Review

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Reviews

Comprehensive Survey of Combinatorial Library Synthesis: 2004

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This is the eighth annual review in an ongoing series of comprehensive reviews in combinatorial chemistry highlighting developments in new methodology and synthesis of small molecule libraries.[1] The survey tallies 388 chemical libraries published in 2004,[2−465] categorized according to biologically active libraries (Tables 1−5), libraries without disclosed biological activity (Tables 6−10), solid- and solution-phase reagents and scavengers (Table 11), linkers (Table 12), and polymer-supported chiral ligands (Table 13).

Affymax[258] and Pharmacopeia[153,154] independently reported the discovery of follicle-stimulating hormone (FSH) receptor agonists. The binding of FSH with its receptor constitutes a protein−protein interaction.

In addition to FSH agonist discovery, Pharmacopeia and their collaborators published the results of screening and optimization programs on glycine-2 transporter inhibitors[457] and selective p38 kinase inhibitors.[461] The company is one of the original combinatorial chemistry companies founded in 1993, having licensed electrophoric-based encoding technology from Columbia University. Over the past decade, Pharmacopeia has amassed 7.5 million discrete small molecule compounds. The compound collection has been screened against dozens of targets, spanning all target classes: proteases, kinases, nonproteolytic enzymes, GPCRs, integrins, transporters, and other nonGPCRs. Diller and Hobbs[467] published a statistical analysis of the company's historical high-throughput screening data examining the relationship between physical properties and substructures on the likelihood of compounds' displaying biological activity, irrespective of target class (structural properties versus hit rate). Data mining revealed that rotatable bond count had the most significant impact on hit rate, with more rigid structures preferred. The optimal rotatable bond count was 6. Structures possessing functional groups capable of making strong intermolecular interactions were also favored. Compounds devoid of an amide bond were 2-fold more likely to be biologically active than compounds with just a single amide bond. Averages for molecular weight, lipophilicity, and numbers of hydrogen-bond donors and acceptors were in the typical range for drug molecules.

Fragment-based approach was used to identify modulators of metabotropic glutamate receptor 5.[243] In a similar vein, a "directed" fragment-based approach furnished growth hormone secretagogue receptor (GHS-R) antagonists.[448]

A computational approach to the design of small molecule ligands for GPCRs activated by positively charged peptide ligands was described by Neurocrine Biosciences.[227] The Pharmacopeia group published a review on library design strategies for targeting kinases and GPCRs.[468]

NeoGenesis honed an affinity selection-mass spectrometry (AS-MS) method for ligand identification.[9] A protein is exposed to a collection of compounds, and any protein−ligand complex formed is separated by rapid, low-temperature, microscale size-exclusion chromatography. Dissociation of the ligand in a subsequent step and mass spectral analysis identifies its structure. As proof-of-concept, the methodology was applied to the discovery of dihydrofolate reductase inhibitors. Merck, in collaboration with NeoGenesis, identified a novel BACE-1 inhibitor from a multimillion compound library using AS-MS.[89]

Diversity-oriented synthesis (DOS) libraries prepared by split−pool and parallel synthesis were reported by the

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Schreiber group.[55,212,221,248] These sophisticated libraries contain skeletally and stereochemically diverse small molecules earmarked as biological probes in chemical genetics. A quantitative method for measuring the relationship between compound diversity and hit rate (cellular activity) was described,[212,469] as well as a strategy guide for preparing DOS libraries.[470] Also from Harvard University, the first 65-member library of DNA-tethered macrocycles employing DNA-template organic synthesis (DTS) was published by D. Liu and co-workers.[456] DTS methodology was developed for the synthesis of *N*-acyloxazolidines.[466]

A new safety-catch linker was developed permitting the release of aldehydes and alcohols via the Pummerer rearrangement.[358] Perfluoroarylsulfonate linkers were shown to behave as triflate equivalents in Pd-catalyzed deoxygenation and cross-coupling reactions.[62,323] Microwave irradiation of methanolic ammonia solutions of halides and sulfonates affords high yields of amine salts without significant dimerization.[341] Two new examples of an expanding repertoire of polymer-supported ionic liquids as catalysts for nucleophilic substitution[209] and the Stetter reaction,[22] and an ionic liquid-based AMEBA-type linker,[102] were reported.

