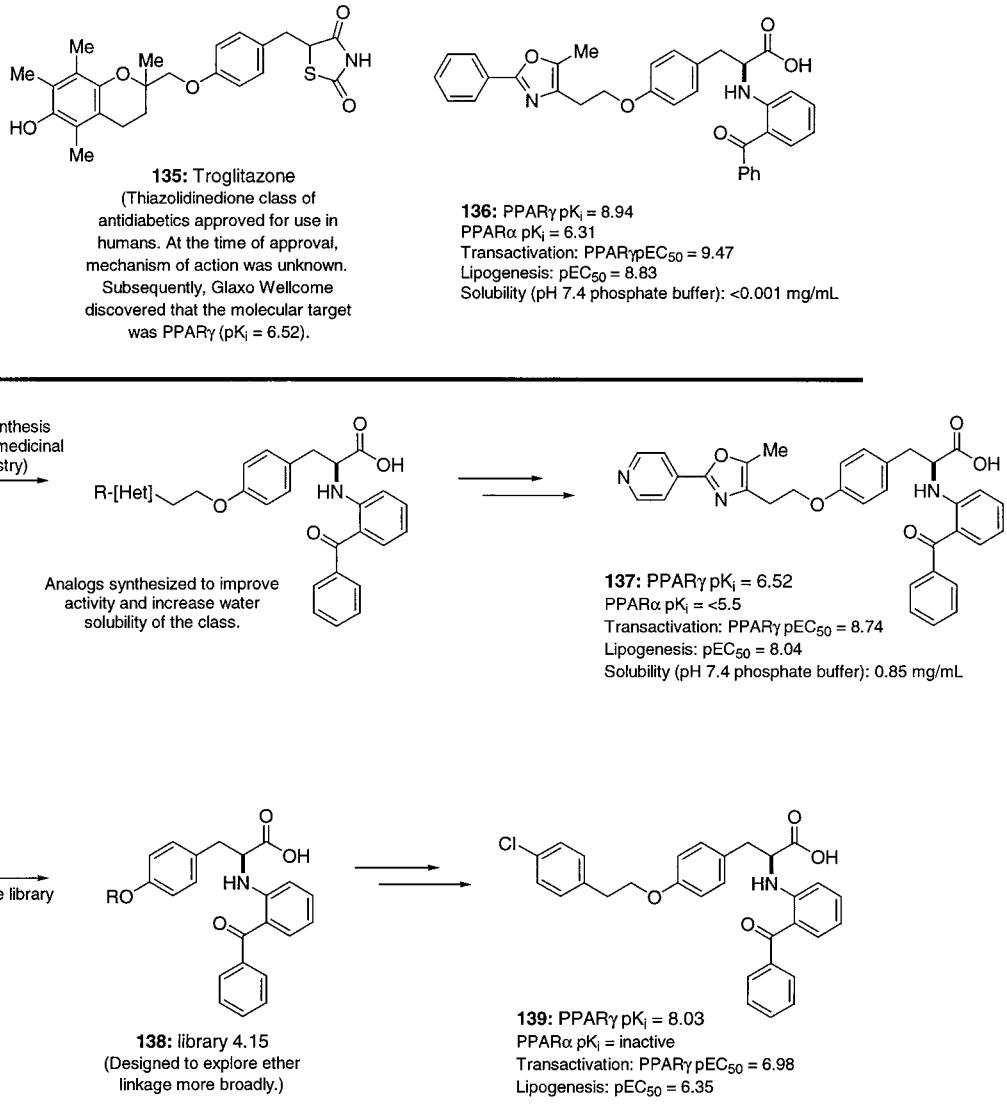


Figure 16. Optimization of nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) agonists.[14]

came from industry and, again, with approximately a 2−3:1 ratio of library syntheses carried out on solid- versus solution-phase.

Considering the biologically active libraries of Tables 1−5, the entries across the target class are: 26% for proteolytic enzymes, ca. 15% for both nonproteolytic enzymes and GPCRs, 23% for non-GPCR targets, and 20% for the cytotoxics and antimicrobials. Solid-phase synthesis accounts for ca. 65% of the contributions, and with the exception of the cytotoxic and antiinfective category, solid-phase was the preferred method for library construction by a >2:1 margin. In the case of libraries without disclosed biological data (Tables 6−10), there is a fairly equal distribution of constructs among the collections of scaffold derivatization, acyclic, monocyclic, bicyclic, and spirocyclic synthesis. These constructs account for 95% of the entries; only a few laboratories described polycyclic and macrocyclic libraries. Interestingly, about equal numbers of solution- and solid-phase synthesis of scaffold derivatization constructs were reported, while in all other categories, solid-phase was the method of choice. Up to 85% of the monocyclic ring syntheses were carried out on solid-phase.

Structure-based design and molecular modeling integrated with library design and synthesis proved quite effective as

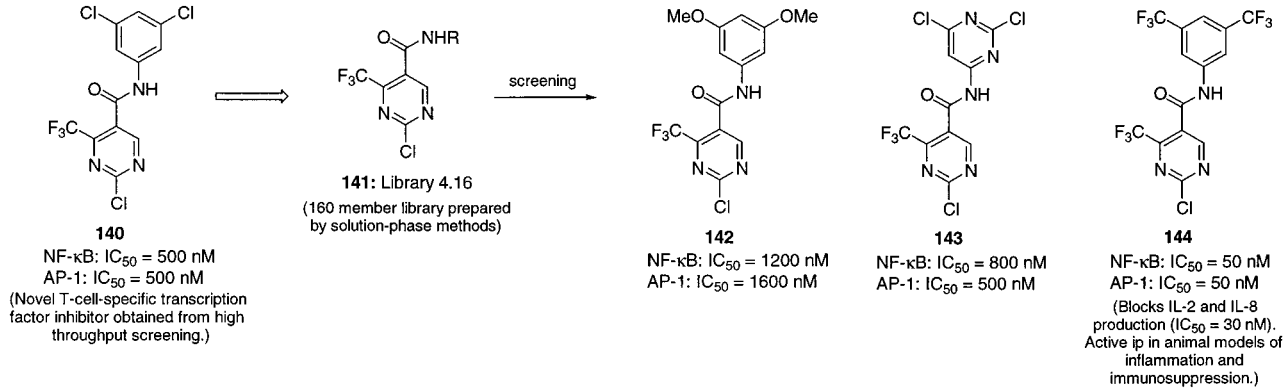


Figure 17. Inhibitors of NF-κB and AP-1-mediated gene expression.[46]

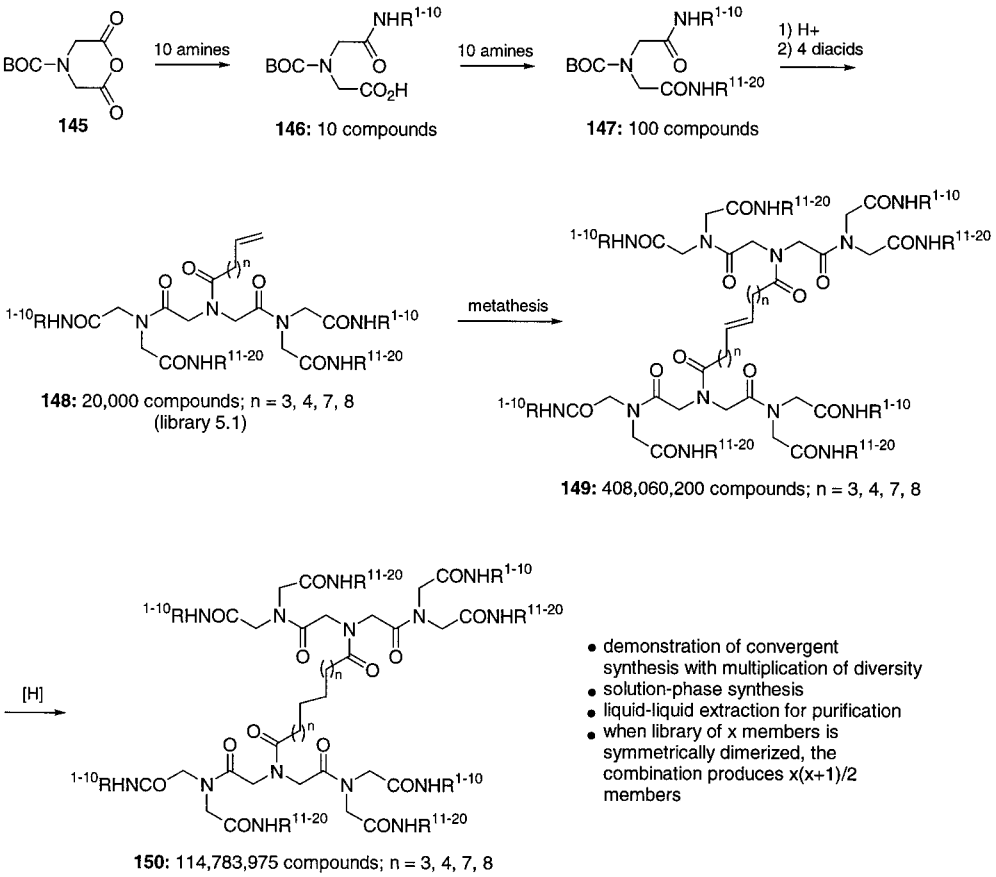


Figure 18. Boger's multistep convergent solution-phase synthesis of combinatorial libraries from iminodiacetic anhydride. Synthesis of library 5.1.[8]

applied to the discovery and optimization of lead structures. These computational techniques were essential components in the design of several libraries including: (1) Affymax's DKP-based metalloprotease inhibitor libraries (libraries 1.1 and 1.2),[47] (2) the selection of N-derivatizing reagents for Ellman's β-hydroxyethylamines (library 1.4),[26] (3) the selection of cyclic diamino acid P_2-P_4 surrogates in statine library 1.6,[11] (4) retrospective analysis of Vertex's new class for HIV inhibitors,[55] (5) the selection of the bicyclic template in libraries 1.11 and 1.12 of β-strand mimetics,[38] (6) the proline amide libraries 1.14 and 1.15 yielding thrombin inhibitors,[28,58] (7) the phenothiazine library 2.5 leading to a new class of COX-2 inhibitors,[45] (8) analysis of the structural basis for the binding of substituted purines to human CDK2-cyclin A kinase complex,[60] (9) Merck's somatostatin receptor subtype selective agonists (libraries 3.5a−d),[41] and (10) the work of Schreiber on the identification of selective Src and Hck domain binders (libraries 4.11 and 4.12).[21,32]

The detailed descriptions of the SAR development of thrombin inhibitors from Merck (library 1.15)[58] and of PPARγ agonists from Glaxo Wellcome (library 4.15)[14] aptly demonstrate the synergy of combinatorial chemistry with traditional medicinal chemistry for lead optimization purposes, defining ligand affinity, selectivity, functional activity, aqueous solubility, and oral bioavailability. Specifically, the thrombin inhibitor case[58] represents the first example in which a lead compound, with a poor pharmacokinetic profile, was optimized on solid-phase to yield directly a potent, selective, efficacious, orally bioavailable agent. These are particularly timely accounts as there is appeal in establishing

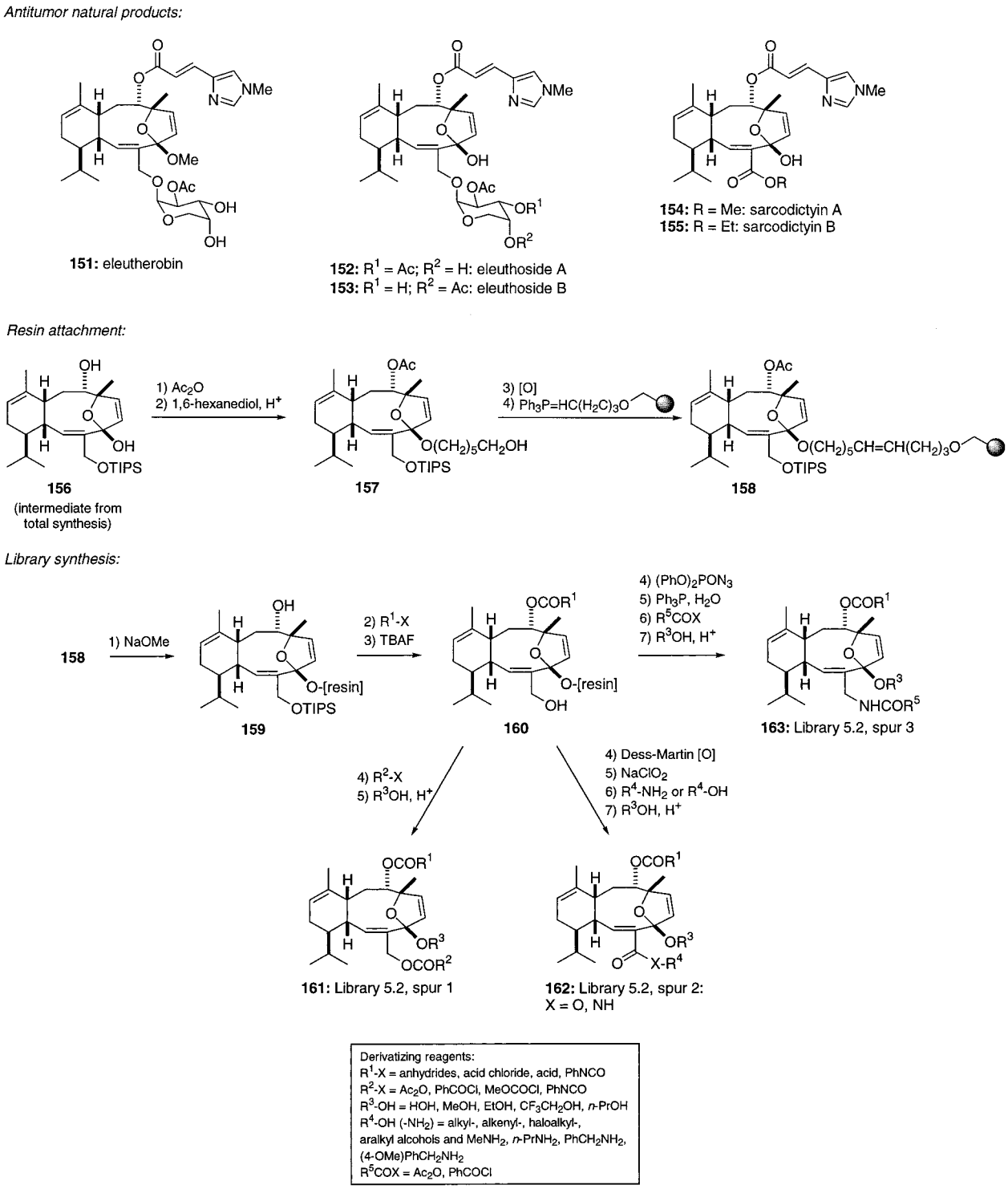


Figure 19. Nicolaou's sarcodictyin analogue library 5.2.[35]

whether libraries may be of value in solving pharmacokinetic and toxicological problems associated with late stage discovery activities.

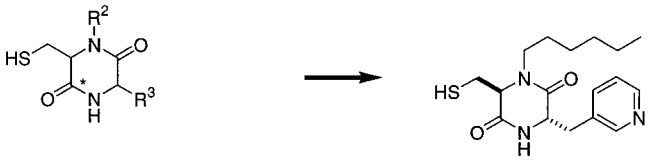
Last, the role of serendipity in drug discovery cannot be overlooked. Despite the heroic efforts on the part of the combinatorial chemist to define synthon compatibility and optimal reaction parameters for any given library, chemistry does not always proceed as planned. This was beautifully demonstrated in the discovery of the slow binding, irreversible phosphomannose isomerase inhibitor **101**, wherein a deletion adduct, formed through incomplete coupling of the first of three building blocks to solid support, was ultimately found as the enzyme inhibitor (library 2.8).[6]

Acknowledgment. The authors thank Ms. Karen Rivera for her expert assistance in the preparation of this manuscript, particularly for chemical structure drawing.

Table 1. Chemical Libraries Targeted for Proteases[a]

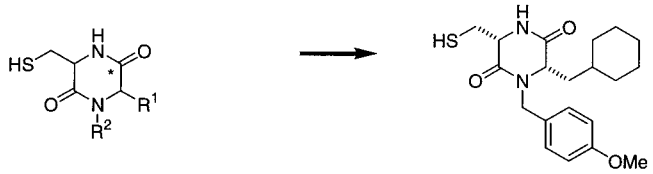
Metalloproteases

Library: 1.1
Name: Diketopiperazine
Size: 684 members
Affiliation: Affymax [47]
Note: 36 pools of 19 DKPs per pool. Intracyclative cleavage from solid support.



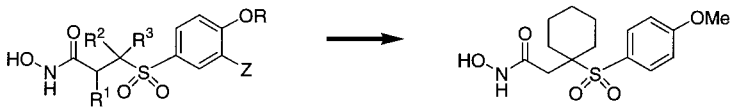
Enzyme: Collagenase-1 (human)
Activity: IC_{50} = 2 μM

Library: 1.2
Name: Diketopiperazine
Size: 684 members
Affiliation: Affymax [47]
Note: 36 pools of 19 DKPs per pool. Regioisomeric to library 1.1. Intracyclative cleavage from solid support.



Enzyme: Collagenase-1 (human)
Activity: IC_{50} = 30 nM (collagenase-1); 79 nM (gelatinase-B, human); 3800 nM (stromelysin-1, human)

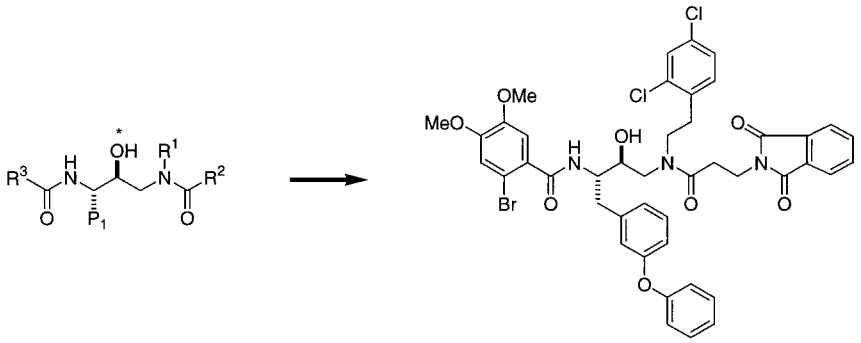
Library: 1.3
Name: Hydroxamic acid
Size: >300 members
Affiliation: Rhone-Poulenc Rorer [10]
Note: Solution-phase synthesis of individual compounds.
Cross reference: library 2.7



Enzyme: Gelatinase-A
Activity: K_i = 10 nM (gelatinase-A, human); 50 nM (stromelysin-1, human); 200 nM (collagenase-1, human); >1,000 nM (phosphodiesterase (PDE4; guinea pig)

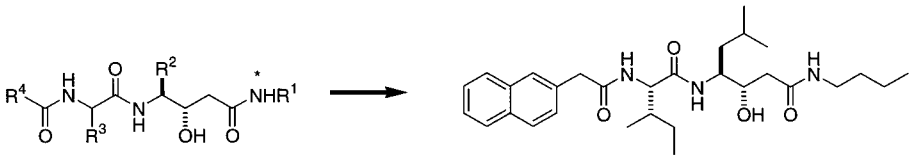
Aspartic acid proteases

Library: 1.4
Name: β-Hydroxyethylamine
Affiliation: Ellman, J. A.; *et al.* [26]
Size: 204 members

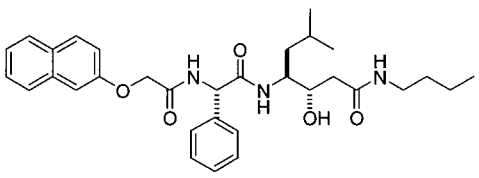


Enzyme: Cathepsin D (human liver)
Activity: K_i = 0.7 nM

Library: 1.5
Name: Statine amide
Size: 13,020
Affillation: Pharmacopeia, Inc. [12]
Note: Encoded library using molecular tags.



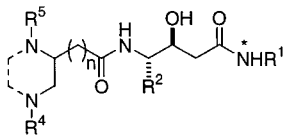
Enzyme: Plasmepsin-II (malaria; *Plasmodium falciparum*)
Activity: K_i = 50 nM (K_i = 320 nM, human cathepsin D)

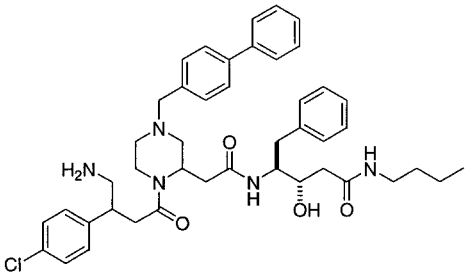


Enzyme: Cathepsin D (human liver)
Activity: K_i = 110 nM (K_i = 5800 nM, malarial plasmepsin II)

Table 1. (Continued)

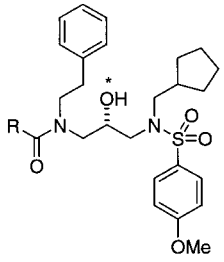
Library: 1.6
Name: Statine amide
Affilliation: Pharmacopeia, Inc. [11]
Size: 18,900 members

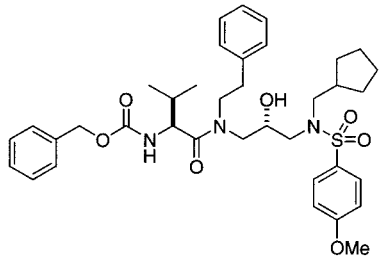




Enzyme: Plasmepsin-II (malaria; *Plasmodium falciparum*)
Activity: K_i = 490 nM (mixture of four diastereomers)

Library: 1.7
Name: β-Hydroxyethylamine
Affilliation: Vertex [55]
Size: 30 members
Note: Optimization library using THP linker.

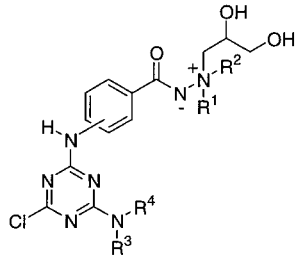


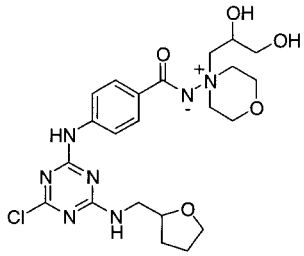


Enzyme: HIV-1 protease
Activity: K_i = 7 nM

Serine proteases

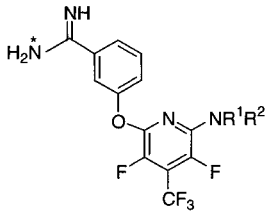
Library: 1.8
Name: Triazine
Size: 262 members
Affilliation: ArQule, Inc. [20]
Note: Solution-phase synthesis.