New developments in multicomponent reactions continue to appear in the literature.[6,10,24,32,98,106,109,146,148,174,215,231,256,309,310,424,433] One noteworthy development was the work of Pirrung and Sarma.[309,310] They discovered tremendous rate enhancements in the Passerini and Ugi reactions (with α- and β-amino acids) when carried out in water at room temperature. Small demonstration libraries were synthesized. Products were isolated by simple filtration of the precipitated compounds. A new reagent, MP-glyoxylate, was shown to be a formaldehyde equivalent in the 3-CC of imidazoheterocycles.[256]

Last, Taddei collected and reviewed experimental procedures for functional group color tests on solid support,[471] and new self-indicating amine scavenger resins[81] and pH-indicating resins[135] were described by Bradley.

Methionine Aminopeptidase-2 (MetAP2) Inhibitors. MetAP2 is a potential molecular target for angiogenic-based diseases. The therapeutic rationale for this target is derived from studies with fumagilin, a naturally occurring irreversible inhibitor of MetAP2 displaying antiangiogenic properties. TNP-470, a semisynthetic analogue of fumagilin, inhibits angiogenesis and tumor growth in vivo. MetAP2 is a metalloenzyme that removes the N-terminal initiator methionine residue of nascent proteins. Bestatin and amastatin, 3-amino-2-hydroxyamides, are known reversible inhibitors of MetAP2 and its isoenzyme, MetAP1. Compound **1** possessing the methionine side chain inhibits MetAP2 with a $K_i = 5.7\ \mu$M and MetAP-1 with a $K_i = 63\ \mu$M (Figure 1). X-ray crystallography analysis of MetAP2 reveals its S1′ binding pocket can accommodate larger P1′ side chains, which fortuitously also trend toward greater selectivity relative to MetAP1. This is exemplified by the P1′ cyclohexylmethyl-containing inhibitor **2**: $K_i = 0.6\ \mu$M, MetAP2; $K_i = 84\ \mu$M, MetAP1 (140-fold selective). Sheppard and co-workers at Abbott constructed library 1.2 (**3**), keeping P1′ constant and exploring alternative functionality for the P2′ alanine residue in **2**.[361] This was carried out by solution-phase parallel synthesis in which the corresponding Boc-protected 3-amino-2-hydroxy acid was coupled with over 500 amines (amino acids and non-amino acids) via its activated HOAT ester. The SAR obtained revealed a preference for hydrophobic functionality, for example, halogenated arylalkyl and naphthylalkyl. In particular, naphthylamide **4** showed a 4-fold increase in binding affinity for MetAP2, albeit with somewhat diminished selectivity (75-fold) versus dipeptide **2**. Follow-up library 1.3 (**5**) was then prepared in which the P1′ side chains (R^1) and amines (R^2) were combined in a 2-dimensional array. In this instance, inhibitory potency and selectivity were found dependent upon *both* $R^1$and R^2. The SAR obtained from the follow-up library was not immediately interpretable. A series of enzyme−inhibitor complexes solved by X-ray crystallography indicated significant movement of the enzyme's nonactive site residues accommodating variation of those portions of the inhibitor structure protruding out of the active site. Combinatorial synthesis was credited with optimization against unique and highly variable binding modes, affording MetAP2 inhibitors **6** (K_i = 190 nM) and **7** (K_i = 20 nM), each displaying >500-fold selectivity versus MetAP1.

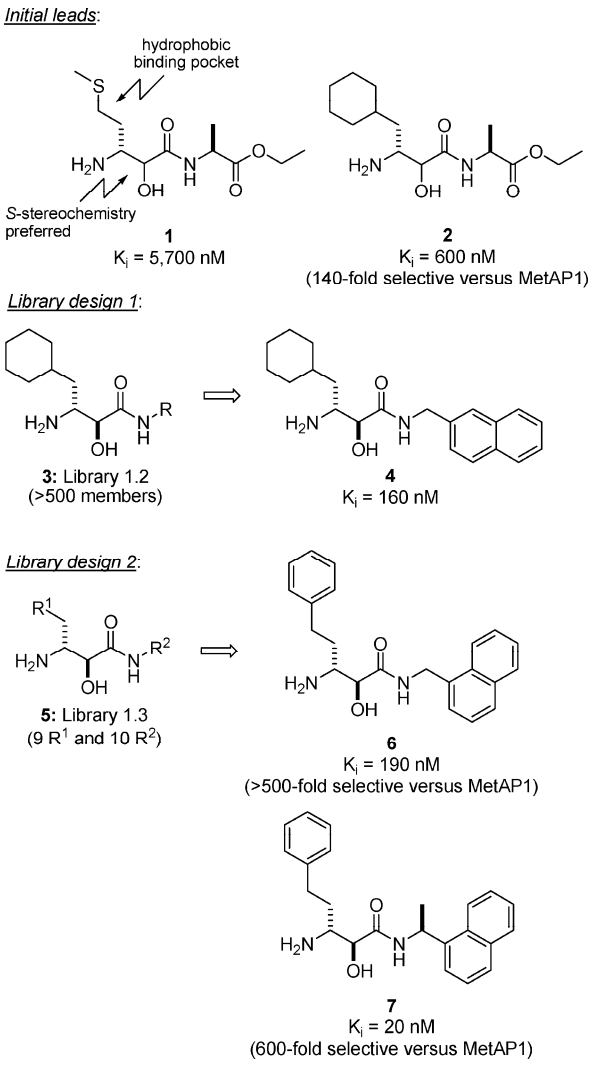


Figure 1. Methionine aminopeptidase-2 (MetAP2) inhibitors.[361]

Optimization of Cyclin-Dependent Kinase 5/p25 (ckd5/p25) Inhibitors. The formation and deposition of cytotoxic neurofibrillary tangles in the brain is a hallmark of Alz-

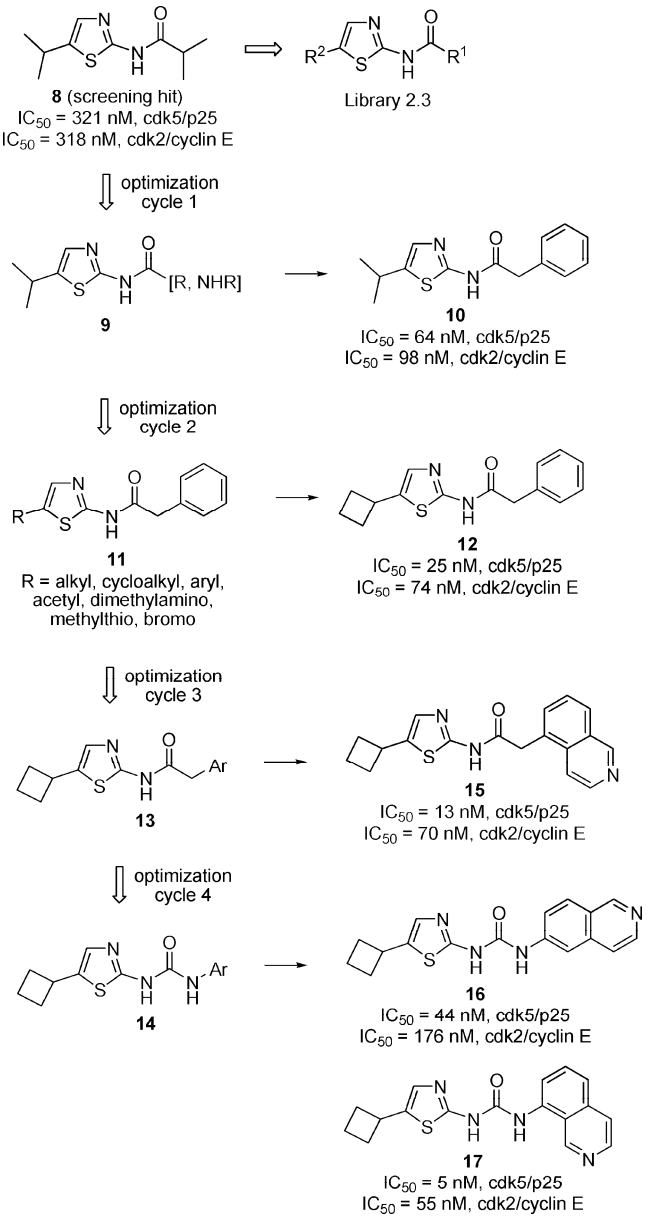


Figure 2. Stepwise optimization of 2-aminothiazole inhibitors of cdk5/p25.[164]