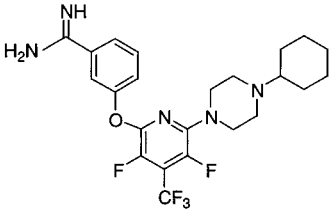




Enzyme: Factor Xa
Activity: K_i = 700 nm (mixture of diastereomers; 50% inhibition of plasmin @10 μM)

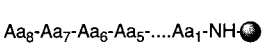
Library: 1.9
Name: Amidinophenoxypyrimidine
Affilliation: Berlex Biosciences [31]
Size: >400





Enzyme: Factor Xa
Activity: K_i = 495 nM

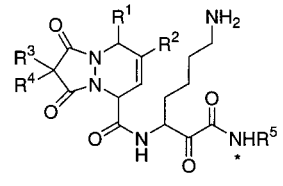
Library: 1.10
Name: Octapeptide
Size: Not defined (large)
Affilliation: Selectide Corp. [39]
Note: L-Amino acids only.
On-bead assay.

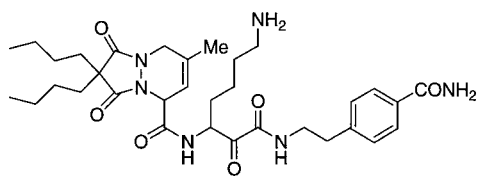


Tyr-Ile-Arg-Lys-Ala-Ala-Phe-Trp-NH_2

Enzyme: Factor Xa
Activity: K_i = 5 μM

Library: 1.11
Name: β-Strand mimetic
Size: ca. 100 members
Affilliation: Molecumetics Ltd. [38]
Note: Diels-Alder reaction using resin-bound diene.

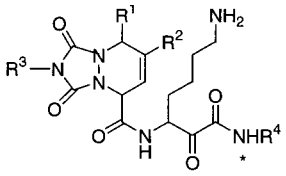


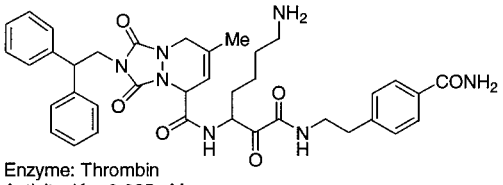


Enzyme: Thrombin
Activity: K_i = 10 nM

Table 1. (Continued)

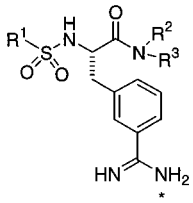
Library: 1.12
Name: β-Strand mimetic
Size: ca. 1500 members
Affilliation: Molecumetics Ltd. [38]
Note: Diels-Alder reaction using resin-bound diene.

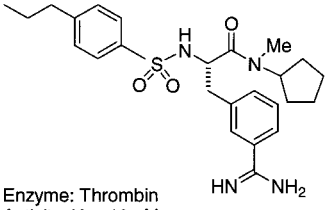




Enzyme: Thrombin
Activity: K_i = 0.035 nM

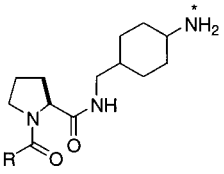
Library: 1.13
Name: Benzamidine sulfonamide
Affilliation: LG Chemical Ltd. [22]
Size: Not defined.

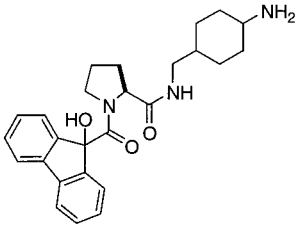




Enzyme: Thrombin
Activity: K_i = 10 nM

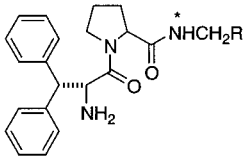
Library: 1.14
Name: Proline amide
Size: ca. 200
Affilliation: Merck [58]
Note: Optimization library, coapplication with structure-based design.

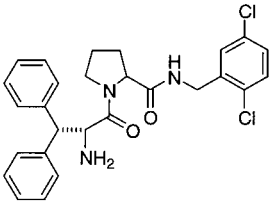




Enzyme: Thrombin (human)
Activity: K_i = 1.5 nM (K_i = 860 nM, trypsin)
Orally bioavailable: 74% at 5 mg/kg (dog),
C_{max} = 4.6 μM at 40 min, iv plasma $t_{1/2}$ = ca. 4 h.

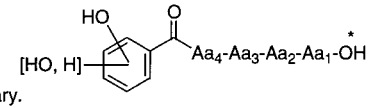
Library: 1.15
Name: Proline amide
Size: ca.18
Affilliation: Merck [28]
Note: Optimization library, coapplication with structure-based design.

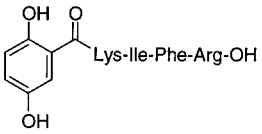




Enzyme: Thrombin (human)
Activity: K_i = 3.0 nM

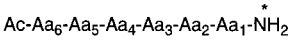
Library: 1.16
Name: Tetrapeptide
Size: 390,625 members
Ref: Kundu, B.; *et al.* [23]
Note: Nazumamide analog library. Natural and unnatural amino acids used.





Enzyme: Thrombin
Activity: IC_{50} = 1.9 uM

Library: 1.17
Name: Hexapeptide
Size: 52,000,000 members
Ref: Lindberg, I.; *et al.* [54]
Note: Houghten library used in screening.

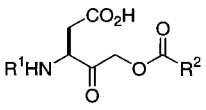


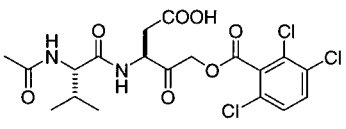
Ac-Leu-Leu-Arg-Val-Lys-Arg-NH_2

Enzyme: Prohormone convertase (mouse)
Activity: K_i = 3.2 nM (PC-1); K_i = 360 nM (PC-2)
K_i = 1440 nM (furin, human)

Cysteine proteases

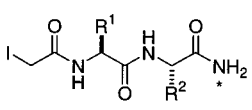
Library: 1.18
Name: Acyloxymethyl ketone
Size: 590 members
Affilliation: Parke-Davis [52]
Note: Solution-phase synthesis.

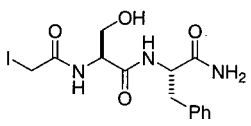




Enzyme: Interleukin-1β converting enzyme (ICE)
Activity: K_i = 113 nM

Library: 1.19
Name: N-Iodo acetyldipeptide
Size: ca. 100 members
Ref: McKendrick, J.E.; *et al.* [30]
Note: Optimal inactivators were identified from iodoacetate mixtures using ESI-MS.



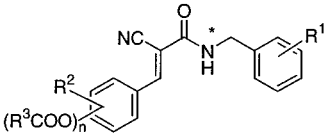


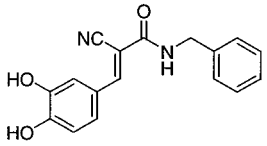
Enzyme: Hepatitis A virus 3C proteinase
Activity: k_2 = 840 $M^{-1}s^{-1}$

[a] The asterisk (∗) represents the point of attachment to the solid support.

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

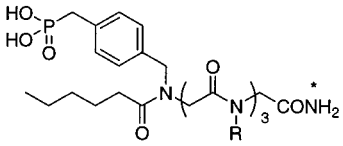
Library: 2.1
Name: Tyrphostin analog
Size: 432 members
Affilliation: IRORI [43]
Note: Solid-phase synthesis using radio frequency tags.

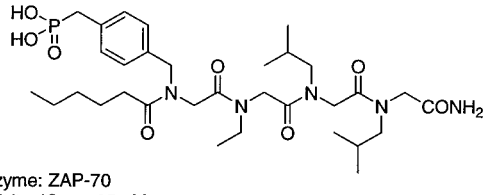




Enzyme: Jak-2
Activity: Blocks leukemia cell growth

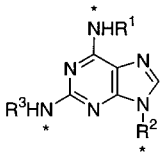
Library: 2.2
Name: Tetrapeptoid
Size: 27 members
Affilliation: Novartis [40]

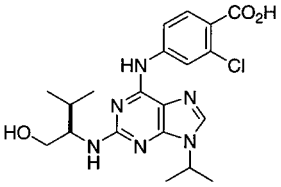




Enzyme: ZAP-70
Activity: IC_{50} = 25 uM

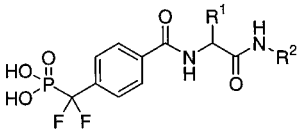
Library: 2.3
Name: Trisubstituted purine
Size: not disclosed
Affilliation: Schultz, P. G.; *et al.* [60]
Note: First generation libraries carried out on solid-phase using mutiple attachment strategies. Solution-phase synthesis employed for optimization. Details not disclosed.

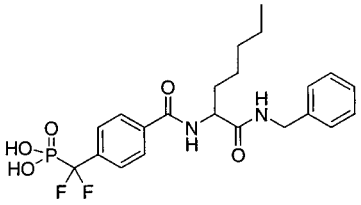




Enzyme: CDK2-cyclin A (human)
Activity: IC_{50} = 6 nM (IC_{50} = 9 nM, cdk2-cyclin E; IC_{50} = 6 nM, cdc2-cyclin B)

Library: 2.4
Name: α,α-Difluoromethylene-phosphoric acid
Size: 108 members
Affilliation: Li, Z.; *et al.* [27]
Note: Ugi four-component condensation using RINK resin.

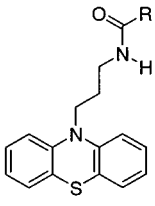


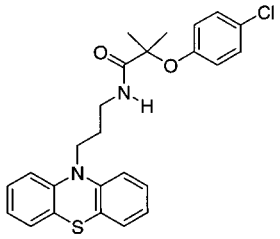


Enzyme = Protein tyrosine phosphatase (PTPα, PTPβ, PTPε)
Activity = >50% inhibition of PTPε @100 μM

Other enzymes (mammalian)

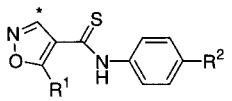
Library: 2.5
Name: Phenothiazine
Size: 48 members
Affilliation: Abbott Labs. [45]
Note: Solution-phase synthesis. Structure-based design.

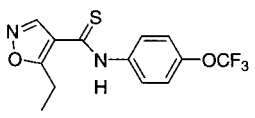




Enzyme: Cyclooxygenase-2 (COX-2; human)
Activity: IC_{50} = 1.3 μM (IC_{50} >50 μM, COX-1)

Library: 2.6
Name: Isoxazolylthioamide
Size: ca. 25
Affilliation: Novartis [2]
Note: Derivatives of leflunomide.



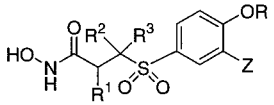


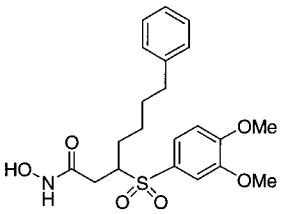
Enzyme: Dihydroorotate dehydrogenase (recombinant human)
Activity: IC_{50} = 700 nM

Table 2. (Continued)

Other enzymes (non-mammalian)

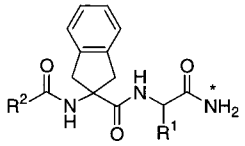
Library: 2.7
Name: Hydroxamic acid
Size: >300 members
Affilliation: Rhone-Poulenc Rorer [10]
Note: Solution-phase synthesis.
Cross-reference: library 1.3

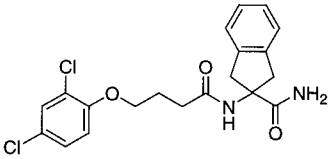




Enzyme: Phosphodiesterase-4 (PDE-4)
Activity: 1.0 nM (guinea pig macrophage homogenate)

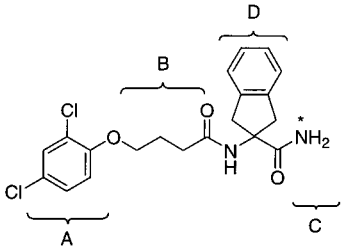
Library: 2.8
Name: N-acylated didpeptide
Size: 1296 members
Affilliation: Affymax [6]
Note: Inhibitor found in the library was a deletion adduct formed through incomplete coupling of the first amino acid.

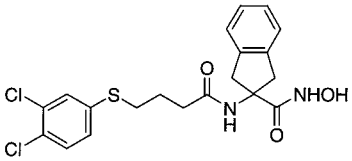




Enzyme: Phosphomannose isomerase (PMI; *C. albicans*)
Activity: K_i = 27 μM (slow-binding, irreversible inactivation)

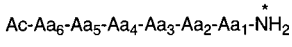
Library: 2.9
Name: Phenoxybutyric acid amide
Size: ca. 700 members total
Affilliation: Affymax [6]
Note: Multiple optimization libraries prepared based on the 27 μM lead obtained in library 2.8.





Enzyme: Phosphomannose isomerase (PMI; *C. albicans*)
Activity: K_i = 4 μM (slow-binding, irreversible inactivation; K_i = 26 μM, human PMI)
Microbe: *C. albicans*: MIC = 80 μM

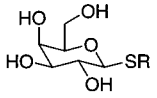
Library: 2.10
Name: L-Hexapeptide
Affilliation: Mooser, G.; *et al.* [16]
Size: >1,000,000 members

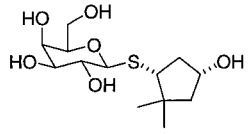


Ac-Phe-Phe-Arg-Glu-Tyr-Trp-NH_2

Enzyme: Glucosyltransferase-I (GFT-I; *Streptococcus sorinus*)
Activity: K_D = 1,400 uM

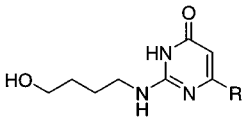
Library: 2.11
Name: 1-Thio-β-galactopyranoside
Size: >3,000 members
Affilliation: Hindsgaul, O.; *et al.* [36]
Note: Solution-phase synthesis.

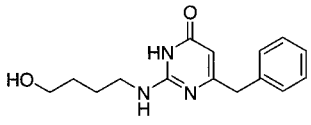




Enzyme: β–Galactosidase (*E. coli*)
Activity: K_i = 1.7 μM

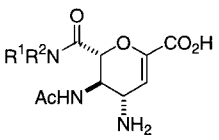
Library: 2.12
Name: 4(3*H*)-Pyrimidinone
Size: 6 members
Affilliation: Botta, M.; *et al.* [37]
Note: Solution-phase synthesis.

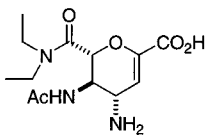




Enzyme: HIV-1 reverse transcriptase
Activity: K_i = 75 μM (TIBO/nevirapine resistant mutant; K_i = 410 μM, wild type)

Library: 2.13
Name: Dihydropyrancarboxamides
Size: 80 members
Affilliation: Glaxo Wellcome [63]
Note: Solution-phase synthesis.





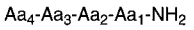
Enzyme: Influenza A virus sialidase
Activity: IC_{50} = 3 nM (Flu A sialidase; IC_{50} = 360 nM, Flu B sialidase)

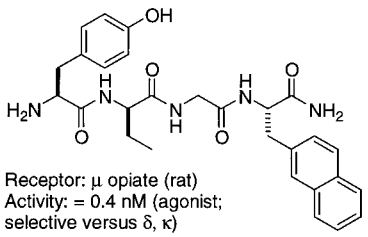
[a] The asterisk (∗) represents the point of attachment to the solid support.

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

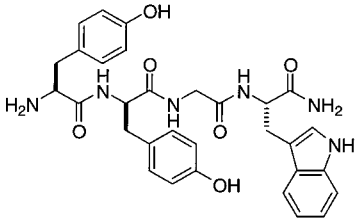
Opiate receptors

Library: 3.1
Name: Tetrapeptide
Size: 6,250,000 members
Ref: Dooley, C. T.; *et al.* [17]
Note: Mixture-based positional scanning format. L-, D-natural and unnatural amino acids.

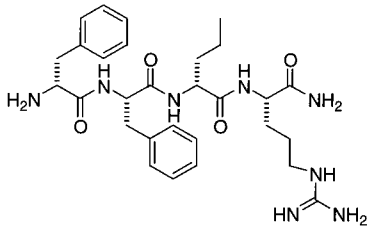




Receptor: μ opiate (rat)
Activity: = 0.4 nM (agonist; selective versus δ, κ)

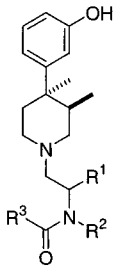


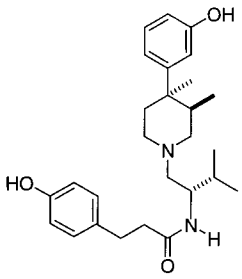
Receptor: δ opiate (rat)
Activity: 3 nM (agonist; selective versus κ)



Receptor: κ opiate (guinea pig)
Activity: 1.2 nM (agonist; selective versus μ, δ)

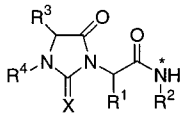
Library: 3.2
Name: 3-Hydroxyphenyl piperidine
Size: 288 members
Affiliation: Res. Triangle Inst. [48]
Note: Solution-phase synthesis using optically active (+)-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine.

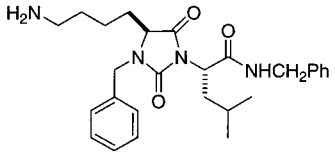




Receptor: κ opiate (guinea pig)
Activity: 6.9 nM (antagonist; μ/κ = 57; δ/κ = >870)

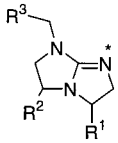
Library: 3.3
Name: Hydantoin
Size: 38,880 members
Affiliation: Houghten, R. A.; *et al.* [33]





Receptor: σ opiate
Activity: IC_{50} = 62 nM

Library: 3.4
Name: Bicyclic guanidine
Size: 102,459 members
Affiliation: Houghten, R. A.; *et al.* [33]

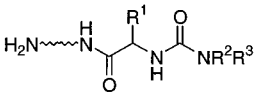


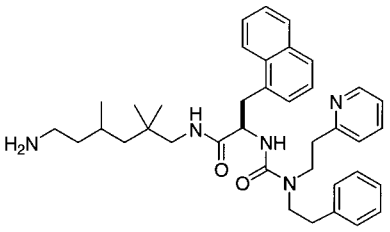
Structure not disclosed.

Receptor: κ opiate
Activity: IC_{50} = 37 nM

Somatostatine receptors

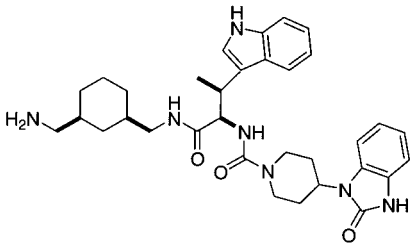
Libraries: 3.5a-d
Name: Peptidomimetic
Size: >100,000 members total
Affiliation: Merck [41]
Note: Multiple libraries based on amino acid amide theme. Original lead was a C-/N-derivatized tryptophan residue (see text). Split-pool synthesis and deconvolution methodology; not disclosed whether synthesis was carried out by solid- or solution-phase methods.



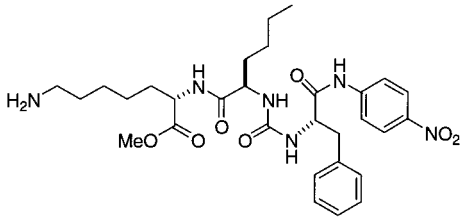


Receptor: Somatostatin-1 (sstr1; human)
Activity: K_i = 1.4 nM (agonist; >100x selective vs. sstr2-5)

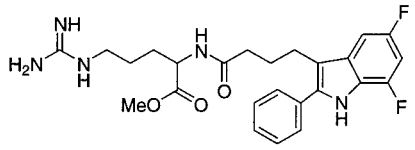
Table 3. (Continued)



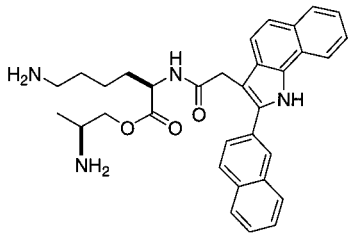
Receptor: Somatostatin-2 (sstr2; human)
Activity: K_i = 0.5 nM agonist; (>1000x selective vs. sstr1,3-5)



Receptor: Somatostatin-3 (sstr3; human)
Activity: K_i = 24 nM (agonist; >50x selective vs. sstr1,2,4,5)

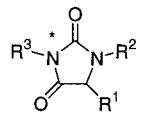


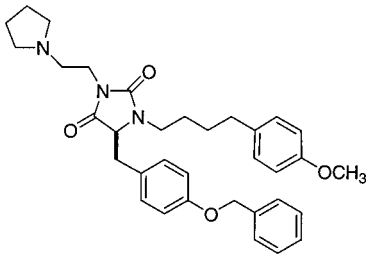
Receptor: Somatostatin-4 (sstr4; human)
Activity: K_i = 0.7 nM (agonist; >100x selective vs. sst1-3,5)



Receptor: Somatostatin-5 (sstr5; human)
Activity: K_i = 0.4 nM (agonist; K_i = 3.4 nM, sstr1; >100x selective vs. sstr2-4)

Library: 3.6
Name: Hydantoin
Size: >60 members
Affiliation: Glaxo Wellcome [42]
Note: Intracyclative cleavage. Original lead was a thiazolidinone (pIC_{50} = 5.85: selective sstr5 agonist) obtained from an Affymax general screening library.





Receptor: Somatostatin-5 (sstr5; recombinant human)
Activity: $_pIC_{50}$ = 6.5 (agonist; selective against sstr2)

Library: 3.7
Name: D-Hexapeptide
Size: 64,000,000 members
Affiliation: American Cyanamid [56]
Note: Library synthesis via positional scanning protocol. Primary screening using SRIF-responsive yeast growth assay.

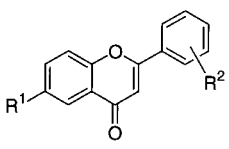
Ac-D-Aa_6-D-Aa_5-....D-Aa_1-NH_2*

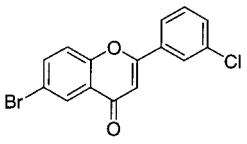
Ac-D-His-D-Phe-D-Ile-D-Arg-D-Trp-D-Phe-NH_2

Receptor: Somatostatin-2 (sstr2; rat)
Activity: K_i = 172 nM (antagonist; sstr5: K_i = ca. 230 nM)

Benzodiazepine receptors

Library: 3.8
Name: Flavone
Size: 36 members
Ref: Marder, M.; *et al.* [29]
Note: Solution-phase synthesis.





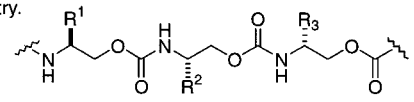
Receptor: Benzodiazepine (rat)
Activity: 17 nM

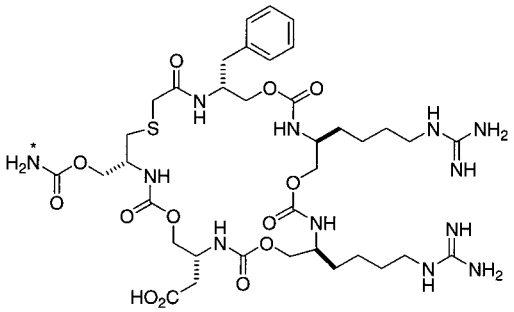
[a] The asterisk (*) represents the point of attachment to the solid support.

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

Integrin receptors

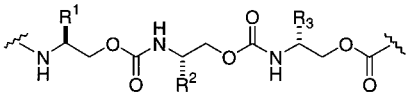
Library: 4.1
Name: Cyclic oligocarbamate
Size: 530,000 members
Affiliation: Schultz, P. G.; *et al.* [13]
Note: Solid-phase synthesis. Sequencing performed using MALDI mass spectrometry.

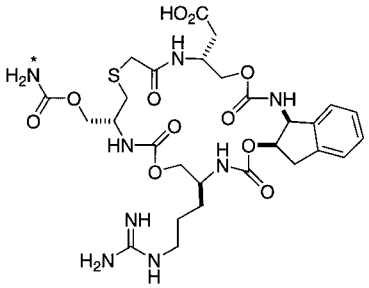




Target: GPIIb/IIIa
Activity: IC_{50} = 4.9 nM

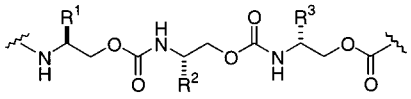
Library: 4.2
Name: Cyclic oligocarbamate
Size: 20,000 members
Affiliation: Schultz, P. G.; *et al.* [13]
Note: See library 4.1.

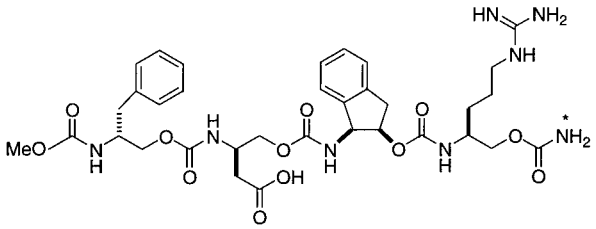




Target: GPIIb/IIIa
Activity: IC_{50} = 3.9 nM

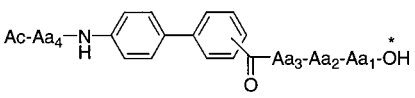
Library: 4.3
Name: Cyclic oligocarbamate
Size: 20,000 members
Affiliation: Schultz, P. G.; *et al.* [13]
Note: See library 4.1.

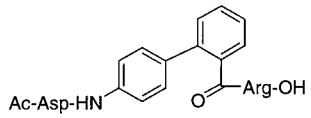




Target: GPIIb/IIIa
Activity: IC_{50} = 13 nM

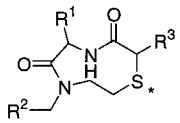
Library: 4.4
Name: Biaryl
Size: ca. 275,000 members total
Affiliation: Schering-Plough [34]
Note: Multiple split-pool libraries.

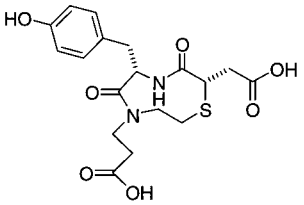




Receptor: $\alpha_v\beta_3$ (human)
Activity: IC_{50} = 34 μM

Library: 4.5
Name: Turn mimetic
Size: 5,500 members
Affiliation: Ellman, J. A.; *et al.* [44]
Note: Reductive cleavage of disulfide and intramolecular cyclization. From the 5000+ library, a subset of 2304 members having an Asp residue was selected for screening.

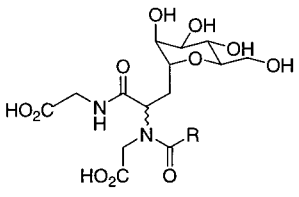


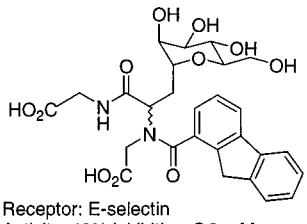


Receptor: $\alpha_4\beta_1$(integrin-CS1)
Activity: IC_{50} = 5.0 μM

Selectins

Library: 4.6
Name: Sialyl Lewis X mimetic
Size: 11 members
Affiliation: Wong, C.-H.; *et al.* [50]
Note: Ugi four-component reaction.

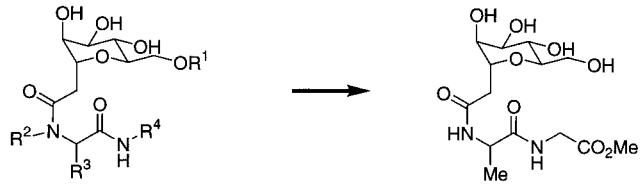




Receptor: E-selectin
Activity: 48% inhibition @3 mM

Table 4. (Continued)

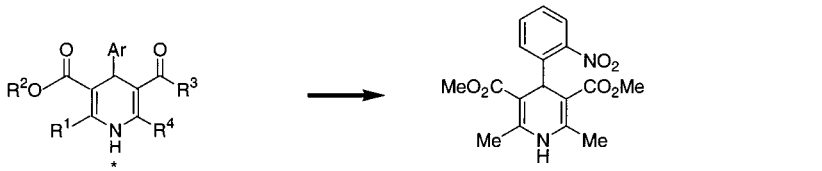
Library: 4.7
Name: Sialyl Lewis X mimetic
Size: 15 members
Affiliation: Wong, C.-H.; *et al.* [50]
Note: Ugi four-component reaction.



Receptor: E-selectin
Activity: IC_{50} = 360 μM

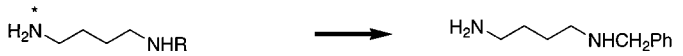
Ion channels and uptake mechanisms

Library: 4.8
Name: 1,4-Dihydropyridine
Size: 300 members
Affiliation: Affymax [19]



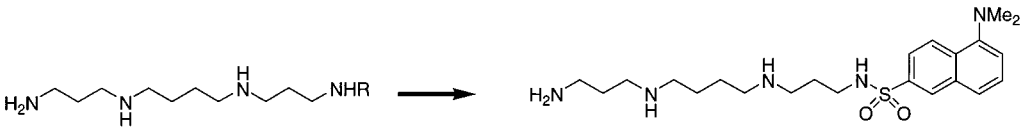
Target: Calcium channels (rat cerebral cortex)
Activity: IC_{50} = 12 nM

Library: 4.9
Name: Polyamine
Size: 6 members
Affiliation: Uriac, P.; *et al.* [49]



Target: Inhibition of [^{14}C]putrescine uptake
Activity: IC_{50} = 14.4 μM

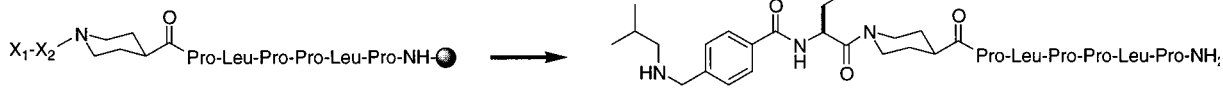
Library: 4.10
Name: Polyamine
Size: 6 members
Affiliation: Uriac, P.; *et al.* [49]



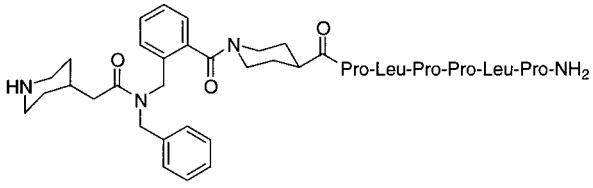
Target: Inhibition of [^{14}C]putrescine uptake
Activity: IC_{50} = 0.46 μM

Domain interactions

Library: 4.11
Name: Peptidomimetic
Size: 2,499 members
Affiliation: Schreiber, S. L.; *et al.* [21]
Note: Encoding using photo cleavable tags. On-bead assay.

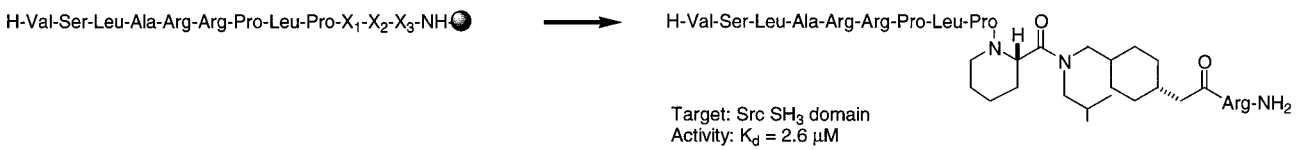


Target: Src SH3 domain
Activity: K_d = 0.9 μM



Target: Hck SH3 domain
Activity: K_d = 1.3 μM (K_D = 46 μM,Src SH3 domain; K_d= 215 μM, PI3K SH3 domain)

Library: 4.12
Name: Peptidomimetic
Size: 125,000 members
Affiliation: Schreiber, S. L.; *et al.* [32]
Note: Encoding using photo cleavable tags. On-bead assay.



Target: Src SH_3 domain
Activity: K_d = 2.6 μM

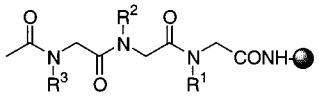
Table 4. (Continued)

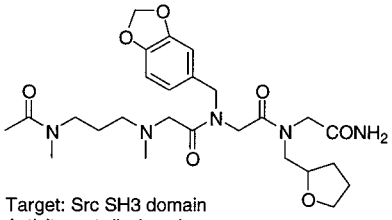
Library: 4.13
Name: Decapeptide
Size: 14 members
Affiliation: Muir, T. W.; *et al.* [59]
Note: Encoded library using amino acid scanning.

H-Pro-Pro-Pro-Ala-X_1-Pro-Pro-X_2-Lys-Arg-(encoding Aa)-OH* → H-Pro-Pro-Pro-Ala-Phe-Pro-Pro-Lys-Lys-Arg-(encoding (pCl)Phe)-OH

Target: c-Crk SH3 domain
Activity: K_d = ca 0.5 μM

Library: 4.14
Name: Peptoid
Size: 1000 members
Affiliation: Glaxo Wellcome [51]
Note: On-bead assay. Encoded synthesis using stable isotopes.

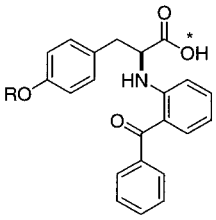


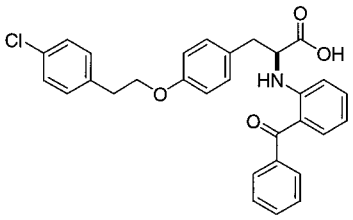


Target: Src SH3 domain
Activity: not disclosed

Nuclear receptors, transcription factors, and other receptors

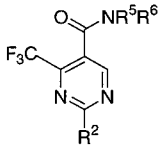
Library: 4.15
Name: N-(2-Benzoylphenyl)-L-tyrosine ether
Size: ca. 75
Affiliation: Glaxo Wellcome [14]
Note: Solid-and solution-phase Mitsunobu etherification.

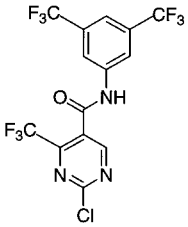




Receptor: Nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ)
Activity: PPARγ pK_i = 8.03 (PPARα inactive)

Library: 4.16
Name: Substituted pyrimidine
Size: ca. 160 members
Affiliation: Signal Pharm., Inc. [46]
Note: Solution-phase parallel synthesis.

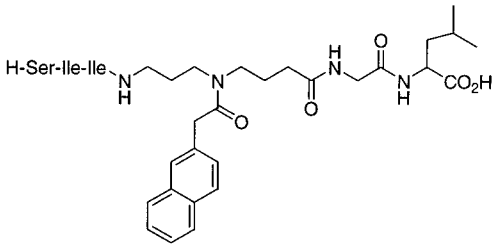




Transcription factors: NF-κB and AP-1
Activity: IC_{50} (NF-κB) = 50 nM
Activity: IC_{50} (AP-1) = 50 nM

Library: 4.17
Name: Peptidomimetic
Size: 104 members
Affiliation: Bianco, A.; *et al.* [57]
Note: Four sub-libraries of 26 members each where Aa is defined by Leu, Ile, Val, and Met.

H-Ser-Ile-Ile-spacer-Aa-OH*



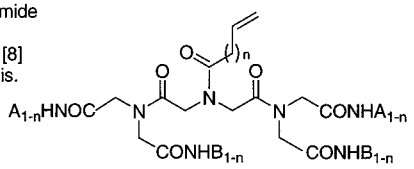
Target: MHC-I (mouse)
Activity: H-$2K^b$ stabilization (C_{stab50}) = ca. 5 μM

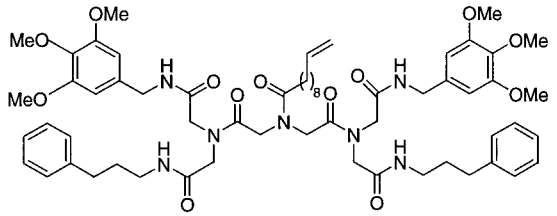
[a] The asterisk (*) represents the point of attachment to the solid support.

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

Cytotoxic agents

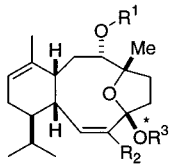
Library: 5.1
Name: Iminodiacetic acid diamide
Size: 20,200 members
Affiliation: Boger, D. L.; *et al.* [8]
Note: Solution phase synthesis.

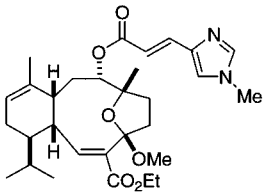




Target: L-1210 cells (in vitro cytotoxic assay)
Activity: 0.6 μg/mL

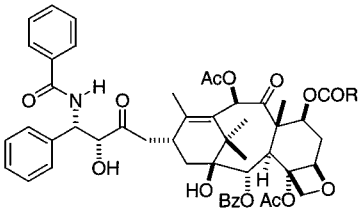
Library: 5.2
Name: Sarcodictyin analog
Size: ca. 65 member
Affiliation: Nicolaou, K. C.; *et al.* [35]
Note: Combination of solution- and solid-phase methodology.

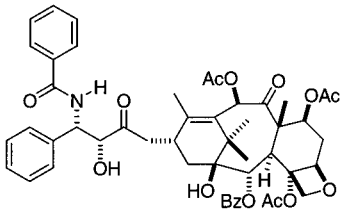




Target: Ovarian cancer cells (1A9)
Activity: IC_{50} = 2.0 uM

Library: 5.3
Name: Taxol analog
Size: ca. 26 members
Affiliation: Georg, G. I. ; *et al.* [7]
Note: Solution-phase synthesis.

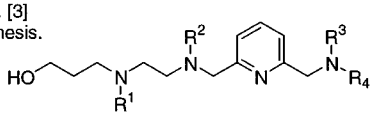


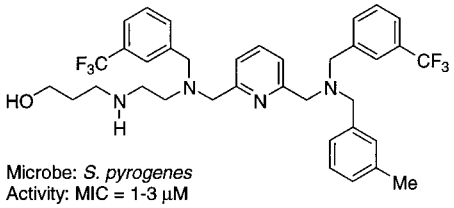


Assay: Microtubule assembly
Activity: ED_{50}/ED_{50} (Paclitaxel) = 0.7

Antimicrobial agents

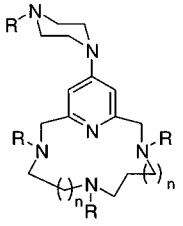
Library: 5.4
Name: Pyridinopolyamine
Size: 1,638 members
Affiliation: Isis Pharm., Inc. [3]
Note: Solution-phase synthesis.

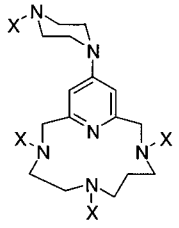




Microbe: *S. pyrogenes*
Activity: MIC = 1-3 μM

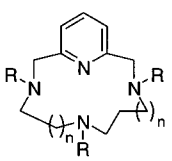
Library: 5.5
Name: Piperazinylpolyazacyclophane
Size: 16,000 members total
Affiliation: Isis Pharm., Inc. [5a]
Note: Solution-phase synthesis of 26 libraries.

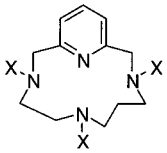




Microbe: *S. pyrogenes*
Activity: MIC = 2-10 μM (625 component mixture; deconvolution not performed)

Library: 5.6
Name: Polyazapyrimidinocyclophane
Size: 4,275 members
Affiliation: Isis Pharm., Inc. [4a]
Note: Solution-phase synthesis of 40 libraries.

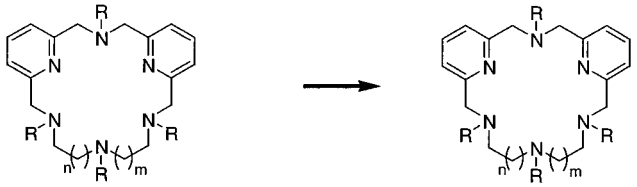




Microbe: *S. pyrogenes*
Activity: MIC = 1-5 μM (ca. 40 component mixture; deconvolution not performed)

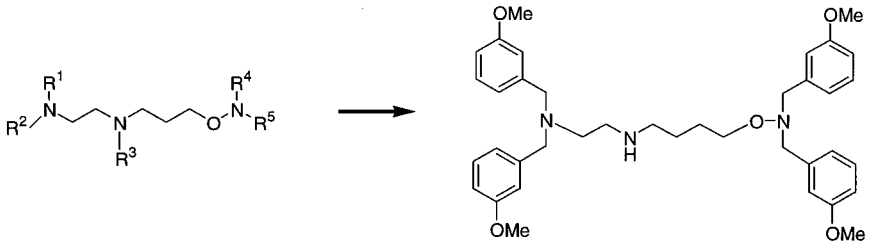
Table 5. (Continued)

Library: 5.7
Name:
Polyazadipyridinocyclophane
Size: 24,875 members
Affiliation: Isis Pharm., Inc. [4b]
Note: Solution-phase synthesis of 29 libraries. Some mixtures active against the HIV-1 tat/TAR protein-RNA interaction.



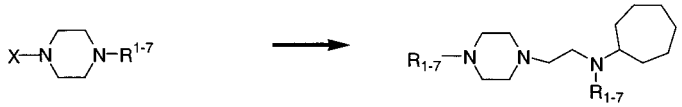
Microbe: *S. pyrogenes*
Activity: MIC = 2-5 μM (625 component mixture; deconvolution not performed)

Library: 5.8
Name: Oxyamine
Size: 15 members
Affiliation: Isis Pharm., Inc. [24]
Note: Solution-phase synthesis.



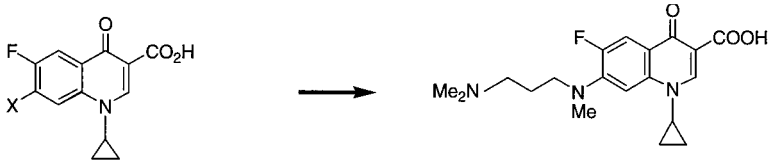
Microbe: *S. pyrogenes*
Activity: MIC = 1-5 μM

Library: 5.9
Name: Piperazine
Size: ca. 100 members
Affiliation: Isis Pharm., Inc. [25]
Note: Solution-phase synthesis.



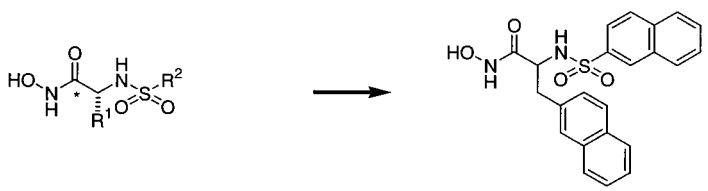
Microbe: *S. pyrogenes*
Activity: MIC = 25-50 μM (49 component mixture; deconvolution not performed)

Library: 5.10
Name: Quinolone
Size: 68 members
Affiliation: Mitscher, L. A.; *et al.* [18]
Note: Solution-phase synthesis.



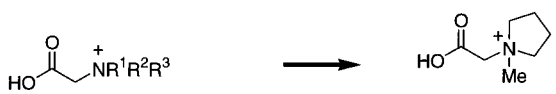
Microbe: *S. aureus* ATCC 6538P
Activity: MIC = 0.78 μg/mL

Library: 5.11
Name: Hydroxamic acid
Size: 1,296 members
Affiliation: ProtoGene Lab. [9]
Note: 96 well parallel array synthesizer used. Resin bound carboxylic acid (Wang ester) cleaved with aq hydroxylamine.



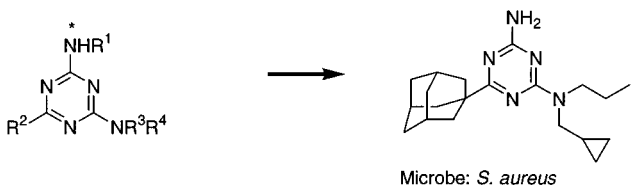
Microbe: *E. coli*
Activity: MIC = 0.7-1.5 μM

Library: 5.12
Name: Trialkylamino acetate
Size: 7 members
Affiliation: Pichereau, V.; *et al.* [15]



Microbe: *S. meliloti*
Activity: D*max* = 0.6

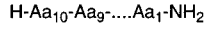
Library: 5.13
Name: Triazine
Size: 46,000 members
Affiliation: Affymax [62]
Note: Encoded library (36 x 36 x 36) on photocleavable linker. Screening using a two-dimensional agar format.



Microbe: *S. aureus*
Activity: MIC = 4 μg/mL

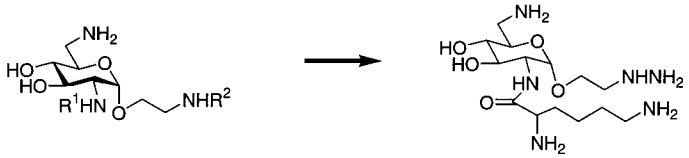
Table 5. (Continued)

Library: 5.14
Name: Decapeptide
Size: 40,353,607 members
Affiliation: Mogam Biotech. Res. Inst. [61]
Note: Positional scanning using tea-bags.



H-Lys-Lys-Val-Val-Phe-Lys-Val-Lys-Phe-Lys-NH_2
Microbe: *C. albicans* ATCC 36232
Activity: MIC = 0.78 μg/mL (irreversible growth inhibition)

Library: 5.15
Name: Aminoglycoside mimetic
Size: 24 members
Affiliation: Wong, C.-H.; *et al.* [53]
Note: Solution-phase synthesis. The 16S ribosome is the target for aminoglycoside antibiotics.

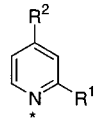


Target: A-site 16S ribosomal RNA
Activity: K_d = 15 μM (wild-type RNA model)

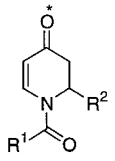
[a] The asterisk (*) represents the point of attachment to the resin.

Table 6. Scaffold Derivatization[a]

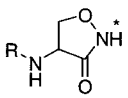
Solid-phase



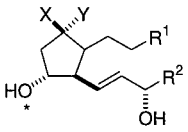
- SIBA Neurosci. [93]
- 5 ex; 65-75%
- up to 30% 1,2,5,6-tetrahydropyridine



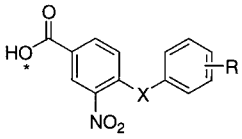
- SIBA; Neurosci. [92]
- 18 ex; 19-62%
- 1,4-addition to N-acylated-4-alkoxypyridine



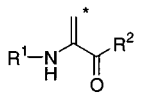
- Versicor [116]
- 80 members
- derivatization of resin-bound cycloserine



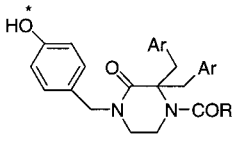
- Ellman, J. A. [209]
- 11 ex; 49-60%



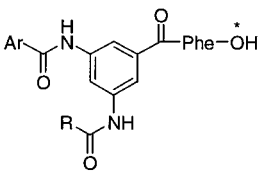
- Oxford Diversity [224]
- 17 ex; 40-58%
- biaryl ether formation; X = O,S



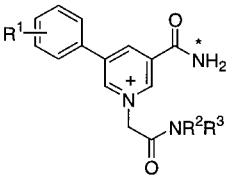
- Tanabe Seiyaku [229]
- 7 ex; 31-86%
- β-elimination of S-linked cysteine derivatives



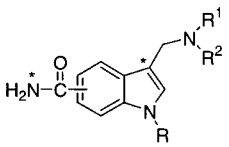
- Schering-Plough [232]
- 30 members
- C-alkylation of resin-bound 2-ketopiperazine



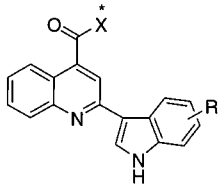
- Schering-Plough [171]
- 75 ex; 80-90%



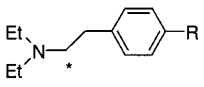
- SKB [150]
- 11 ex; 25-80%
- Suzuki biaryl coupling



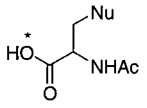
- R. W. Johnson [231]
- 10 ex; 90-100%
- Mannic reaction of resin-bound indoles



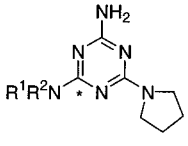
- Sepracor [123]
- 9 ex; 38-100%
- from resin-bound quinoline N-oxide; X = OH, NRR



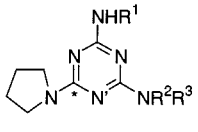
- R. W. Johnson [69]
- 14 ex; 45-95%
- Et_2NH-mediated cleavage of resin-bound sulfonate esters



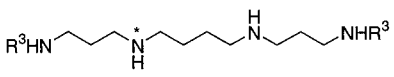
- Barbaste, M. [65]
- 2 members
- Michael addition of 1,2,4-triazole or pyrazole



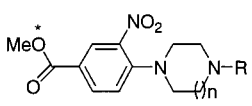
- Hoffmann-La Roche [161]
- 6 members
- from resin-bound thiouronium salt



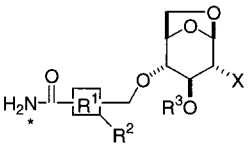
- Hoffmann-La Roche [161]
- 8 ex; 29-85%
- thiol resin and cyanuric chloride



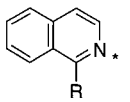
- Bradley, M. [177]
- 4 members



- Sun, C.-M. [178]
- 12 ex; >95%
- Nucleophilic aryl substitution (S_nAr)

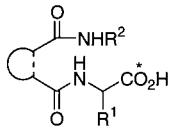


- Novartis [84]
- 40 ex; 14-95%
- levoglucosan; X = OR; NRR; SR

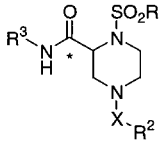


- Miller, R. B. [155]
- 5 ex; ~ 50%
- alkylation of resin-bound Reissert complex

Table 6. (Continued)

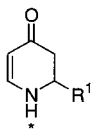


- Scios [183]
- 40 ex; 70-90%
- ring opening and amidation of anhydrides

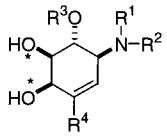


- Arris [82]
- 2816 members
- amine cleavage of ester linkage

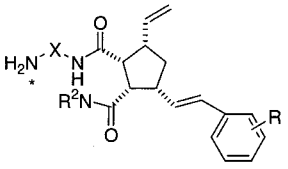
- Nova Nordisk [190]
- 12 ex; 34-78%
- Curtius rearrangement



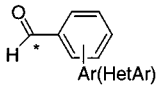
- SIBA Neurosci. [93]
- 7 ex; 31-67%
- C-2 alkylation of acyl pyridiniums



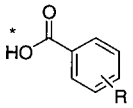
- Novartis [222]
- 6 ex; 73-98%
- Nu ring opening of expoxide; ketal linkage



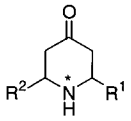
- Sepracor [88]
- 4608 members
- ring opening cross-metathesis on solid-phase



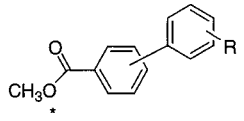
- Snieckus, V. [89]
- 15 ex; 45-95%
- acetal linker



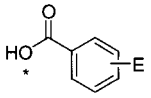
- Snieckus, V. [90]
- 22 ex; 71-75%
- Stille cross-coupling



- SIBA Neurosci. [91]
- 3 ex; 27-32%
- 1,4-addition to dihydropyridone

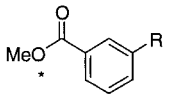


- Schotten, T. [235]
- 18 ex; 52-98%
- Suzuki coupling on soluble polymer support

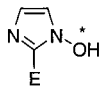


- Knochel, P. [236]
- 12 ex; > 90%
- resin-bound Grignard reagent; heteroaryl also used.

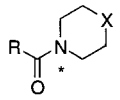
- Park-Davis [245]
- 12 ex; 0-85%
- reductive cleavage of resin-bound arylsulfonates



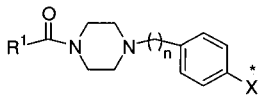
- Kang, S.-K. [246]
- 5 ex; 55-94%
- CuI-catalyzed cross-coupling of resin-bound aryl iodide with organostannanes.



- Begtrup, M. [244]
- 8 ex; 52-93%
- ortho-lithiation



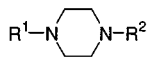
- Schering-Plough [249]
- 11 ex; 40-97%
- N-dealkylation with acid chlorides; X = CH_2, NBn



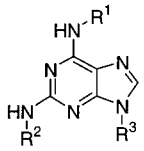
- Meiji Seika Kaisha [257]
- 6 ex; 31-70%
- asymmetric N,N'-disubstituted piperazine; X = OH, COOH

- Pfizer [238]
- 27 ex; 59-100%
- use of indole linker

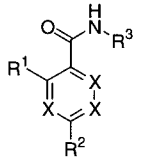
Solution-phase



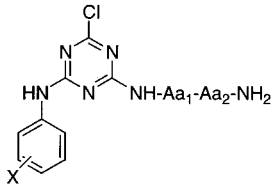
- Neurocrine Biosci. [228]
- 1086 members
- N-alkylation and N-acylation using water soluble base



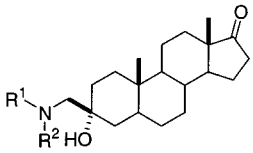
- Abell, C. [106]
- ca. 19 ex; 54-98%
- from 2,6-dichloropurine



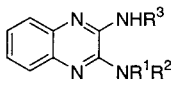
- Signal Pharm. [207]
- >4500 members
- acylation reaction using ion-exchange resins



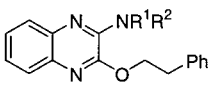
- ArQule [20]
- 400 members



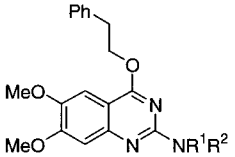
- Poirier, D. [158]
- 20 ex; 40-70%
- epoxide ring opening then N-acylation



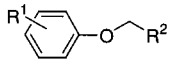
- Arris [130]
- 384 members
- from 2,3-dichloroquinoxaline; X = NRR, OR



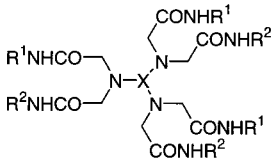
- Arris [130]
- 96 members
- from 2-chloro-3-phenoxyethyl quinoxaline



- Arris [130]
- 96 members
- from 2-chloro-4-phenoxy-6,7-dimethoxy quinazoline

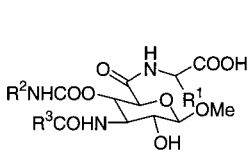


- Higuchi Biosci. [213]
- 15 ex; 59-94%
- polymer-bound diaryl phosphine for Mitsunobu reaction

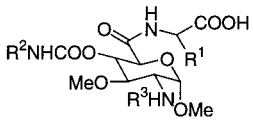


- Boger, D. L. [79]
- 560 members
- from iminodiacetic acid

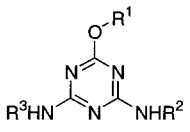
Table 6. (Continued)



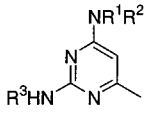
- Transcell Tech. [202]
- >48 members



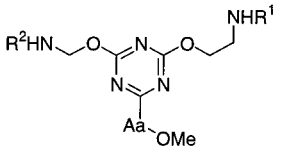
- Transcell Tech. [202]
- >48 members



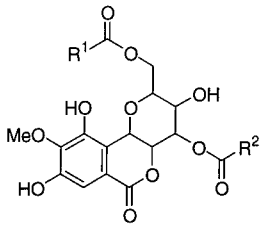
- Arris [130]
- 1920 members
- from cyanuric acid



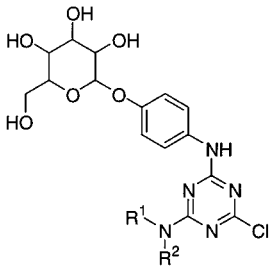
- Arris [130]
- 384 members
- from 2,4-dichloro-6-methylpyrimidine



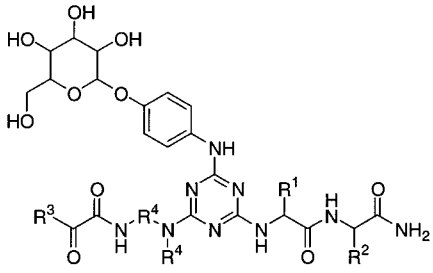
- Falorni, M. [104]
- 39 members



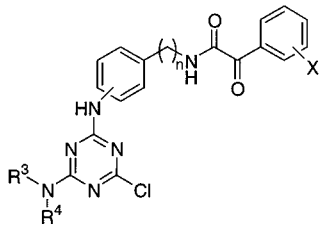
- EnzyMed [167]
- 167 ex; 60-90%
- enzymatic acylation



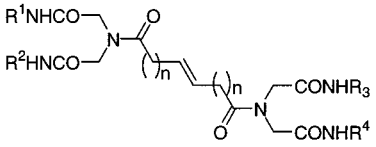
- ArQule [20]
- 320 members



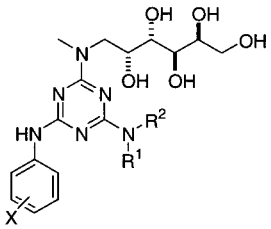
- ArQule [20]
- 320 members



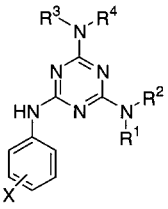
- ArQule [20]
- 2,500 members



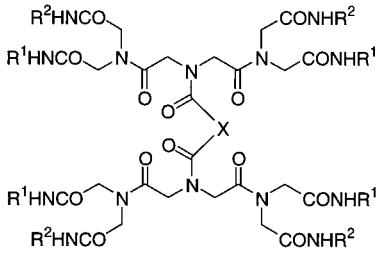
- Boger, D. L. [78a]
- >100,00 members
- multiple libraries
- from iminodiacetic acid



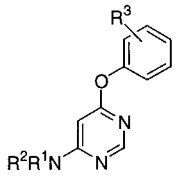
- ArQule [20]
- 6,400 members



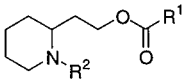
- ArQule [20]
- 12,800 members



- Boger, D. L. [79]
- 1,260 members
- from iminodiacetic acid



- Arris [130]
- 768 members
- from 4,6-dichloropyrimidine

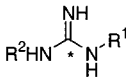


- Searle [204]
- 9 ex; 47-60%
- Mitsunobu reaction with "tagged resin" capture method

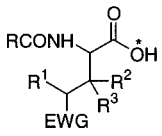
[a] The asterisk (∗) represents the point of attachment to the solid support.

Table 7. Acyclic Synthesis[a]

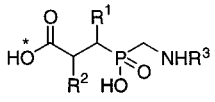
Solid-phase



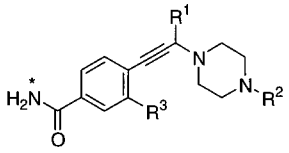
- BMS [99]
- 13 ex; 0-100%
- amine-mediated cleavage of resin-bound thiopseudoureas



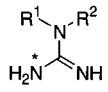
- Dominguez, E. [100]
- 15 ex; 0-88%
- Michael addition to benzophenone imine



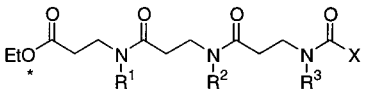
- Pfizer [101]
- 7 ex; 22-44%



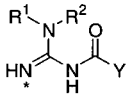
- R. W. Johnson [103]
- 13 ex; 70-89%
- Sonogashira and Mannich reactions



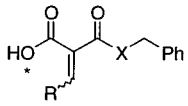
- Amgen [132]
- 40 ex; 40-85%
- novel thiourea linker



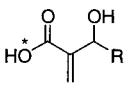
- Monsanto [119]
- 4,096 members
- successive Michael additions to acrylic amides



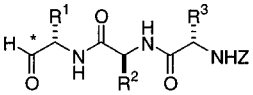
- Amgen [132]
- 40 members
- novel thiourea linker; Y = OR, R



- Monsanto [120]
- 8 ex; 47-100%
- Knoevenagel condensation; X = NH, O

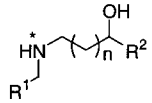


- Jung, G. [189]
- 26 members
- Baylis-Hillman reaction

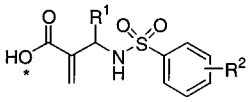


- Cambridge Combin. [118]
- 27 members
- ozonolysis of resin-bound allylic amine

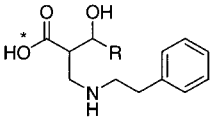
- Lilly [102]
- 9 members
- amine-mediated cleavage of resin bound carbamates



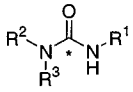
- BMS [186]
- 24 ex; 30-73%
- amines released from Knorr resin



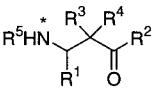
- Jung, G. [188]
- 16 ex; 70-90%
- three-component condensation



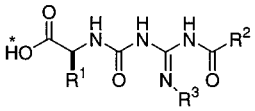
- Jung, G. [189]
- 25 members
- Baylis-Hillman followed by 1,4-amine addition



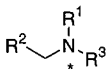
- DuPont [184]
- 10 ex; 77-99%
- thermolytic cleavage of oxime-carbamates



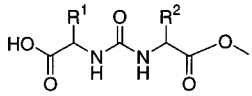
- Kobayashi, S. [146]
- 6 members
- condensation of resin-bound imine and silylenol ether with $Yb(OTf)_3$



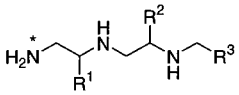
- Ganesan, A. [155]
- 12 ex; 53-93%



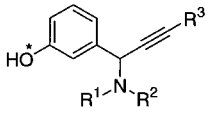
- Amgen [175]
- 14 ex; 10-70%
- Hofmann elimination; >95% purity



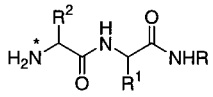
- Organon [173]
- >100; 70-100%
- also performed in solution-phase



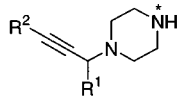
- Houghten, R. A. [174]
- >100,000 members
- borane reduction of resin-bound N-acylated dipeptides



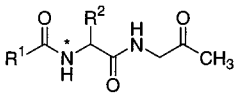
- R. W. Johnson [164]
- 3 ex; >80%
- Mannich reaction with resin-bound amines or resin-bound aldehydes



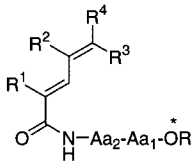
- Microside [152]
- 10 ex; 37-71%
- N-linked peptide synthesis



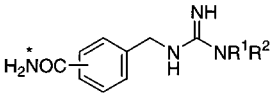
- R. W. Johnson [164]
- 21 ex; >80%
- Mannich reaction with resin-bound amines or resin-bound aldehydes



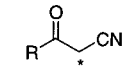
- Armstrong, R. W. [137]
- 96 members
- Ugi four-component condensation on Rink resin



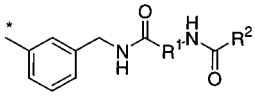
- Molecumetics [76]
- 6 ex; 60-80%
- diene synthesis via Stille coupling or Wittig reaction



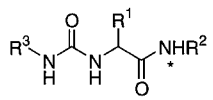
- Tularik [134]
- 10 ex; 65-95%



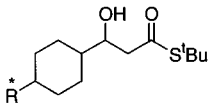
- Ganesan, A. [198]
- 7 ex; 30-50%
- acylation of active methylene and decarboxylation



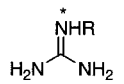
- SKB [125]
- 50 members
- self-coded library facilitating MS analysis



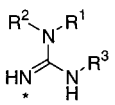
- Houghten, R. A. [33]
- 125,000 members
- from amino acid amide



- Gennari, C. [109]
- 5-10 ex; 18-60%
- Aldol reaction with resin-bound arylaldehydes



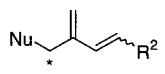
- Anslyn, E. V. [192]
- 9 ex; 5-84%
- includes oligomeric guanidinium synthesis



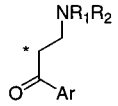
- Amgen [132]
- 40 members
- novel thiourea linker; R^3 = alkyl, allyl, aryl

- P&G [113]
- 7 ex; 27-89%
- $TBSONH_2$-mediated cleavage of Kaiser oximates

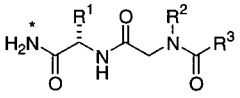
Table 7. (Continued)



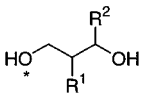
- Blechert, S. [252]
- 13 ex; 32-86%
- Ru-catalyzed yne-ene cross metathesis and Pd-catalyzed cleavage



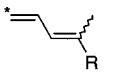
- Novo Nordisk [242]
- 15 ex; 0-100%
- decarboxylation-based traceless linker



- R. W. Johnson [243]
- 96 members
- use of visual encoding process

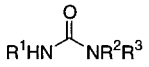


- Tietze, L. F. [255]
- 7 ex; 40-60%
- Pd-catalyzed allylic substitution of β-keto esters then reduction

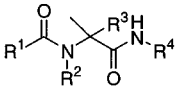


- Blechert, S. [253]
- 6 ex; ca. 60%
- Ru-catalyzed yne-ene cross metathesis

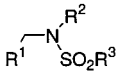
Solution-phase



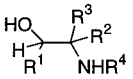
- Texas Biotech. [187]
- 14 ex; 46-100%
- from nitrophenyl carbamates



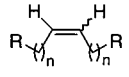
- LG Chem. [139]
- 14 ex; 30-70%
- Ugi four-component condensation



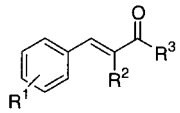
- Ley, S. V. [153]
- 96 ex; range of purity
- polymer-supported reagents



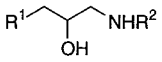
- Ley, S. V. [80]
- 29 ex; 17-99%
- polymer-supported reagents



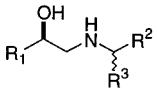
- Ward, T. R. [81]
- ca. 10 members
- self-metathesis of internal olefins



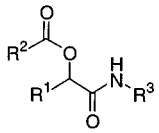
- Ley, S. V. [121]
- 10 ex; 8-95%
- polymer supported reagents



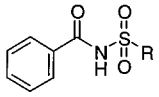
- Janda, K. D. [124]
- 20 members
- resin capture



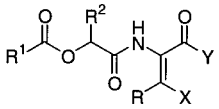
- Lilly [197]
- 96 ex; ~ 80%
- reductive amination of ethanolamines



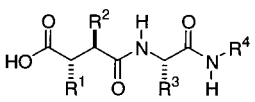
- Rhone-Poulenc [73]
- four-component Passerini reaction



- Merck Frosst [205]
- 25 ex; 56-79%
- acylation using polymer carbodiimide



- Armstrong, R. W. [136]
- 21 ex; 0-90%
- three-component Passerini reaction

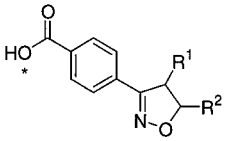


- British Biotech Pharm. [251]
- 15 ex; 18-91%
- Ugi four-component condensation

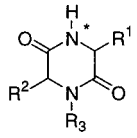
[a] The asterisk (∗) represents the point of attachment to the solid support.

Table 8. Monocyclic Ring Synthesis[a]

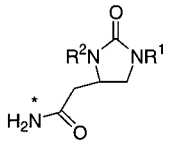
Solid-phase



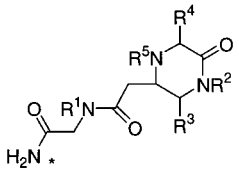
- Ontogen [94]
- 7 ex; 40-94%
- resin-bound aldoximes



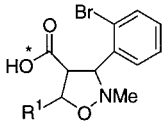
- Alberico, F. [98]
- 5 members



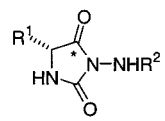
- Chiron [112]
- 8 members
- tandem aminoacylation-Michael addition



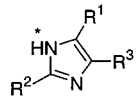
- Chiron [111]
- 11 ex; 36-93%
- intramolecular Michael addition



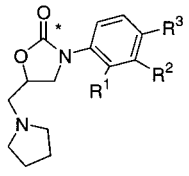
- Jung, G. [117]
- 5 ex; 24-45%
- nitrone addition to resin-bound acrylate



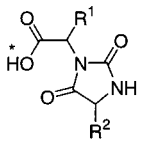
- Janda, K. D. [230]
- 10 ex; 62-80%
- intracyclative cleavage from soluble polymer



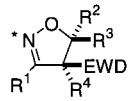
- Merck [74]
- 12 ex; 53-99%
- Munchnone [3+2] cyclo-addition with a nitrile



- Merck KGaA [85]
- 11 ex; 71-100%
- intracyclative cleavage

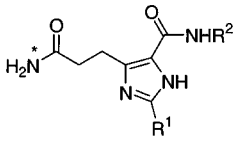


- Jung, G. [68]
- 35 members
- intramolecular cyclization of N,N'-ureas

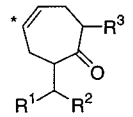


- Kobayashi, S. [145]
- 13 ex; 47-89%
- 1,3-dipolar cycloaddition then DDQ-mediated reductive cleavage

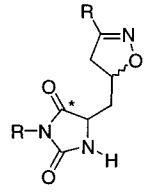
Table 8. (Continued)



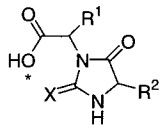
- Glaxo Wellcome [51]
- 20 members
- isotope encoded library



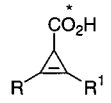
- Amgen [184]
- 10 ex; 15-36%
- intracyclative metathesis cleavage



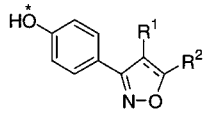
- Kurth, M. J. [180]
- ca. 6 ex; 90%
- intracyclative cleavage following 1,3-dipolar cycloaddition



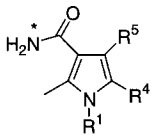
- Oxford Asym. [70]
- 96 members
- intramolecular condensation of amide and isocyanate; X = O, S



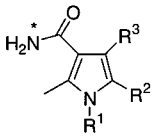
- Joglar, J. [87]
- 4 ex; 10-30%
- intermolecular carbene-alkyne cyclopropenation



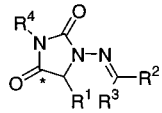
- Schering-Plough [195]
- 10 ex; 60-80%
- resin-bound nitrile oxide



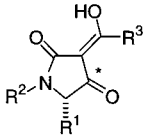
- Jung, G. [210]
- 22 ex; 46-90%
- resin-bound enaminones and nitroalkenes



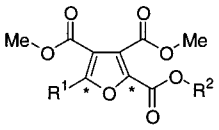
- Jung, G. [211]
- 18 members
- resin-bound enaminones and 2-bromoketones



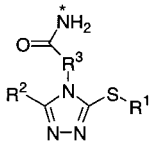
- P&G [225]
- 14 ex; 15-58%
- intracyclative cleavage



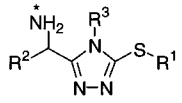
- Affymax [191]
- 21 ex; 51-92%
- intracyclative cleavage



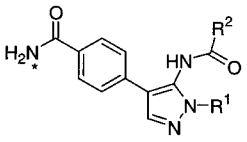
- Austin, D. J. [223]
- 18 members
- cycloaddition-cycloreversion metathesis



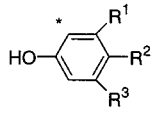
- Parke-Davis [226]
- 60 members



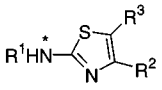
- Parke-Davis [226]
- 60 members



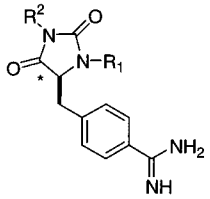
- Glaxo Wellcome [227]
- 8 members
- 5-aminopyrazole synthesis then N-acylation



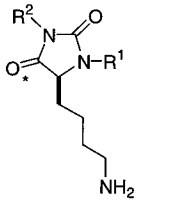
- Katritzky, A. R. [133]
- 12 ex; 50-85%
- simultaneous cyclization-cleavage reaction



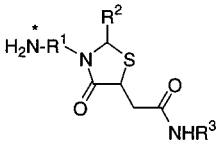
- Tularik [135]
- 10 ex; 89-99%
- Hantzsch thiazole synthesis



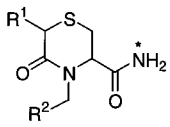
- LG Chem. [138]
- 6 ex; 80-90%
- intracyclative cleavage



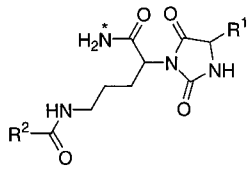
- LG Chem. [138]
- 5 ex; 80-90%
- intracyclative cleavage



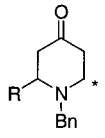
- Amgen [168]
- 9 ex; 65-85%
- 1000 members



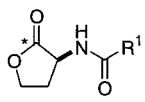
- Houghten, R. A. [169, 33]
- 10 ex; 15-95%
- from cysteine and 2-bromo carboxylic acids



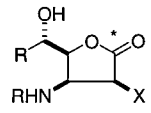
- Houghten, R. A. [170]
- 15 ex; 85-95%



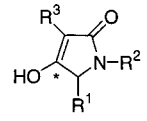
- Barco, A. [66]
- 5 members
- tandem elimination and Michael addition



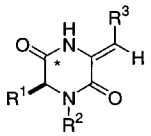
- CheilJedang [143]
- 9 ex; 32-53%
- intracyclative cleavage from methionine



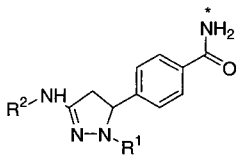
- Kobayashi, S. [144]
- 12 ex; 50-80%
- Aldol reaction with resin-bound silyl enol ethers; X = H, Me, OBn



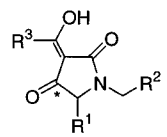
- Ganesan, A. [147]
- 11 ex; 60-91%
- intracyclative cleavage



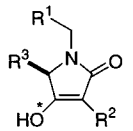
- Li, W.-R. [154]
- 10 ex; 40-75%
- intracyclative cleavage



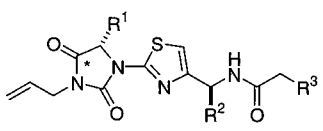
- Nielsen, J. [157]
- 24 ex; 70-95%



- Hoffmann-La Roche [220]
- 12 ex; 11-61%
- intracyclative cleavage

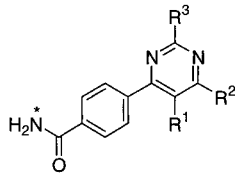


- R. W. Johnson [162]
- 13 ex; 67-100%
- intracyclative cleavage

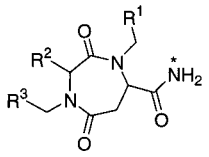


- Hoffmann-La Roche [203]
- 18 members
- intracyclative cleavage

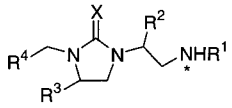
Table 8. (Continued)



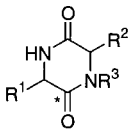
- Novartis [159]
- 9 ex; 38-98%
- condensation of imidates with resin-bound unsaturated ketones



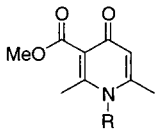
- Houghten, R. A. [33]
- 40 members
- intramolecular lactam formation



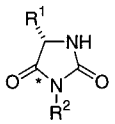
- Houghten, R. A. [33]
- size not defined
- resin-bound triamine from reduction of acylated dipeptide; X = O, S



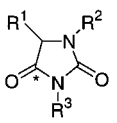
- Bayer [205]
- >600 mem; 25-50%
- intracyclative cleavage



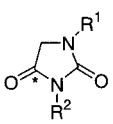
- Tidwell, T. T. [239]
- 4 ex; 91-90%
- acetylketene cycloaddition with soluble polymer-bound enamines



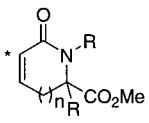
- Liskamp, R. M. J. [77]
- 42 ex; 40-100%
- intracyclative cleavage



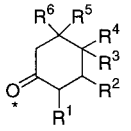
- Liskamp, R. M. J. [77]
- 6 ex; 85-100%
- intracyclative cleavage



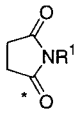
- Liskamp, R. M. J. [77]
- 6 ex; 88-99%
- intracyclative cleavage



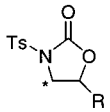
- Ruties, P. J. T. [256]
- 8 ex; 0-97%
- ring-closing metathesis



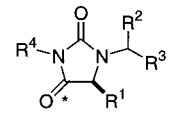
- Barrett, A. G. M. [233]
- 5 members
- Tebbe olefination of resin-bound unsaturated ester, Diels-Alder and hydrolysis



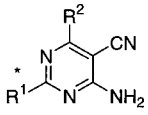
- Tidwell, T. T. [239]
- 6 ex; 51-96%
- soluble polymer-supported ketenyl esters



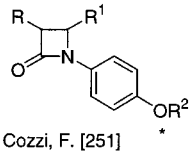
- Zwanenburg, B. [254]
- 3 ex; ca. 70%
- intracyclative cleavage



- Lee, Y.-S. [247]
- 20 ex; 12-98%
- transimination to yield resin-bound ketimines; reduction; intracyclative cleavage

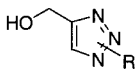


- Hoffmann-La Roche [248]
- 20 ex; 30-80%
- ketene dithioacetal and thiouronium salt; R^1 = H SR, NRR; R^2 = SR, NRR

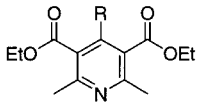


- Cozzi, F. [251]
- 9 ex; 30-56%
- [2+2] cycloaddition; imine generated on soluble support

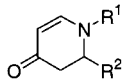
Solution-phase



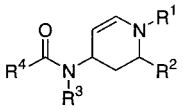
- Norris, P. [165]
- 3 ex; 80%
- azide dipolar cyclo-addition using soluble polymer support



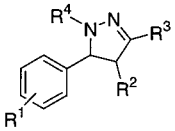
- EnzyMed [95]
- 96 members
- Hantzsch synthesis



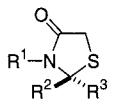
- Park-Davis [97]
- 40 members
- hetero Diels-Alder



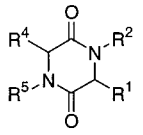
- Park-Davis [97]
- 88 members
- hetero Diels-Alder, L-Selectide, reductive amination, acylation



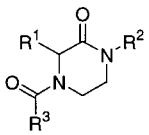
- Ley, S.V. [121]
- 7ex; 92-95%
- polymer-supported reagents



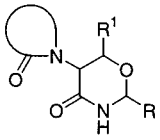
- Park-Davis [64]
- 22 members
- use of scavenger resins



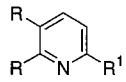
- RPR [126, 128]
- >96 ex; 20-95%
- Ugi four-component condensation



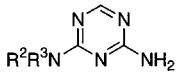
- RPR [127, 128]
- 12 ex; 70-85%
- Ugi four-component condensation using mono-Boc diamines



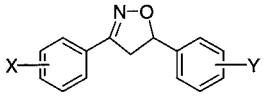
- Seneci, P. [179]
- 24 ex; 10-80%
- hetero Diels-Alder



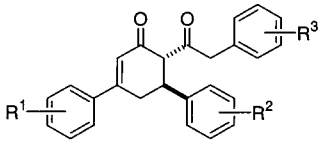
- Sauer, J. [176]
- 10 ex; 45-94%
- oligopyridines from Diels-Alder reaction of 1,2,4-triazines and dienophile



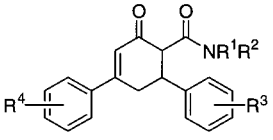
- Hoffmann-La Roche [160]
- 6 ex; 80-95%
- from thiouronium salts



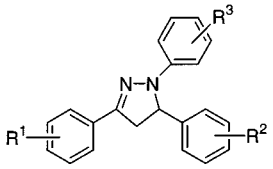
- ArQule [185]
- 1,280 members
- chalcone and hydroxylamine



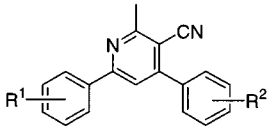
- ArQule [185]
- 7680 members
- chalcone and acetoacetanilides



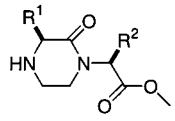
- ArQule [185]
- 12,800 members
- chalcone and acetoacetamides



- ArQule [185]
- 7,680 members
- chalcone and phenylhydrazines



- ArQule [185]
- 1,280 members
- chalcone and 3-aminocrotonitrile

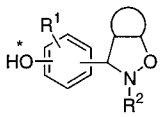


- Just, G. [250]
- 6 ex; > 80%
- intramolecular Fukayama alkylation; one ex. on solid-phase

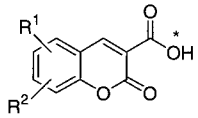
[a] The asterisk (*) represents the point of attachment to the solid support.

Table 9. Bicyclic and Spirocyclic Ring Synthesis[a]

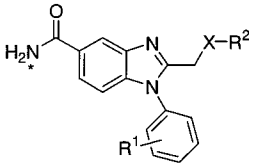
Solid-phase



- Jung, G. [117]
- 12 ex; 0-87%
- 1,3-dipolar cycloaddition

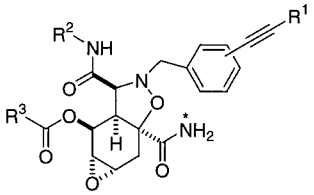


- Nova Nordisk [218]
- 8 ex; 16-40%
- Knoevenagel condensation

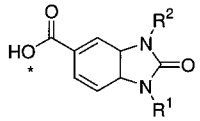


- Affymax [212]
- 24 ex; 55-95%
- X = NH, NR^3 or S

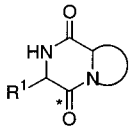
- Selectide [216]
- 8 ex; 18-87%
- intracyclative cleavage via N-acyliminium ion cyclization



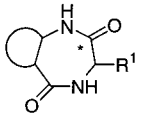
- Schreiber, S. L. [208]
- 2.18 million members
- derived from shikimic acid



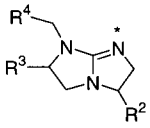
- Berlex Biosci. [221]
- 13 ex; 90-100%
- from 4-fluoro-3-nitrobenzoic acid



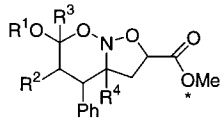
- Bayer [201]
- >600 mem; 25-50%
- intracyclative cleavage



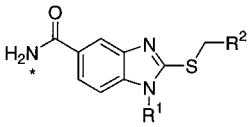
- Bayer [201]
- >600 mem; 25-50%
- intracyclative cleavage



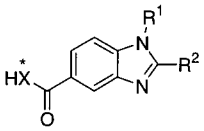
- Houghten, R. A. [33]
- 102,459 members
- from triamine generated from reduction of acylated dipeptide



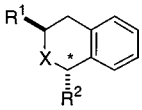
- Scheeren, H. W. [149]
- 6 ex; 33-52%
- tandem[4+2]/[3+2] cycloaddition of enol ethers with nitrostyrenes and resin-bound acrylate



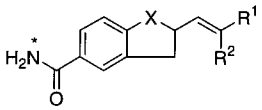
- R. W. Johnson [151]
- 16 ex; 74-99%
- resin-bound phenylenediamines and TCDI



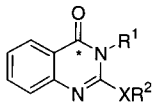
- Amgen [163]
- 160 members
- from 4-fluoro-3-nitro-benzoic acid; X = NH, O



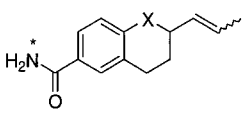
- Craig, D. [96]
- 10 ex; 10-47%
- tandem hetero Diels-Alder and Lewis-acid mediated cleavage; X = O, NTs



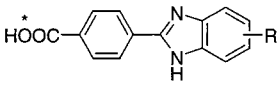
- Hoffmann-La Roche [217]
- 12 ex; 91-76%
- from *o*-iodoanilines and *o*-iodo-phenols; X = O, NSO_2R, NCOR



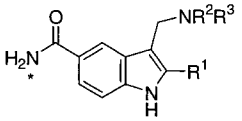
- Hoffmann-La Roche [215]
- 12 ex; 42-85%
- from *o*-azidobenzoic acids and intracyclative cleavage; X = S, NR^3



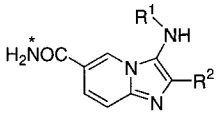
- Hoffmann-La Roche [217]
- 3 ex; 84-93%
- from *o*-iodoanilines or *o*-iodophenols; X = O, NTs



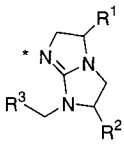
- Novartis [206]
- 5 members
- condensation of phenylene-diamines with resin-bound aldehyde



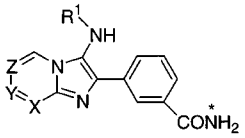
- R. W. Johnson [231]
- 10 ex; 81-95%
- from *o*-iodosulfonanilide via tandem Pd-catalyzed heteroannulation of alkyne and Mannich condensation



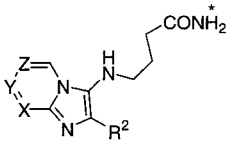
- Millennium [75]
- 3 ex; 30-80%
- three-component condensation



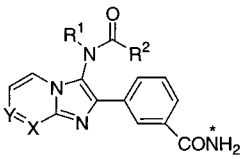
- Houghten, R. A. [174]
- >200 members
- cyclization of reduced N-acylated dipeptides



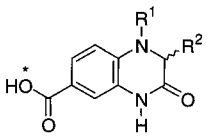
- Millennium [75]
- 5 ex; 0-78%
- three-component condensation



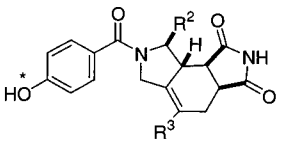
- Millennium [75]
- 7 ex; 5-50%
- three-component condensation



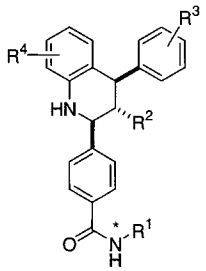
- Millennium [75]
- 6 ex; 20-80%
- three-component condensation



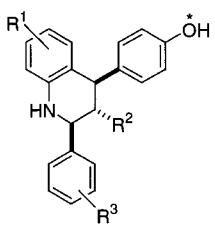
- DuPont Merck [166]
- 7 ex; ~50%
- from 4-fluoro-3-nitro-benzoic acid



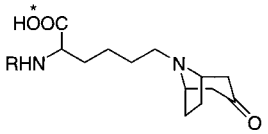
- SKB [122]
- 1800 members
- olefin-alkyne metathesis tandem Diels-Alder



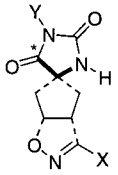
- Amgen [140]
- 50 members, 60-87%
- three-component condensation



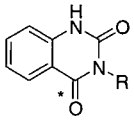
- Amgen [140]
- 32 ex; 61-85%
- three-component condensation



- Unden, A. [131]
- 1 ex; 93%
- Robinson's tropone synthesis on resin-bound lysine

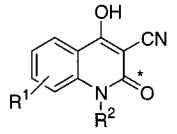


- Kurth, M. J. [181]
- 6 ex; 20-30%
- intracyclative cleavage

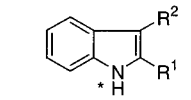


- Cadus Pharm. [196]
- 12 ex; 72-81%
- intracyclative cleavage

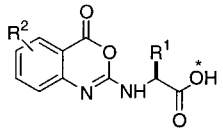
Table 9. (Continued)



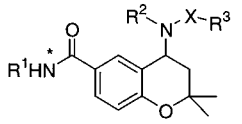
- Ganesan, A. [199]
- 15 ex; 22-95%
- intracyclative cleavage



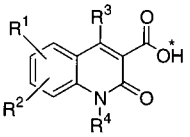
- Merck [200]
- 6 ex; 53-97%
- THP-linked iodoaniline



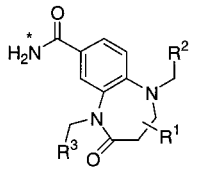
- Versicor [115]
- 13 ex; members
- from amino acid and carbamate-linked anthranilic acid



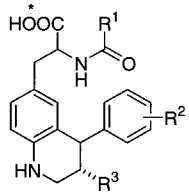
- Axys Pharm. [83]
- 8,800 members
- titanium-mediated reductive amination (X = CO, CONH, CSNH)



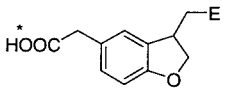
- Nova Nordisk [219]
- 7 ex; 60-99%
- intramolecular Knoevenagel condensation



- Affymax [193]
- >18 ex; 56-90%

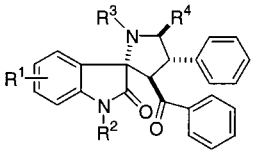


- Amgen [142]
- 40 ex; 62-92%
- three-component condensation

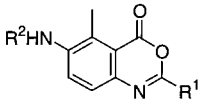


- Armstrong, R. W. [237]
- 6 ex; 5-45%
- SmI_2-mediated radical cyclization/anionic capture

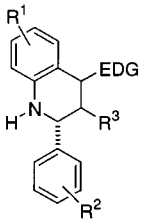
Solution-phase



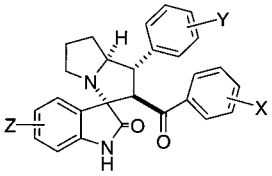
- ArQule [107]
- 25,600 members
- azomethine ylide and chalcone



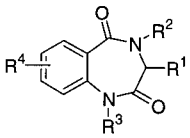
- Searle [182]
- 35 ex; 30-99%



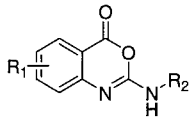
- Cerep [67]
- 1,920 members
- three-component cycloaddition



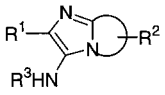
- ArQule [185]
- 25,600 members
- chalcone, isatins and L-proline



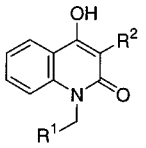
- RPR [128, 129]
- ca. 12 ex; 50-70%
- Ugi four-component condensation using N-Boc anthranilic acids



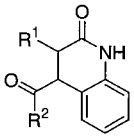
- Berlex Biosci. [86]
- 13 ex; 73-93%
- resin-bound carbodiimide



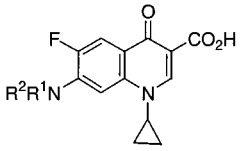
- RPR [72]
- 31 ex; 40-98%
- multi-component reaction



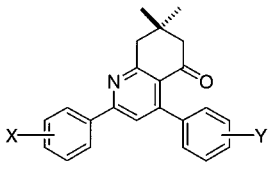
- Ganesan, A. [148]
- 10 ex; 78-96%
- intramolecular Claisen-type condensation



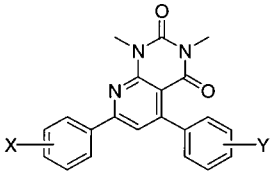
- RPR [128]
- 1 ex; 50%
- Ugi condensation



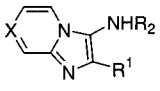
- Mitscher, L. A. [108]
- 107 members



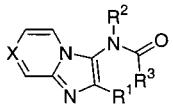
- ArQule [185]
- 7,680 members
- chalcone and 3-amino-5,5-dimethylcyclohexenone



- ArQule [185]
- 1,280 members
- chalcone and 6-amino-1,3-dimethyluracil



- Millennium Pharm. [234]
- 60 members
- three-component condensation

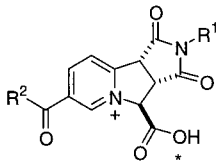


- Millennium Pharm. [234]
- 60 members
- three-component condensation then acylation

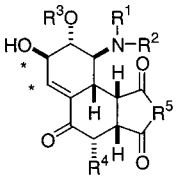
[a] The asterisk (*) represents the point of attachment to the solid support.

Table 10. Polycyclic Ring Synthesis[a]

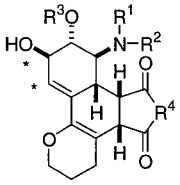
Solid-phase



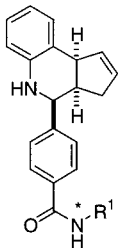
- SKB [71]
- 96 members
- multi-component Tsuge reaction with resin-bound pyridinium methylides



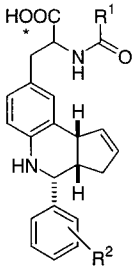
- Novartis [222]
- 3 ex; 81-96%
- dehydration of resin-bound 1,2-diols; ketal linkage



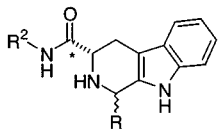
- Novartis [222]
- 3 ex; 61-71%
- dehydration of resin-bound 1,2-diols; ketal linkage



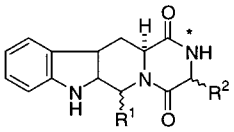
- Amgen [140]
- 10 ex; 69-86%
- three-component condensation



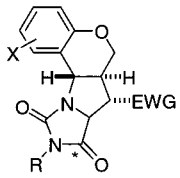
- Amgen [142]
- 10 ex' 61-92%
- three-component condensation



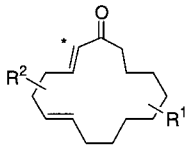
- Arris [105]
- 345 members
- Pictet-Spengler reaction



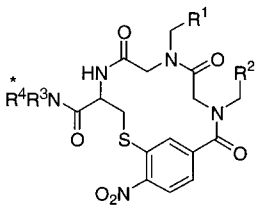
- van Loevezijn, A. [214]
- 42 ex; 50-99%
- Pictet-Spengler reaction and intracyclative cleavage



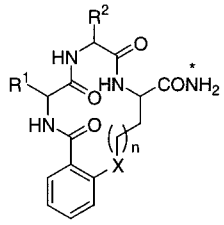
- Kurth, M. J. [114]
- 6 ex; 6-15%
- use of azomethine ylide; intracyclative cleavage



- Nicolaou, K. C. [172]
- 12 ex; ~ 65%
- intramolecular keto-phosphonate condensation

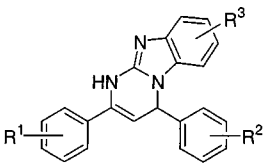


- Amgen [141]
- 12 ex; 55-70%
- S_NAr cyclization



- Burgess, K. [240]
- 12 members
- S_NAr cyclization; X = O, S, NR

Solution-phase



- ArQule [185]
- 7,680 members
- chalcone and aminobenzimidazoles

[a] The asterisk (∗) represents the point of attachment to the solid support.

References and Notes

(1) Dolle, R. E. Comprehensive survey of chemical libraries yielding enzyme inhibitors, receptor agonists and antagonists, and other biologically active agents: 1992 through 1997. *Mol. Diversity* **1998**, *3*, 199−233.

(2) Albert, R.; Knecht, H.; Andersen, E.; Hungerford, V.; Schreier, M. H.; Papageorgiou, C. Isoxazolylthioamides as potential immunosuppressants: A combinatorial chemistry approach. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2203−2208.

(3) An, H.; Haly, B. D.; Cook, P. D. Discovery of novel pyridinopolyamines with potent antimicrobial activity: deconvolution of mixtures synthesized by solution-phase combinatorial chemistry. *J. Med. Chem.* **1998**, *41*, 706−716.

(4) (a) An, H.; Wang, T.; Mohan, V.; Griffey, R. H.; Cook, P. D. Solution phase combinatorial chemistry. Discovery of 13- and 15-membered polyazapyridinocyclophane libraries with antibacterial activity. *Tetrahedron* **1998**, *54*, 3999−4012. (b) Wang, T.; An, H.; Vickers, T. A.; Bharadwaj, R.; Cook, P. D. Synthesis of novel polyazadipyridinocyclophane scaffolds and their application for the generation of libraries. *Tetrahedron* **1998**, *54*, 7955−7976.

(5) (a) An, H.; Haly, B. D.; Cook, P. D. New piperazinyl polyazacyclophane scaffolds, libraries and biological activities. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2345−2350. (b) An, H.; Cook, P. D. A solution-phase combinatorial chemistry methodology for drug discovery. *Recent Res. Dev. Org. Chem*. **1998**, *2*, 473−488.

(6) Bhandari, A.; Jones, D. G.; Schullek, J. R.; Vo, K.; Schunk, C. A.; Tamanaha, L. L.; Chen, D.; Yuan, Z.; Needels, M. C.; Gallop, M. A. Exploring structure−activity relationships around the phosphomannose isomerase inhibitor AF14049 via combinatorial synthesis. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2303−2308.

(7) Bhat, L.; Liu, Y.; Victory, S. F.; Himes, R. H.; Georg, G. I. Synthesis and evaluation of Paclitaxel C7 derivatives: Solution phase synthesis of combinatorial libraries. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3181−3186.

(8) Boger, D. L.; Chai, W.; Jin, Q. Multistep convergent solution-phase combinatorial synthesis and deletion synthesis deconvolution. *J. Am. Chem. Soc*. **1998**, *120*, 7220−7225.
(9) Brennan, T.; Biddison, G.; Frauendorf, A.; Schwarcz, L.; Keen, B.; Ecker, D. J.; Davis, P. W.; Tinder, R.; Swayze, E. E. Two-dimensional parallel array technology as a new approach to automated combinatorial solid-phase organic synthesis. *Biotechnol. Bioeng*. **1998**, *61*, 33−45.
(10) Burns, C. J.; Groneberg, R. D.; Salvino, J. M.; McGeehan, G.; Condon, S. M.; Morris, R.; Morrissette, M.; Mathew, R.; Darnbrough, S.; Neuenschwander, K.; Scotese, A.; Djuric, S. W.; Ullrich, J.; Labaudiniere, R. Nanomolar inhibitors for two distinct biological target families from a single synthetic sequence: A next step in combinatorial library design. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2848−2850.
(11) Caroll, C. D.; Johnson, T. O.; Tao, S.; Lauri, G.; Orlowski, M.; Gluzman, I. Y.; Goldberg, D. E.; Dolle, R. E. Evaluation of a structure-based statine cyclic diamino amide encoded combinatorial library against plasmepsin II and cathepsin D. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3203−3206.
(12) Carroll, C. D.; Patel, H.; Johnson, T. O.; Guo, T.; Orlowski, M.; He, Z.-M.; Cavallaro, C. L.; Guo, J.; Oksman, A.; Gluzman, I. Y.; Connelly, J.; Chelsky, D.; Goldberg, D. E.; Dolle, R. E. Identification of potent inhibitors of *Plasmodium falciparum* plasmepsin II from an encoded statine combinatorial library. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2315−2320.
(13) Cho, C. Y.; Youngquist, R. S.; Paikoff, S. J.; Beresini, M. H.; Hebert, A. R.; Berleau, L. T.; Liu, C. W.; Wemmer, D. E.; Keough, T.; Schultz, P. G. Synthesis and screening of linear and cyclic oligocarbamate libraries. Discovery of high affinity ligands for GPIIb/IIIa. *J. Am. Chem. Soc*. **1998**, *120*, 7706−7718.
(14) Collins, J. L.; Blanchard, S. G.; Boswell, G. E.; Charifson, P. S.; Cobb, J. E.; Henke, B. R.; Hull-Ryde, E. A.; Kazmierski, W. M.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J.; Lenhard, J. M.; Orband-Miller, L. A.; Gray-Nunez, Y.; Parks, D. J.; Plunkett, K. D.; Tong, W.-Q. N-(2-Benzoylphenyl)-L-tyrosine PPARγ agonists. 2. Structure−activity relationship and optimization of the phenyl alkyl ether moiety. *J. Med. Chem*. **1998**, *41*, 5037−5054.
(15) Cosquer, A.; Pichereau, V.; Le Mee, D.; Le Roch, M.; Renault, J.; Carboni, B.; Uriac, P.; Bernard, T. Toxicity and osmoprotective activities of analogues of glycine betaine obtained by solid-phase organic synthesis towards *Sinorhizobium meliloti*. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 49−54.
(16) Devulapalle, K. S.; Mooser, G. Preliminary screening of a hexapeptide combinatorial library for glucosyltransferase (GTF-I) inhibitor. *Protein Pept. Lett.* **1998**, *5*, 159−162.
(17) Dooley, C. T.; Ny, P.; Bidlack, J. M.; Houghten, R. A. Selective ligands for the μ, δ, and κ opioid receptors identified from a single mixture based tetrapeptide positional scanning combinatorial library. *J. Biol. Chem*. **1998**, *273*, 18848−18856.
(18) Frank, K. E.; Devasthale, P. V.; Gentry, E. J.; Ravikumar, V. T.; Keschavarz-Shokri, A.; Mitscher, L. A.; Nilius, A.; Shen, L. L.; Shawar, R.; Baker, W. R. A simple, inexpensive apparatus for performance of preparative scale solution phase multiple parallel synthesis of drug analogues. II. Biological evaluation of a retrospective library of quinolone antiinfective agents. *Comb. Chem. High Throughput Screening* **1998**, *1*, 89−99.
(19) Gordeev, M. F.; Patel, D. V.; England, B. P.; Jonnalagadda, S.; Combs, J. D.; Gordon, E. M. Combinatorial synthesis and screening of a chemical library of 1,4-dihydropyridine calcium channel blockers. *Bioorg. Med. Chem*. **1998**, *6*, 883−889.
(20) Gustafson, G. R.; Baldino, C. M.; O'Donnell, M.-M. E.; Sheldon, A.; Tarsa, R. J.; Verni, C. J.; Coffen, D. L. Incorporation of carbohydrates and peptides into large triazine-based screening libraries using automated parallel synthesis. *Tetrahedron* **1998**, *54*, 4051−4065.
(21) Kapoor, T. M.; Andreotti, A. H.; Schreiber, S. L. Exploring the specificity of two homologous SH3 domains using structure-based, split-pool synthesis and affinity-based selection. *J. Am. Chem. Soc*. **1998**, *120*, 23−29.
(22) Kim, S. W.; Hong, J. S.; Koh, C. Y.; Lee, E. J.; Lee, K. Solid-phase synthesis of benzamidine-derived sulfonamide libraries. *Mol. Diversity* **1998**, *3*, 133−136.
(23) Kundu, B.; Bauser, M.; Betschinger, J.; Kraas, W.; Jung, G. Identification of a potent analogue of Nazumamide A through iteration of combinatorial tetrapeptide libraries. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1669−1672.
(24) Kung, P.-P.; Bharadwaj, R.; Fraser, A. S.; Cook, D. R.; Kawasaki, A. M.; Cook, P. D. Solution-phase synthesis of novel linear oxyamine combinatorial libraries with antibacterial activity. *J. Org. Chem*. **1998**, *63*, 1846−1852.
(25) Kung, P.-P.; Cook, P. D. Solution-phase simultaneous addition of functionalities (SPSAF) and chemical transformation to prepare N,N′-disubstituted piperazine libraries. *Biotechnol. Bioeng*. **1998**, *61*, 119−125.
(26) Lee, C. E.; Kick, E. K.; Ellman, J. A. General solid-phase synthesis approach to prepare mechanism-based aspartyl protease inhibitor libraries. Identification of potent cathepsin D inhibitors. *J. Am. Chem. Soc*. **1998**, *120*, 9735−9747.
(27) Li, Z.; Yeo, S. L.; Pallen, C. J.; Ganesan, A. Solid-phase synthesis of potential protein tyrosine phosphatase inhibitors via the Ugi four-component condensation. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2443−2446.
(28) Lumma, W. C., Jr.; Witherup, K. M.; Tucker, T. J.; Brady, S. F.; Sisko, J. T.; Naylor-Olsen, A. M.; Lewis, S. D.; Lucas, B. J.; Vacca, J. P. Design of novel, potent, noncovalent inhibitors of thrombin with nonbasic P-1 substructures: Rapid structure−activity studies by solid-phase synthesis. *J. Med. Chem*. **1998**, *41*, 1011−1013.
(29) Marder, M.; Viola, H.; Bacigaluppo, J. A.; Colombo, M. I.; Wasowski, C.; Wolfman, C.; Medina, J. H.; Ruveda, E. A.; Paladini, A. C. Detection of benzodiazepine receptor ligands in small libraries of flavone derivatives synthesized by solution phase combinatorial chemistry. *Biochem. Biophys. Res. Commun.* **1998**, *249*, 481−485.
(30) Mckendrick, J. E.; Frormann, S.; Luo, C.; Semchuck, P.; Vederas, J. C.; Malcolm, B. A. Rapid mass spectrometric determination of preferred irreversible proteinase inhibitors in combinatorial libraries. *Int. J. Mass Spectrom.* **1998**, *176*, 113−124.
(31) Mohan, R.; Yun, W.; Buckman, B. O.; Liang, A.; Trinh, L.; Morrissey, M. M. Solid-phase synthesis of N-substituted amidinophenoxy pyridines as factor XA inhibitors. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1877−1882.
(32) Morken, J. P.; Kapoor, T. M.; Feng, S.; Shirai, F.; Schreiber, S. L. Exploring the leucine-proline binding pocket of the Src SH3 domain using structure-based, split-pool synthesis and affinity-based selection. *J. Am. Chem. Soc*. **1998**, *120*, 30−36.
(33) Nefzi, A.; Dooley, C.; Ostresh, J. M.; Houghten, R. A. Combinatorial chemistry: from peptides and peptidomimetics to small organic and heterocyclic compounds. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2273−2278.
(34) Neustadt, B. R.; Smith, E. M.; Lindo, N.; Nechuta, T.; Bronnenkant, A.; Wu, A.; Armstrong, L.; Kumar, C. Construction of a family of biphenyl combinatorial libraries: structure−activity studies utilizing libraries of mixtures. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2395−2398.
(35) Nicolaou, K. C.; Winssinger, N.; Vourloumis, D.; Ohshima, T.; Kim, S.; Pfefferkorn, J.; Xu, J.-Y.; Li, T. Solid and solution phase synthesis and biological evaluation of combinatorial sarcodictyin libraries. *J. Am. Chem. Soc*. **1998**, *120*, 10814−10826.
(36) Nilsson, U. J.; Fournier, E. J.-L.; Hindsgaul, O. Solid-phase extraction on C18 silica as a purification strategy in the solution synthesis of a 1-thio-β-D-galactopyranoside library. *Bioorg. Med. Chem*. **1998**, *6*, 1563−1575.
(37) Nizi, E.; Botta, M.; Corelli, F.; Manetti, F.; Messina, F.; Maga, G. Solid-phase synthesis of 2,6-disubstituted-4(3*H*)-pyrimidinones targeting HIV-1 reverse transcriptase. *Tetrahedron Lett.* **1998**, *39*, 3307−3310.
(38) Ogbu, C. O.; Qabar, M. N.; Boatman, P. D.; Urban, J.; Meara, J. P.; Ferguson, M. D.; Tulinsky, J.; Lum, C.; Babu, S.; Blaskovich, M. A.; Nakanishi, H.; Ruan, F.; Cao, B.; Minarik, R.; Little, T.; Nelson, S.; Nguyen, M.; Gall, A.; Kahn, M. Highly efficient and versatile synthesis of libraries of constrained β-strand mimetic. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2321−2326.
(39) Ostrem, J. A.; Al-Obeidi, F.; Safar, P.; Safarova, A.; Stringer, S. K.; Patek, M.; Cross, M. T.; Spoonamore, J.; LoCascio, J. C.; Kasireddy, P.; Thorpe, D. S.; Sepetov, N.; Lebl, M.; Wildgoose, P.; Strop, P. Discovery of a novel, potent, and specific family of factor Xa inhibitors via combinatorial chemistry. *Biochemistry* **1998**, *37*, 1053−1059.
(40) Revesz, L.; Bonne, F.; Manning, U.; Zuber, J.-F. Solid-phase synthesis of a biased mini tetrapeptoid-library for the discovery of monodentate itam mimics as ZAP-70 inhibitors. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 405−408.
(41) Rohrer, S. P.; Birzin, E. T.; Mosley, R. T.; Berk, S. C.; Hutchins, S. M.; Shen, D.-M.; Xiong, Y.; Hayes, E. C.; Parmar, R. M.; Foor, F.; Mitra, S. W.; Degrado, S. J.; Shu, M.; Klopp, J. M.; Cai, S.-J.; Blake,

A.; Chan, W. W. S.; Pasternak, A.; Yang, L.; Patchett, A. A.; Smith, R. G.; Chapman, K. T.; Schaeffer, J. M. Rapid Identification of subtype-selective agonists of the somatostatin receptor through combinatorial chemistry. *Science* **1998**, *282*, 737−740.

(42) Scicinski, J. J.; Barker, M. D.; Murray, P. J.; Jarvie, E. M. The solid-phase synthesis of a series of trisubstituted hydantoin ligands for the somatostatin SST_5 receptor. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3609−3614.

(43) Shi, S.; Xiao, X.-y.; Czarnik, A. W. A combinatorial synthesis of tyrphostins via the "directed sorting" method. *Biotechnol. Bioeng*. **1998**, *61*, 7−12.

(44) Souers, A. J.; Virgilio, A. A.; Schurer, S. S.; Ellman, J. A. Novel inhibitors of $\alpha 4\beta 1$ integrin receptor interactions through library synthesis and screening. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2297−2302.

(45) Stewart, K. D.; Loren, S.; Frey, L.; Otis, E.; Klinghofer, V.; Hulkower, K. I. Discovery of a new cyclooxygenase-2 lead compound through 3-D database searching and combinatorial chemistry. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 529−534.

(46) Sullivan, R. W.; Bigam, C. G.; Erdman, P. E.; Palanki, M. S. S.; Anderson, D. W.; Goldman, M. E.; Ransone, L. J.; Suto, M. J. 2-Chloro-4-(trifluoromethyl)pyrimidine-5-[N-(3′,5′-bis(trifluoromethyl)phenyl]carboxamide: A potent inhibitor of NF-kB- and AP-1-mediated gene expression identified using solution-phase combinatorial chemistry. *J. Med. Chem*. **1998**, *41*, 413−419.

(47) Szardenings, A. K.; Harris, D.; Lam, S.; Shi, L.; Tien, D.; Wang, Y.; Patel, D. V.; Navre, M.; Campbell, D. A. Rational design and combinatorial evaluation of enzyme inhibitor scaffolds: identification of novel inhibitors of matrix metalloproteinases. *J. Med. Chem*. **1998**, *41*, 2194−2200.

(48) Thomas, J. B.; Fall, M. J.; Cooper, J. B.; Rothman, R. B.; Mascarella, S. W.; Xu, H.; Partilla, J. S.; Dersch, C. M.; McCullough, K. B.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of an opioid κ receptor subtype-selective N-substituent for (+)-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine. *J. Med. Chem*. **1998**, *41*, 5188−5197.

(49) Tomasi, S.; Le Roch, M.; Renault, J.; Corbel, J.-C.; Uriac, P.; Carboni, B.; Moncoq, D.; Martin, B.; Delcros, J.-G. Solid phase organic synthesis of polyamine derivatives and initial biological evaluation of their antitumoral activity. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 635−640.

(50) Tsai, C.-Y.; Park, W. K. C.; Weitz-Schmidt, G.; Brnst, B.; Wong, C.-H. Synthesis of sialyl lewis X mimetics using the Ugi four-component reaction. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2333−2338.

(51) Wagner, D. S.; Markworth, C. J.; Wagner, C. D.; Schoenen, F. J.; Rewerts, C. E.; Kay, B. K.; Geysen, H. M. Ratio encoding combinatorial libraries with stable isotopes and their utility in pharmaceutical research. *Comb. Chem. High Throughput Screening* **1998**, *1*, 143−153.

(52) Warmus, J. S.; Ryder, T. R.; Hodges, J. C.; Kennedy, R. M.; Brady, K. D. Rapid optimization of an ICE inhibitor synthesis using multiple reaction conditions in a parallel array. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2309−2314.

(53) Wong, C.-H.; Hendrix, M.; Manning, D. D.; Rosenbohm, C.; Greenberg, W. A. A library approach to the discovery of small molecules that recognize RNA: use of a 1,3-hydroxyamine motif as core. *J. Am. Chem. Soc*. **1998**, *120*, 8319−8327.

(54) Apletalina, E.; Appel, J.; Lamango, N. S.; Houghten, R. A.; Lindberg, I. Identification of inhibitors of prohormone convertases 1 and 2 using a peptide combinatorial library. *J. Biol. Chem*. **1998**, *273*, 26589−26595.

(55) Baker, C. T.; Salituro, F. G.; Court, J. J.; Deininger, D. D.; Kim, E. E.; Li, B.; Novak, P. M.; Rao, B. G.; Pazhanisamy, S.; Schairer, W. C.; Tung, R. D. Design, synthesis, and conformational analysis of a novel series of HIV protease inhibitors. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3631−3636.

(56) Baumbach, W. R.; Carrick, T. A.; Pausch, M. H.; Bingham, B.; Carmignac, D.; Robinson, I. C. A. F.; Houghten, R.; Eppler, C. M.; Price, L. A.; Zysk, J. R. A linear hexapeptide somatostatin antagonist blocks somatostatin activity in vitro and influences growth hormone release in rats. *Mol. Pharmacol*. **1998**, *54*, 864−873.

(57) Bianco, A.; Brock, C.; Zabel, C.; Walk, T.; Walden, P.; Jung, G. New synthetic non-peptide ligands for classical major histocompatibility complex class I molecules. *J. Biol. Chem*. **1998**, *273*, 28759−28765.

(58) Brady, S. F.; Stauffer, K. J.; Lumma, W. C.; Smith, G. M.; Ramjit, H. G.; Lewis, S. D.; Lucas, B. J.; Gardell, S. J.; Lyle, E. A.; Appleby, S. D.; Cook, J. J.;Holahan, M. A.; Stranieri, M. T.; Lynch, J. J., Jr.; Lin, J. H.; Chen, I.-W.; Vastag, K.; Naylor-Olsen, A. M.; Vacca, J. P. Discovery and development of the novel potent orally active thrombin inhibitor N-(9-hydroxy-9-fluorenecarboxy)prolyl *trans*-4-aminocyclohexylmethyl amide (L-372,460): coappliction of structure-based design and rapid multiple analogue synthesis on solid support. *J. Med. Chem*. **1998**, *41*, 401−406.

(59) Camarero, J. A.; Ayers, B.; Muir, T. W. Studying receptor−ligand interactions using encoded amino acid scanning. *Biochemistry* **1998**, *37*, 7487−7495.

(60) Gray, N. S.; Wodicka, L.; Thunnissen, A.-M. W. H.; Norman, T. C.; Kwon, S.; Espinoza, F. H.; Morgan, D. O.; Barnes, G.; LeClerc, S.; Meijer, L.; Kim, S.-H.; Lockhart, D. J.; Schultz, P. G. Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors. *Science* **1998**, *281*, 533−538.

(61) Hong, S. Y.; Oh, J. E.; Kwon, M. Y.; Choi, M. J.; Lee, J. H.; Lee, B. L.; Moon, H. M.; Lee, K. H. Identification and characterization of novel antimicrobial decapeptides generated by combinatorial chemistry. *Antimicrob. Agents Chemother*. **1998**, *42*, 2534−2541.

(62) Silen, J. L.; Lu, A. T.; Solas, D. W.; Gore, M. A.; Maclean, D.; Shah, N. H.; Coffin, J. M.; Bhinderwala, N. S.; Wang, Y.; Tsutsui, K. T.; Look, G. C.; Campbell, D. A.; Hale, R. L.; Navre, M.; DeLuca-Flaherty, C. R. Screening for novel antimicrobials from encoded combinatorial libraries by using a two- dimensional agar format. *Antimicrob. Agents Chemother*. **1998**, *42*, 1447−1453.

(63) Smith, P. W.; Sollis, S. L.; Howes, P. D.; Cherry, P. C.; Starkey, I. D.; Cobley, K. N.; Weston, H.; Scicinski, J.; Merritt, A.; Whittington, A.; Wyatt, P.; Taylor, N.; Green, D.; Bethell, R.; Madar, S.; Fenton, R. J.; Morley, P. J.; Pateman, T.; Beresford, A. Dihydropyrancarboxamides related to Zanamivir: a new series of inhibitors of influenza virus sialidases. 1. Discovery, synthesis, biological activity, and structure−activity relationships of 4-guanidino- and 4-amino-4*H*-pyran-6-carboxamides. *J. Med. Chem*. **1998**, *41*, 787−797.

(64) Ault-Justus, S. E.; Hodges, J. C.; Wilson, M. W. Generation of a library of 4-thiazolidinones utilizing polymer supported quench (PSQ) reagent methodology. *Biotechnol. Bioeng*. **1998**, *61*, 17−22.

(65) Barbaste, M.; Rolland-Fulcrand, V.; Roumestant, M.-L.; Viallefont, P.; Martinez, J. Rapid solid-phase synthesis of α-amino acids. *Tetrahedron Lett.* **1998**, *39*, 6287−6290.

(66) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. Polymer-bound 4-benzylsulfonyl-1-triphenylphosphoranylidene-2-butane as a tool for the solid-phase synthesis of substituted piperidin-4-one derivatives. *Tetrahedron Lett.* **1998**, *39*, 7591−7594.

(67) Baudelle, R.; Melnyk, P.; Deprez, B.; Tartar, A. Parallel synthesis of polysubstituted tetrahydroquinolines. *Tetrahedron* **1998**, *54*, 4125−4140.

(68) Bauser, M.; Winter, M.; Valenti, C. A.; Wiesmuller, K.-H.; Jung, G. Synthesis of hydantoins via *N*,*N*′-ureas derived from polymer-bound amino acids. *Mol. Diversity* **1998**, *3*, 257−260.

(69) Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. Arylsulfonate esters in solid-phase organic synthesis. II. Compatibility with commonly used reaction conditions. *Tetrahedron Lett*. **1998**, *39*, 979−982.

(70) Bhalay, G.; Cowell, D.; Hone, N. D.; Scobie, M.; Baxter, A. D. Multiple solid-phase synthesis of hydantoins and thiohydantoins. *Mol. Diversity* **1998**, *3*, 195−198.

(71) Bicknell, A. J.; Hird, N. W.; Readshaw, S. A. Efficient robotic synthesis. Multicomponent preparation of a tricyclic template by solid-phase Tsuge reaction. *Tetrahedron Lett*. **1998**, *39*, 5869−5872.

(72) Bienayme, H.; Bouzid, K. A new heterocyclic multicomponent reaction for the combinatorial synthesis of fused 3-aminoimidazoles. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2234−2237.

(73) Bienayme, H. Reagent explosion: an efficient method to increase library size and diversity. *Tetrahedron Lett.* **1998**, *39*, 4255−4258.

(74) Bilodeau, M. T.; Cunningham, A. M. Solid-supported synthesis of imidazoles: a strategy for direct resin-attachment to the imidazole core. *J. Org. Chem*. **1998**, *63*, 2800−2801.

(75) Blackburn, C. A three-component solid-phase synthesis of 3-aminoimidazo[1,2-a]azines. *Tetrahedron Lett*. **1998**, *39*, 5469−5472.

(76) Blaskovich, M. A.; Kahn, M. Solid-phase preparation of dienes. *J. Org. Chem*. **1998**, *63*, 1119−1125.

(77) Boeijen, A.; Kruijtzer, J. A. W.; Liskamp, R. M. J. Combinatorial chemistry of hydantoins. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2375−2380.

(78) (a) Boger, D. L.; Chai, W. Solution-phase combinatorial synthesis: convergent multiplication of diversity via the olefin metathesis reaction. *Tetrahedron* **1998**, *54*, 3955−3970. (b) Boger, D. L.; Goldberg, J.; Jiang, W.; Chai, W.; Ducray, P.; Lee, J. K.; Ozer, R. S.; Anderson, C.-M. Higher order iminodiacetic acid libraries for probing protein−protein interactions. *Bioorg. Med. Chem*. **1998**, *6*, 1347−1378.

(79) Boger, D. L.; Ducray, P.; Chai, W.; Jiang, W.; Goldberg, J. Higher order iminodiacetic acid libraries for probing protein protein interactions. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2339−2344.

(80) Bolli, M. H.; Ley, S. V. Development of a polymer bound Wittig reaction and use in multi-step organic synthesis for the overall conversion of alcohols to β-hydroxyamines. *J. Chem. Soc., Perkin Trans. 1* **1998**, *1*, 2243−2246.

(81) Brandli, C.; Ward, T. R. Libraries via metathesis of internal olefins, *Helv. Chim. Acta* **1998**, *81*, 1616−1621.

(82) Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. Generation of a piperazine-2-carboxamide library: a practical application of the phenol-sulfide react and release linker. *Tetrahedron Lett*. **1998**, *39*, 1295−1298.

(83) Breitenbucher, J. G.; Hui, H. C. Titanium-mediated reductive amination on solid support: extending the utility of the 4-hydroxythiophenol linker. *Tetrahedron Lett*. **1998**, *39*, 8207−8210.

(84) Brill, W. K.-D.; De Mesmaeker, A.; Wendeborn, S. Solid-phase synthesis of levoglucosan derivatives. *Synlett* **1998**, 1085−1090.

(85) Buchstaller, H.-P. Solid phase synthesis of oxazolidinones via a novel cyclisation/cleavage reaction. *Tetrahedron* **1998**, *54*, 3465−3470.

(86) Buckman, B. O.; Morrissey, M. M.; Mohan, R. Solution-phase parallel synthesis of benzoxazines using a polymer-supported carbodiimide. *Tetrahedron Lett*. **1998**, *39*, 1487−1488.

(87) Cano, M.; Camps, F.; Joglar, J. Solid-phase synthesis of cyclopropenes, *Tetrahedron Lett*. **1998**, *39*, 9819−9822.

(88) Cao, J.; Cuny, G. D.; Hauske, J. R. Ring opening cross-metathesis on solid support: a combinatorial library synthesis of highly functionalized cyclopentanes. *Mol. Diversity* **1998**, *3*, 173−179.

(89) Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Bakker, W. I.; Snieckus, V. The Suzuki-Miyaura cross coupling reactions on solid support. Link to solution phase directed *ortho* metalation. The Leznoff acetal linker approach to biaryl and heterobiaryl aldehydes. *Tetrahedron Lett*. **1998**, *39*, 4179−4182.

(90) Chamoin, S.; Houldsworth., S.; Snieckus, V. The Stille cross coupling reactions on solid support. Link to solution phase directed *ortho* metalation. An ester linker approach to styryl, biaryl and heterobiaryl carboxylic acids. *Tetrahedron Lett*. **1998**, *39*, 4175−4178.

(91) Chen, C.; McDonald, I. A.; Munoz, B. Synthesis of dihydropyridone scaffolds on solid support: resin activation/capture approach/REACAP technology. *Tetrahedron Lett.* **1998**, *39*, 217−220.

(92) Chen, C.; Munoz, B. Solid-phase synthesis of N-acyl-2-substituted-dihydro-4-pyridone: resin activation/capture approach/REACAP technology. *Tetrahedron Lett*. **1998**, *39*, 6781−6784.

(93) Chen, C.; Munoz, B. Solid-phase synthesis of 2,4-disubstituted pyridine and tetrahydropyridine derivatives: resin activation/capture approach/REACAP technology. *Tetrahedron Lett* **1998**, *39*, 3401−3404.

(94) Cheng, J.-F.; Mjalli, A. M. M. Solid-phase synthesis of Δ^2-isoxazolines, *Tetrahedron Lett*. **1998**, *39*, 939−942.

(95) Cotterill, I. C.; Usyatinsky, A. Y.; Arnold, J. M.; Clark, D. S.; Dordick, J. S.; Michels, P. C.; Khmelnitsky, Y. L. Microwave assisted combinatorial chemistry−synthesis of substituted pyridines. *Tetrahedron Lett* **1998**, *39*, 1117−1120.

(96) Craig, D.; Robson, M. J.; Shaw, S. J. Traceless linkers for solid-phase synthesis. Homo- and hetero-Diels−Alder reactions of o-quinodimethanes. *Synlett* **1998**, 1381−1383.

(97) Creswell, M. W.; Bolton, G. L.; Hodges, J. C.; Meppen, M. Combinatorial synthesis of dihydropyridone libraries and their derivatives. *Tetrahedron* **1998**, *54*, 3983−3998.

(98) del Fresno, M.; Alsina, J.; Royo, M.; Barany, G.; Albericio, F. Solid-phase synthesis in diketopiperazines, useful scaffolds for combinatorial chemistry. *Tetrahedron Lett*. **1998**, *39*, 2639−2642.

(99) Dodd, D. S.; Wallace, O. B. Solid-phase synthesis of N,N′ substituted guanidines. *Tetrahedron Lett.* **1998**, *39*, 5701−5704.

(100) Dominguez, E.; O'Donnell, M. J.; Scott, W. L. Solid phase synthesis of substituted glutamic acid derivatives via Michael addition reactions. *Tetrahedron Lett*. **1998**, *39*, 2167−2170.

(101) Dorff, P. H.; Chiu, G.; Goldstein, S. W.; Morgan, B. P. Solid-phase synthesis of phosphinopeptoids as transition state analogue inhibitors. *Tetrahedron Lett*. **1998**, *39*, 3375−3378.

(102) Dressman, B. A.; Singh, U.; Kaldor, S. W. Solid-phase synthesis of urea libraries using a diversifiable thiophenoxy carbonyl linker. *Tetrahedron Lett*. **1998**, *39*, 3631−3634.

(103) Dyatkin, A. B.; Rivero, R. A. The solid-phase synthesis of complex propargylamines using the combination of Sonogashira and Mannich reactions. *Tetrahedron Lett*. **1998**, *39*, 3647−3650.

(104) Falorni, M.; Giacomelli, G.; Mameli, L.; Porcheddu, A. New 1,3,5-triazine derivatives as templates for the homogeneous phase synthesis of chemical libraries. *Tetrahedron Lett.* **1998**, *39*, 7607−7610.

(105) Fantauzzi, P. P.; Yager, K. M. Synthesis of diverse tetrahydro-β-carboline-3-carboxamides and -2,3-bis-lactams on a versatile 4-hydroxythiophenol-linked solid support. *Tetrahedron Lett*. **1998**, *39*, 1291−1294.

(106) Fiorini, M. T.; Abell, C. Solution-phase synthesis of 2,6,9-trisubstituted purine. *Tetrahedron Lett*. **1998**, *39*, 1827−1830.

(107) Fokas, D.; Ryan, W. J.; Casebier, D. S.; Coffen, D. L. Solution phase synthesis of a spiro[pyrrolidine-2,3′-oxindole] library via a three component 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett*. **1998**, *39*, 2235−2238.

(108) Frank, K. E.; Jung, M.; Mitscher, L. A. A simple, inexpensive apparatus for performance of preparative scale solution phase multiple parallel synthesis of drug analogues. 1. Preparation of a retrospective library of quinolone antiinfective agents. *Comb. Chem. High Throughput Screening* **1998**, *1*, 73−87.

(109) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Aboutayab, K.; Donghi, M.; Paterson, I. Stereocontrolled synthesis of polyketide libraries: boron-mediated aldol reactions with aldehydes on solid support. *Tetrahedron* **1998**, *54*, 14999−15016.

(110) Gennari, C.; Longari, C.; Ressel, S.; Salom, B.; Piarulli, U.; Ceccarelli, S.; Mielgo, A. Synthesis of combinatorial libraries of vinylogous sulfonamidopeptides (vs-peptides). *Eur. J. Org. Chem*. **1998**, 2437−2449.

(111) Goff, D. A. A peptoid based synthesis of di- and trisubstituted 2-oxopiperazines on solid support. *Tetrahedron Lett*. **1998**, *39*, 1473−1476.

(112) Goff, D. A. The synthesis of 2-imidazolidones on solid support by tandem aminoacylation/michael addition. *Tetrahedron Lett.* **1998**, *39*, 1477−1480.

(113) Golebiowski, A.; Klopfenstein, S. Solid supported synthesis of hydroxamic acids. *Tetrahedron Lett*. **1998**, *39*, 3397−3400.

(114) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. Solid-phase synthesis: intramolecular azomethine ylide cycloaddition (-proline) and carbanilide cyclization (-hydantoin) reactions. *J. Org. Chem*. **1998**, *63*, 3081−3086.

(115) Gordeev, M. F. Combinatorial approaches to pharmacophoric heterocycles: a solid-phase synthesis of 3,1-benzoxazine-4-ones. *Biotechnol. Bioeng*. **1998**, *61*, 13−16.

(116) Gordeev, M. F.; Luehr, G. W.; Hui, H. C.; Gordon, E. M.; Patel, D. V. Combinatorial chemistry of natural products: solid-phase synthesis of D- and L-cycloserine derivatives. *Tetrahedron* **1998**, *54*, 15879−15890.

(117) Haap, W. J.; Kaiser, D.; Walk, T. B.; Jung, G. Solid-phase synthesis of diverse isoxazolidines via 1,3-dipolar cycloaddition. *Tetrahedron* **1998**, *54*, 3705−3724.

(118) Hall, B. J.; Sutherland, J. D. A practical method for the combinatorial synthesis of peptide aldehydes. *Tetrahedron Lett.* **1998**, *39*, 6593−6596.

(119) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. Solid-phase synthesis of β-peptoids: N-substituted β-aminopropionic acid oligomers. *J. Org. Chem.* **1998**, *63*, 708−718.

(120) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M. Knoevenagel condensation of unsymmetrical malonamic esters and malonates on a solid support. *Tetrahedron Lett.* **1998**, *39*, 2047−2050.

(121) Haunert, F.; Bolli, M. H.; Hinzen, B.; Ley, S. V. Clean three-step synthesis of 4,5-dihydro-1*H*-pyrazoles starting from alcohols using polymer supported reagents. *J. Chem. Soc., Perkin Trans. 1* **1998**, *1*, 2235−2237.

(122) Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F.; Samanen, J. Combinatorialchemistry. Use of an intramolecular ruthenium-catalyzed olefin/alkyne metathesis reaction in tandem with a Diels−Alder cycloaddition reaction to construct functionalized hexahydroisoindoles. *Tetrahedron Lett*. **1998**, *39*, 6815−6818.

(123) Hoemann, M. Z.; Melikian-Badalian, A.; Kumaravel, G.; Hauske, J. R. Solid-phase synthesis of substituted quinoline and isoquinoline derivatives using heterocyclic *N*-oxide chemistry. *Tetrahedron Lett*. **1998**, *39*, 4749−4752.

(124) Hori, M.; Janda, K. D. A soluble polymer approach to the "Fishing Out" principle: Synthesis and purification of β-amino alcohols. *J. Org. Chem*. **1998**, *63*, 889−894.

(125) Hughes, I. Design of self-coded combinatorial libraries to facilitate direct analysis of ligands by mass spectrometry. *J. Med. Chem*. **1998**, *41*, 3804−3811.
(126) Hulme, C.; Morrissette, M. M.; Volz, F. A.; Burns, C. J. The solution phase synthesis of diketopiperazine libraries via the Ugi reaction: novel application of Armstrong's convertible isonitrile. *Tetrahedron Lett*. **1998**, *39*, 1113−1116.
(127) Hulme, C.; Peng, J.; Louridas, B.; Menard, P.; Krolikowski, P.; Kumar, N. V. Applications of N-BOC-diamines for the solution phase synthesis of ketopiperazine libraries utilizing a Ugi/De-BOC/cyclization (UDC) strategy. *Tetrahedron Lett*. **1998**, *39*, 8047−8050.
(128) Hulme, C.; Peng, J.; Morton, G.; Salvino, J. M.; Herpin, T.; Labaudiniere, R. Novel safety-catch linker and its application with a Ugi/De-BOC/cyclization (UDC) strategy to access carboxylic acids, 1,4-benzodiazepines, diketopiperazines, ketopiperazines and dihydroquinoxalinones. *Tetrahedron Lett*. **1998**, *39*, 7227−7230.
(129) Hulme, C.; Peng, J.; Tang, S.-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. Improved procedure for the solution phase preparation of 1,4-benzodiazepine-2,5-dione libraries via Armstrong's convertible isonitrile and the Ugi reaction. *J. Org. Chem.* **1998**, *63*, 8021−8023.
(130) Johnson, C. R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K. M. Libraries of N-alkylaminoheterocycles from nucleophilic aromatic substitution with purification by solid supported liquid extraction. *Tetrahedron* **1998**, *54*, 4097−4106.
(131) Jonsson, D.; Molin, H.; Unden, A. Solid phase synthesis of tropane derivatives. *Tetrahedron Lett*. **1998**, *39*, 1059−1062.
(132) Josey, J. A.; Tarlton, C. A.; Payne, C. E. Novel linker for the solid-phase synthesis of guanidines. *Tetrahedron Lett*. **1998**, *39*, 5899−5902.
(133) Katritzky, A. R.; Belyakov, S. A.; Fang, Y.; Kiely, J. S. Polymer-supported preparation of substituted phenols: a new example of simultaneous cyclization-cleavage reaction on solid phase. *Tetrahedron Lett*. **1998**, *39*, 8051−8054.
(134) Kearney, P. C.; Fernandez, M.; Flygare, J. A. Solid-phase synthesis of disubstituted guanidines. *Tetrahedron Lett*. **1998**, *39*, 2663−2666.
(135) Kearney, P. C.; Fernandez, M.; Flygare, J. A. Solid-phase synthesis of 2-aminothiazoles. *J. Org. Chem*. **1998**, *63*, 196−200.
(136) Kim, S. W.; Bauer, S. M.; Armstrong, R. W. Multicomponent solution phase synthesis of dehydroamino acid derivatives based on the Passerini reaction. *Tetrahedron Lett*. **1998**, *39*, 7031−7034.
(137) Kim, S. W.; Bauer, S. M.; Armstrong, R. W. Construction of combinatorial chemical libraries using a rapid and efficient solid phase synthesis based on a multicomponent condensation reaction. *Tetrahedron Lett*. **1998**, *39*, 6993−6996.
(138) Kim, S. W.; Koh, J. S.; Lee, E. J.; Ro, S. Solid-phase synthesis of benzamidine and butylamine-derived hydantoin libraries. *Mol. Diversity* **1998**, *3*, 129−132.
(139) Kim, S. W.; Shin, Y. S.; Ro, S. Solution and solid-phase combinatorial synthesis of peptidomimetic library containing diversified α-methylated amimo acids. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1665−1668.
(140) Kiselyov, A. S.; Smith, L., II; Virgilio, A.; Armstrong, R. W. Immobilized aldehydes and olefins in the solid support synthesis of tetrahydroquinolines via a three component condensation. *Tetrahedron* **1998**, *54*, 7987−7996.
(141) Kiselyov, A. S.; Eisenberg, S.; Luo, Y. Solid support synthesis of 14-membered macrocycles containing the thioether bridge via S_NAr methodology. *Tetrahedron* **1998**, *54*, 10635−10640.
(142) Kiselyov, A. S.; Smith, L.; Armstrong, R. W. Solid support synthesis of polysubstituted tetrahydroquinolines via three-component condensation catalyzed by $Yb(OTf)_3$. *Tetrahedron* **1998**, *54*, 5089−5096.
(143) Ko, D.-H.; Kim, D. J.; Lyu, C. S.; Min, I. K.; Moon, H.-s. New cleavage approaches to combinatorial synthesis of homoserine lactones. *Tetrahedron Lett*. **1998**, *39*, 297−300.
(144) Kobayashi, S.; Wakabayashi, T.; Yasuda, M. Efficient synthesis of diverse monosaccharide derivatives in the solid phase. *J. Org. Chem*. **1998**, *63*, 4868−4869.
(145) Kobayashi, S.; Akiyama, R. Lanthanide trifate-catalyzed 1,3-dipolar cycloaddition reactions of polymer-supported nitrones with alkenes for the preparation of diverse 2-isoxazoline derivatives. *Tetrahedron Lett*. **1998**, *39*, 9211−9214.
(146) Kobayashi, S.; Aoki, Y. *p*-Benzyloxybenzylamine (BOBA) resin. A new polymer-supported amine used in solid-phase organic synthesis. *Tetrahedron Lett*. **1998**, *39*, 7345−7348.
(147) Kulkarni, B. A.; Ganesan, A. Solid phase synthesis of tetramic acids. *Tetrahedron Lett.* **1998**, *39*, 4369−4372.
(148) Kulkarni, B. A.; Ganesan, A. Solution-phase combinatorial synthesis of 4-hydroxyquinolin-2(1H)-ones. *Chem. Commun*. **1998**, 785−786.
(149) Kuster, G. J.; Scheeren, H. W. High pressure promoted tandem [4+2]/[3+2] cycloadditions on the solid phase. *Tetrahedron Lett*. **1998**, *39*, 3613−3616.
(150) Lago, M. A.; Nguyen, T. T.; Bhatnagar, P. Solid phase synthesis of a 1,3,5-trisubstituted pyridinium salt library. *Tetrahedron Lett*. **1998**, *39*, 3885−3888.
(151) Lee, J.; Gauthier, D.; Rivero, R. A. Solid Phase Synthesis of 1-Alkyl-2-alkylthio-5-carbamoylbenzimidazoles. *Tetrahedron Lett*. **1998**, *39*, 201−204.
(152) Leger, R.; Yen, R.; She, M. W.; Lee, V. J.; Hecker, S. J. *N*-Linked solid-phase peptide synthesis. *Tetrahedron Lett*. **1998**, *39*, 4171−4174.
(153) Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A.-G.; Hall, B. J. Use of polymer supported reagents for clean multistep organic synthesis: preparation of amines and amine derivatives from alcohols for use in compound library generation. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2239−2241.
(154) Li, W.-R.; Peng, S.-Z. Rational design and synthesis of unsaturated 2,5-dioxopiperazine derivatives as potential protein tyrosine kinase inhibitors. *Tetrahedron Lett*. **1998**, *39*, 7373−7376.
(155) Lin, P.; Ganesan, A. Solid phase synthesis of N-acyl-N′-carbamoylguanidine. *Tetrahedron Lett*. **1998**, *39*, 9789−9792.
(156) Lorsbach, B. A.; Bagdanoff, J. T.; Miller, R. B.; Kurth, M. J. Isoxazolinoisoquinoline heterocycles via solid-phase Reissert and Suzuki reactions. *J. Org. Chem*. **1998**, *63*, 2244−2250.
(157) Lyngso, L. O.; Nielson, J. Solid-phase synthesis of 3-amino-2-pyrazolines. *Tetrahedron Lett*. **1998**, *39*, 5845−5848.
(158) Maltais, R.; Poirier, D. A solution-phase combinatorial parallel synthesis of 3β-amido-3α-hydroxy-5α-androstane-17-ones. *Tetrahedron Lett*. **1998**, *39*, 4151−4154.
(159) Marzinzik, A. L.; Felder, E. R. Key intermediates in combinatorial chemistry: access to various heterocycles from a,β-unsaturated ketones on the solid phase. *J. Org. Chem*. **1998**, *63*, 723−727.
(160) Masquelin, T.; Delgado, Y.; Baumle, V. A facile preparation of a combinatorial library of 2,6-disubstituted triazines. *Tetrahedron Lett*. **1998**, *39*, 5725−5726.
(161) Masquelin, T.; Meunier, N.; Gerber, F.; Rosse, G. Solution and solid-phase synthesis of combinatorial libraries of trisubstituted 1,3,5-triazine. *Heterocycles* **1998**, *48*, 2489−2495.
(162) Matthews, J.; Rivero, R. A. Solid phase synthesis of substituted tetramic acids. *J. Org. Chem*. **1998**, *63*, 4808−4810.
(163) Mayer, J. P.; Lewis, G. S.; McGee, C.; Bankaitis-Davis, D. Solid-phase synthesis of benzimidazoles. *Tetrahedron Lett*. **1998**, *39*, 6655−6658.
(164) McNally, J. J.; Youngman, M. A.; Dax, S. L. Mannich reactions of resin-bound substrates: 2. A versatile three-component solid-phase organic synthesis methodology. *Tetrahedron Lett*. **1998**, *39*, 967−970.
(165) Moore, M.; Norris, P. Dipolar cycloaddition reactions on a soluble polymer-supported dipolarophile: synthesis of sugar-derived triazoles. *Tetrahedron Lett*. **1998**, *39*, 7027−7030.
(166) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. Solid-phase synthesis of benzopiperazinones. *J. Org. Chem*. **1998**, *63*, 1172−1177.
(167) Mozhaev, V. V.; Budde, C. L.; Rich, J. O.; Usyatinsky, A. Y.; Michels, P. C.; Khmelnitsky, Y. L.; Clark, D. S.; Dordick, J. S. Regioselective enzymatic acylation as a tool for producing solution-phase combinatorial libraries. *Tetrahedron* **1998**, *54*, 3971−3982.
(168) Munson, M. C.; Cook, A. W.; Josey, J. A.; Rao, C. An effecient high-speed synthetic route to amino-substituted thiazolidinone libraries. *Tetrahedron Lett.* **1998**, *39*, 7223−7226.
(169) Nefzi, A.; Giulianotti, M.; Houghten, R. A. Solid phase synthesis of 2,4,5-trisubstituted thiomorpholin-3-ones. *Tetrahedron Lett*. **1998**, *39*, 3671−3674.
(170) Nefzi, A.; Ostresh, J. M.; Giulianotti, M.; Houghten, R. A. Efficient solid-phase synthesis of 3,5-disubstituted hydantoins. *Tetrahedron Lett.* **1998**, *39*, 8199−8202.
(171) Neustadt, B. R.; Smith, E. M.; Nechuta, T.; Zhang, Y. Combinatorial libraries based on a novel and readily accessible "centriod" scaffold. *Tetrahedron Lett*. **1998**, *39*, 5317−5320.
(172) Nicolaou, K. C.; Pastor, J.; Winssinger, N.; Murphy, F. Solid phase synthesis of macrocycles by an intramolecular ketophosphonate reaction. Synthesis of a (dl)-muscone library. *J. Am. Chem. Soc*. **1998**, *120*, 5132−5133.
(173) Nieuwenhuijzen, J. W.; Conti, P. G. M.; Ottenheijm, H. C. J.; Linders, J. T. M. Solid and solution phase combinatorial synthesis of ureas. *Tetrahedron Lett*. **1998**, *39*, 7811−7814.

(174) Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. Solid-phase synthesis of trisubstituted bicyclic guanidines via cyclization of reduced N-acylated dipeptides. *J. Org. Chem*. **1998**, *63*, 8622−8623.
(175) Ouyang, X.; Armstrong, R. W.; Murphy, M. M. A novel cleavage technique to generate small molecule compounds and libraries via a two-resin system. *J. Org. Chem.* **1998**, *63*, 1027−1032.
(176) Pabst, G. R.; Schmid, K.; Sauer, J. A new and simple "lego" system for the synthesis of branched oligopyridines. *Tetrahedron Lett*. **1998**, *39*, 6691−6694.
(177) Page, P.; Burrage, S.; Baldock, L.; Bradley, M. The synthesis of symmetrical spermine conjugates using solid-phase chemistry. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1751−1756.
(178) Pan, P.-C.; Sun, C.-M. Soluble polymer-supported synthesis of arylpiperazines. *Tetrahedron Lett*. **1998**, *39*, 9505−9508.
(179) Panunzio, M.; Villa, M.; Missio, A.; Rossi, T.; Seneci, P. Solution phase library of perhydrooxazin-4-ones. *Tetrahedron Lett*. **1998**, *39*, 6585−6588.
(180) Park, K.-H.; Abbate, E.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. Solution- and solid-phase synthesis of novel hydantoin and isoxazoline-containing heterocycles. *Chem. Commun*. **1998**, 1679−80.
(181) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. Diastereoselective solid-phase synthesis of novel hydantoin- and isoxazoline-containing heterocycles. *J. Org. Chem*. **1998**, *63*, 6579−6585.
(182) Parlow, J. J.; Flynn, D. L. Solution-phase parallel synthesis of a benzoxazinone library using complementary molecular reactivity and molecular recognition (CMR/R) purification technology. *Tetrahedron* **1998**, *54*, 4013−4031.
(183) Perumattam, J.; Chakravarty, S.; McEnroe, G. A.; Goehring, R. R.; Mavunkel, B.; Survajjala, S.; Smith, W. W.; Chen, B. Solid phase synthesis of combinatorial libraries using anhydrides as templates. *Mol. Diversity* **1998**, *3*, 121−128.
(184) Piscopio, A. D.; Miller, J. F.; Koch, K. A second generation solid-phase approach to Freidinger lactams: application of Fukuyama's amine synthesis and cyclative release via ring closing metathesis. *Tetrahedron Lett*. **1998**, *39*, 2667−2670.
(185) Powers, D. G.; Casebier, D. S.; Fokas, D.; Ryan, W. J.; Troth, J. R.; Coffen, D. L. Automated parallel synthesis of chalcone-based screening libraries. *Tetrahedron* **1998**, *54*, 4085−4096.
(186) Purandare, A. V.; Poss, M. A. Solid phase synthesis of unsymmetrical secondary amines − application to the synthesis of arylethanolamines and arylpropanolamines. *Tetrahedron Lett*. **1998**, *39*, 935−938.
(187) Raju, B.; Kassir, J. M.; Kogan, T. P. Solution-phase combinatorial synthesis of ureas using nitrophenylcarbamates. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3043−3048.
(188) Richter, H.; Jung, G. Substituted sulfonamides via a three component reaction on solid support. *Tetrahedron Lett*. **1998**, *39*, 2729−2730.
(189) Richter, H.; Jung, G. Solid-phase synthesis of allylic alcohols via the Baylis-Hillman reaction. *Mol. Diversity* **1998**, *3*, 191−194.
(190) Richter, L. S.; Andersen, S. Curtius degradation in solid-phase synthesis. *Tetrahedron Lett*. **1998**, *39*, 8747−8750.
(191) Romoff, T. T.; Ma, L.; Wang, Y.; Campbell, D. A. Solid phase synthesis of 3-acyl-2,4-pyrrolidinediones (3-acyl tetramic acids) via mild cyclative cleavage. *Synlett* **1998**, 1341−1342.
(192) Schneider, S. E.; Bishop, P. A.; Salazar, M. A.; Bishop, O. A.; Anslyn, E. V. Solid phase synthesis of oligomeric guanidiniums. *Tetrahedron* **1998**, *54*, 15063−15086.
(193) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. Solid-phase synthesis of 1,5-benzodiazepin-2-ones. *Tetrahedron Lett*. **1998**, *39*, 8397−8400.
(194) Scialdone, M. A.; Shuey, S. W.; Soper, P.; Hamuro, Y.; Burns, D. M. Phosgenated *p*-nitrophenyl(polystyrene)ketoxime or phoxime resin. A new resin for the solid-phase synthesis of ureas via thermolytic cleavage of oxime-carbamates. *J. Org. Chem*. **1998**, *63*, 4802−4807.
(195) Shankar, B. B.; Yang, D. Y.; Girton, S.; Ganguly, A. K. One pot solid-phase synthesis of isoxazolines. *Tetrahedron Lett*. **1998**, *39*, 2447−2448.
(196) Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. A practical solid-phase synthesis of quinazoline-2,4-diones. *Tetrahedron Lett*. **1998**, *39*, 7235−7238.
(197) Siegel, M. G.; Shuker, A. J.; Droste, C. A.; Hahn, P. J.; Jesudason, C. D.; McDonald, J. H., III; Matthews, D. P.; Rito, C. J.; Thorpe, A. J. The use of high-throughput synthesis and purification in the preparation of a directed library of adrenergic agents. *Mol. Diversity* **1998**, *3*, 113−116.
(198) Sim, M. M.; Lee, C. L.; Ganesan, A. Solid-phase C-acylation of active methylene compounds. *Tetrahedron Lett*. **1998**, *39*, 2195−2198.
(199) Sim, M. M.; Lee, C. L.; Ganesan, A. Solid-phase combinatorial synthesis of 4-hydroxyquinolin-2(1H)-ones. *Tetrahedron Lett*. **1998**, *39*, 6399−6402.
(200) Smith, A. L.; Stevenson, G. I.; Swain, C. J.; Castro, J. L. Traceless solid-phase synthesis of 2,3-disubstituted indoles. *Tetrahedron Lett*. **1998**, *39*, 8317−8320.
(201) Smith, R. A.; Bobko, M. A.; Lee, W. Solid-phase synthesis of a library of piperazinediones and diazepinediones via Kaiser oxime resin. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2369−2374.
(202) Sofia, M. J.; Hunter, R.; Chan, T. Y.; Vaughan, A.; Dulina, R.; Wang, H.; Gange, D. Carbohydrate-based small-molecule scaffolds for the construction of universal pharmacophore mapping libraries. *J. Org. Chem*. **1998**, *63*, 2802−2803.
(203) Stadlwieser, J.; Ellmerer-Muller, E. P.; Tako, A.; Maslouh, N.; Bannwarth, W. Combinatorial solid-phase synthesis of structurally complex thiazolylhydantoines. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1402−1404.
(204) Starkey, G. W.; Parlow, J. J.; Flynn, D. L. Chemically-tagged Mitsunobu reagents for use in solution-phase chemical library synthesis. *Bioorg. Med. Chem. Lett* **1998**, *8*, 2385−2390.
(205) Sturino, C. F.; Labelle, M. A convenient method for the preparation of acylsulfonamide libraries. *Tetrahedron Lett*. **1998**, *39*, 5891−5894.
(206) Sun, Q.; Yan, B. Single bead IR monitoring of a novel benzimidazole synthesis. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 361−364.
(207) Suto, M. J.; Gayo-Fung, L. M.; Palanki, M. S. S.; Sullivan, R. Solution-phase parallel synthesis using ion-exchange resins. *Tetrahedron* **1998**, *54*, 4141−4150.
(208) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. Stereoselective synthesis of over two million compounds having structural features both reminicient of natural products and compatible with miniaturized cell-based assays. *J. Am. Chem. Soc*. **1998**, *120*, 8565−8566.
(209) Thompson, A.; Moore, F. L.; Moon, Y.-C.; Ellman, J. A. Solid phase synthesis of diverse E- and F-series prostaglandins. *J. Org. Chem*. **1998**, *63*, 2066−2067.
(210) Trautwein, A. W.; Jung, G. Solid-phase synthesis of pyrroles from enaminones and nitroalkenes. *Tetrahedron Lett*. **1998**, *39*, 8263−8266.
(211) Trautwein, A. W.; Sussmuth, R. D.; Jung, G. Hantzsch pyrrole synthesis on solid support. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2381−2384.
(212) Tumelty, D.; Schwarz, M. K.; Needels, M. C. Solid-phase synthesis of substituted 1-phenyl-2-aminomethyl-benzimidazoles and 1-phenyl-2-thiomethyl-benzimidazoles. *Tetrahedron Lett*. **1998**, *39*, 7467−7470.
(213) Tunoori, A. R.; Dutta, D.; Georg, G. I. Polymer-bound triphenylphosphine as traceless reagent for Mitsunobu reactions in combinatorial chemistry: synthesis of aryl ethers from phenols and alcohols. *Tetrahedron Lett*. **1998**, *39*, 8751−8754.
(214) van Loevezijn, A.; van Maarseveen, J. H.; Stegman, K.; Visser, G. M.; Koomen, G.-J. Solid phase synthesis of fumitremorgin, verruculogen and tryprostatin analogues based on a cyclization/cleavage strategy. *Tetrahedron Lett*. **1998**, *39*, 4737−4740.
(215) Villalgordo, J. M.; Obrecht, D.; Chucholowsky, A. Solid-phase synthesis of 3*H*-quinazolin-4-ones based on an aza Wittig-mediated annulation strategy. *Synlett* **1998**, 1405−1407.
(216) Vojkovdsky, T.; Weichsel, A.; Patek, M. Solid-phase synthesis of heterocycles containing an 1-acyl-3-oxopiperazine skeleton. *J. Org. Chem*. **1998**, *63*, 3162−3163.
(217) Wang, Y.; Huang, T.-N. Solid-phase synthesis of heterocycles via palladium-catalyzed annulation. *Tetrahedron Lett*. **1998**, *39*, 9605−9608.
(218) Watson, B. T.; Christiansen, G. E. Solid phase synthesis of substituted coumarin-3-caboxylic acids via the Knoevenagel condensation. *Tetrahedron Lett*. **1998**, *39*, 6087−6090.
(219) Watson, B. T.; Christiansen, G. E. Solid phase synthesis of substituted quinolin-2(1*H*)-one-3-carboxylic acids via an intramolecular Knoevenagel condensation. *Tetrahedron Lett*. **1998**, *39*, 9839−9840.
(220) Weber, L.; Iaiza, P.; Biringer, G.; Barbier, P. Solid phase synthesis of 3-acyltetramic acids. *Synlett* **1998**, 1156−58.
(221) Wei, G. P.; Phillips, G. B. Solid phase synthesis of benzimidazolones. *Tetrahedron Lett.* **1998**, *39*, 179−182.
(222) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D. Polymer bound 3,5-cyclohexadiene-1,2-diols as core structures for the development of small molecule libraries. *Synlett* **1998**, 865−868.
(223) Whitehouse, D. L.; Nelson, K. H., Jr.; Savinov, S. S.; Lowe, R. S.; Austin, D. J. A metathetical cycloaddition-cycloreversion approach to the formation of furan scaffold libraries. *Bioorg. Med. Chem*. **1998**, *6*, 1273−1282.

(224) Wijkmans, J. C. H. M.; Culshaw, A. J.; Baxter, A. D. Solid phase synthesis of functionalized biaryl ethers: versatile scaffolds for combinatorial chemistry. *Mol. Diversity* **1998**, *3*, 117−120.
(225) Wilson, L. J.; Li, M.; Portlock, D. E. Solid phase synthesis of 1-aminohydantoin libraries. *Tetrahedron Lett*. **1998**, *39*, 5135−5138.
(226) Wilson, M. W.; Hernandez, A. S.; Calvet, A. P.; Hodges, J. C. Solid-supported syntheses of 3-thio-1,2,4-triazoles. *Mol. Diversity* **1998**, *3*, 95−112.
(227) Wilson, R. D.; Watson, S. P.; Richards, S. A. Solid phase synthesis of 5-aminopyrazoles and derivatives part 2. *Tetrahedron Lett*. **1998**, *39*, 2827−2830.
(228) Xie, Y. F.; Whitten, J. P.; Chen, T. Y.; Liu, Z.; Mccarthy, J. R. Rapid microscale synthesis: solution phase parallel synthesis of a library of piperazines and piperidines using a water soluble base. *Tetrahedron* **1998**, *54*, 4077−4084.
(229) Yamada, M.; Miyajima, T.; Horikawa, H. Solid phase synthesis of dehydroalanine derivatives. *Tetrahedron Lett*. **1998**, *39*, 289−292.
(230) Yoon, J.; Cho, C.-W.; Han, H.; Janda, K. D. Solution and soluble polymer synthesis of 3-aminoimidazoline-2,4-diones. *Chem. Commun*. **1998**, 2703−2704.
(231) Zhang, H.-C.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. Facile substitution of resin-bound indoles via the Mannich reaction. *Tetrahedron Lett*. **1998**, *39*, 4449−4452.
(232) Zhu, Z.; Mckittrick B. Combinatorial modification of 2-ketopiperazine with solid-phase C-alkylation and N-acylations. *Tetrahedron Lett*. **1998**, *39*, 7479−7482.
(233) Ball, C. P.; Barrett, A. G. M.; Commercon, A.; Compere, D.; Kuhn, C.; Roberts, R. S.; Smith, M. L.; Venier, O. Chameleon catches in combinatorial chemistry: Tebbe olefination of polymer supported esters and the synthesis of amines, cyclohexanones, enones, methyl ketones and thiazoles. *Chem. Commun*. **1998**, 2019−2020.
(234) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. Parallel synthesis of 3-aminoimidazo[1,2-a]pyridines and pyrazines by a new three-component condensation. *Tetrahedron Lett*. **1998**, *39*, 3635−3638.
(235) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. Poly(ethyleneglycol) supported liquid-phase synthesis of biaryls. *Synlett* **1998**, 295−297.
(236) Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. Preparation of highly functionalized Grignard reagents by an iodine−magnesium exchange reaction and its application in solid-phase synthesis. *Angew. Chem., Int. Ed*. **1998**, *37*, 1701−1703.
(237) Du, X.; Armstrong, R. W. SmI_2-mediated sequential radical cyclization/anionic capture of aryl iodides on solid support. *Tetrahedron Lett*. **1998**, *39*, 2281−2284.
(238) Estep, K. G.; Neipp, C. E.; Stramiello, L. M. S.; Adam, M. D.; Allen, M. P.; Robinson, S.; Roskamp, E. J. Indole Resin: A versatile new support for the solid-phase synthesis of organic molecules. *J. Org. Chem*. **1998**, *63*, 5300−5301.
(239) Far, A. R.; Tidwell, T. T. Ketenes in soluble polymer bound synthesis: Preparation of succinamides and 4-pyridones. *J. Org. Chem*. **1998**, *63*, 8636−8637.
(240) Feng, Y.; Wang, Z.; Jin, S.; Burgess, K. S_NAr cyclizations to form cyclic peptidomimetics of β-turns. J. *Am. Chem. Soc*. **1998**, *120*, 10768−10769.
(241) Floyd, C. D.; Harnett, L. A.; Miller, A.; Patel, S.; Saroglou, L.; Whittaker, M. Rapid synthesis of matrix metalloproteinase inhibitors via Ugi four-component condensation. *Synlett* **1998**, 637−638.
(242) Garibay, P.; Nielsen, J.; Hoeg-Jensen, T. Decarboxylation-based traceless linking with aroyl acrylic acids. *Tetrahedron Lett*. **1998**, *39*, 2207−2210.
(243) Guiles, J. W.; Lanter, C. L.; Rivero, R. A. A visual tagging process for mix and sort combinatorial chemistry. *Angew. Chem., Int. Ed*. **1998**, *37*, 926−928.
(244) Havez, S.; Begtrup, M.; Vedso, P. Directed *ortho*-lithiation on solid-phase. *J. Org. Chem.* **1998**, *63*, 7418−7420.
(245) Jin, S.; Holub, D. P.; Wustrow, D. J. Reductive cleavage of resin bound arylsulfonates. *Tetrahedron Lett*. **1998**, *39*, 3651−3654.
(246) Kang, S.-K.; Kim, J.-S.; Yoon, S.-K.; Lim, K.-H.; Yoon, S. S. Copper-catalyzed coupling of polymer bound iodide with organostannanes. *Tetrahedron Lett.* **1998**, *39*, 3011−3012.
(247) Lee, S.-H.; Chung, S.-H.; Lee, Y.-S. Preparation of resin-bound ketimines via transimination and its application in the synthesis of hydantoin libraries. *Tetrahedron Lett.* **1998**, *39*, 9469−9472.
(248) Masquelin, T.; Sprenger, D.; Baer, R.; Gerber, F.; Mercadal, Y. A novel solution- and solid-phase approach to 2,4,5-tri- and 2,4,5,6-tetra-substituted pyrimidines and their conversion into condensed heterocycles. *Helv. Chim. Acta*. **1998**, *81*, 646−654.
(249) Miller, M. W.; Vice, S. F.; McCombie, S. W. Mild N-dealkylation of tertiary, benzylic amines with acid chlorides: Application to solid-phase chemistry. *Tetrahedron Lett*. **1998**, *39*, 3429−3432.
(250) Mohamed, N.; Bhatt, U.; Just, G. Efficient synthesis of substituted oxopiperazines from amino acids. *Tetrahedron Lett.* **1998**, *39*, 8213−8216.
(251) Molteni, V.; Annunziata, R.; Cinquini, M.; Cozzi, F.; Benaglia, M. Soluble polymer-supported synthesis of imines and β-lactams. *Tetrahedron Lett.* **1998**, *39*, 1257−1260.
(252) Schurer, S. C.; Blechert, S. Ruthenium-catalylized yne-ene cross metathesis binding to solid support and cleavage by Pd^0-catalysis. *Synlett* **1998**, 166−167.
(253) Schuster, M.; Blechert, S. Ruthenium-catalyzed yne-ene cross metathesis immobilization of functionalized alkynes. *Tetrahedron Lett*. **1998**, *39*, 2295−2298.
(254) ten Holte, P.; Thijs, L.; Zwanenburg, B. Solid-phase synthesis of 3,5-disubstituted 1,3-oxazolidin-2-ones by an activation/cyclo-elimination process. *Tetrahedron Lett*. **1998**, *39*, 7407−7410.
(255) Tietze, L. F.; Hippe, T.; Steinmetz, A. Palladium-catalyzed allylic substitution on solid support. *Chem. Commun*. **1998**, 793−794.
(256) Veerman, J. J. N.; van Maarseveen, J. H.; Visser, G. M.; Kruse, C. G.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. Ring-closing metathesis on solid support: Elaboration of a cyclization/cleavage strategy towards unsaturated α-ester-substituted N-heterocycles. *Eur. J. Org. Chem*. **1998**, 2583−2589.
(257) Yamamoto, Y.; Ajito, K.; Ohtsuka, Y. Model study for preparation of asymmetric N,N′-Disubstituted piperazine library: Efficient synthesis of aryl piperazine and benzyl piperazine derivatives on the solid support. *Chem. Lett*. **1998**, 379−380.
(258) Hirschmann, R.; Yao, W.; Cascieri, M.; Strader, C.; Maechler, L.; Cichy-Knight, M.; Hynes, J., Jr.; van Rijn, R.; Spengeler, P.; Smith, A. B. S., III. Synthesis of potent cyclic hexapeptide NK-1 antagonists. Use of a minilibrary in transforming a peptidal somatostatin receptor ligand into an NK-1 receptor ligand via a polyvalent peptidomimetic. *J. Med. Chem*. **1998**, *39*, 2441−2448.

CC9900192