heimer's disease etiology. One mechanism by which this may occur is through hyperphosphorylation of tau protein by the anomalous cdk5/p25 complex. Inhibitors of this enzyme are therefore of interest as potential therapeutic agents for the treatment of Alzheimer's disease and other neurodegenerative disorders. High-throughput screening for inhibitors of cdk5/p25 complex at Pfizer turned up thiazole **8** (Figure 2).[164] Its submicromolar affinity (IC_{50} = 321 nM), low molecular weight (212 daltons), and chemical tractability made **8** a promising candidate for optimization. Thiazole **8** showed a high degree of selectivity against a broad range of kinases with the exception of cdk2/cyclin E, for which **8** was equipotent (IC_{50} = 318 nM). High-throughput synthesis was used to carry out optimization, which was performed in four cycles (collectively library 2.3). In optimization cycle 1, the 5-isopropyl-2-aminothiazole was conserved and the amino group derivatized, yielding collections of amides and ureas (**9**). This led to phenylacetamide analogue **10** with a ~4-fold increase in affinity (IC_{50} = 64 nM). In the next round of optimization, a set of commercially available and custom-prepared 5-substituted 2-aminothiazoles were acylated with phenylacetyl chloride to yield collection **11**. Keeping the phenylacetamido group constant gave rise to the 5-cyclobutyl analogue **12** with further increased binding affinity (IC_{50} = 25 nM) and selectivity (3-fold). Larger cycloalkyl, alkyl, and phenyl groups at the 5-position decreased potency. Dimethylamino, which is sterically similar to isopropyl, but more polar, also resulted in loss of potency. Following the discovery of the 5-cyclobutyl as the optimal 5-substituent, two further optimization cycles took place, expanding the number of amide (optimization cycle 3; **12** → **13**) and urea derivatives (optimization cycle 4; **13** → **14**). The SAR revealed a preference for fused heteroaryl rings, for example, **15**−**17**. Inhibitor **17** demonstrated a 60-fold improvement in potency at cdk5 (IC_{50} = 5 nM) and a 10-fold selectivity over ckd2. Because only 2 of the 29 conserved ATP binding pocket residues in cdk5 and ckd2 are different, identifying highly selective ckd5 inhibitor is a demanding optimization exercise.

Inhibition of ATPase Activity of Human Papillomavirus 6 (HPV6) E1 Helicase. Infections caused by human papillomavirus result in a range of unpleasant conditions, including plantar and genital warts; laryngeal papillomatosis, a respiratory tract infection; and life-threatening cervical cancer. There are currently no marketed anti-HPV agents. The circular DNA genome encodes for 10 proteins (E1−E8 and L1, L2), which are all common to the >80 types of HPV. Of particular interest is the enzyme E1 (DNA) helicase, a highly conserved HPV protein. Inhibition of the E1 helicase should result in the inhibition of HPV replication, and therefore, the enzyme is considered an attractive molecular target for antiviral intervention. A high-throughput screen, measuring ATPase activity of recombinant HPV6 E1 helicase, was developed at Boehringer Ingelheim.[124] Evaluation of the company's compound collection resulted in the discovery of ((4-phenyl)phenylsulfonyl)acetic acid **18** as a reversible micromolar inhibitor of the enzyme (IC_{50} = 2 μM; Figure 3). Acid **18** was subjected to a two-part hit-to-lead campaign. Part one explored the SAR of the sulfonylacetic acid and phenyl ring regions of the screening hit. This was carried out by traditional synthesis. An extensive survey of carboxylic acid isosteres and modifications to the sulfonyl group (>12 analogues) resulted in significant loss of activity, for example, **19** and **20**. Similar exploration of the aryl ring revealed that the biaryl ring was required for activity (**18** → **21**, **22**), wherein the 4-phenyl ring tolerated substitution at the *meta* and *para* positions (**18** → **23**, **24**). With this nascent SAR in hand, part two of the hit-to-lead exercise was initiated. Parallel synthesis was employed to further define the scope of 4-phenyl substituents with the goal of increasing the affinity of **18**. Synthons **25a**,**b** and **26a**,**b** were synthesized and coupled with a diverse set of commercially available amines to generate amide library 2.29 (**27**: ~100 analogues total). Increased potency was achieved within the libraries with IC_{50} values ranging from 400 nM up to >80 000 nM. The most potent analogues were the meta-substituted series of primary amides bearing a hydrophobic aromatic residue. Representative of the SAR were **29** (IC_{50}

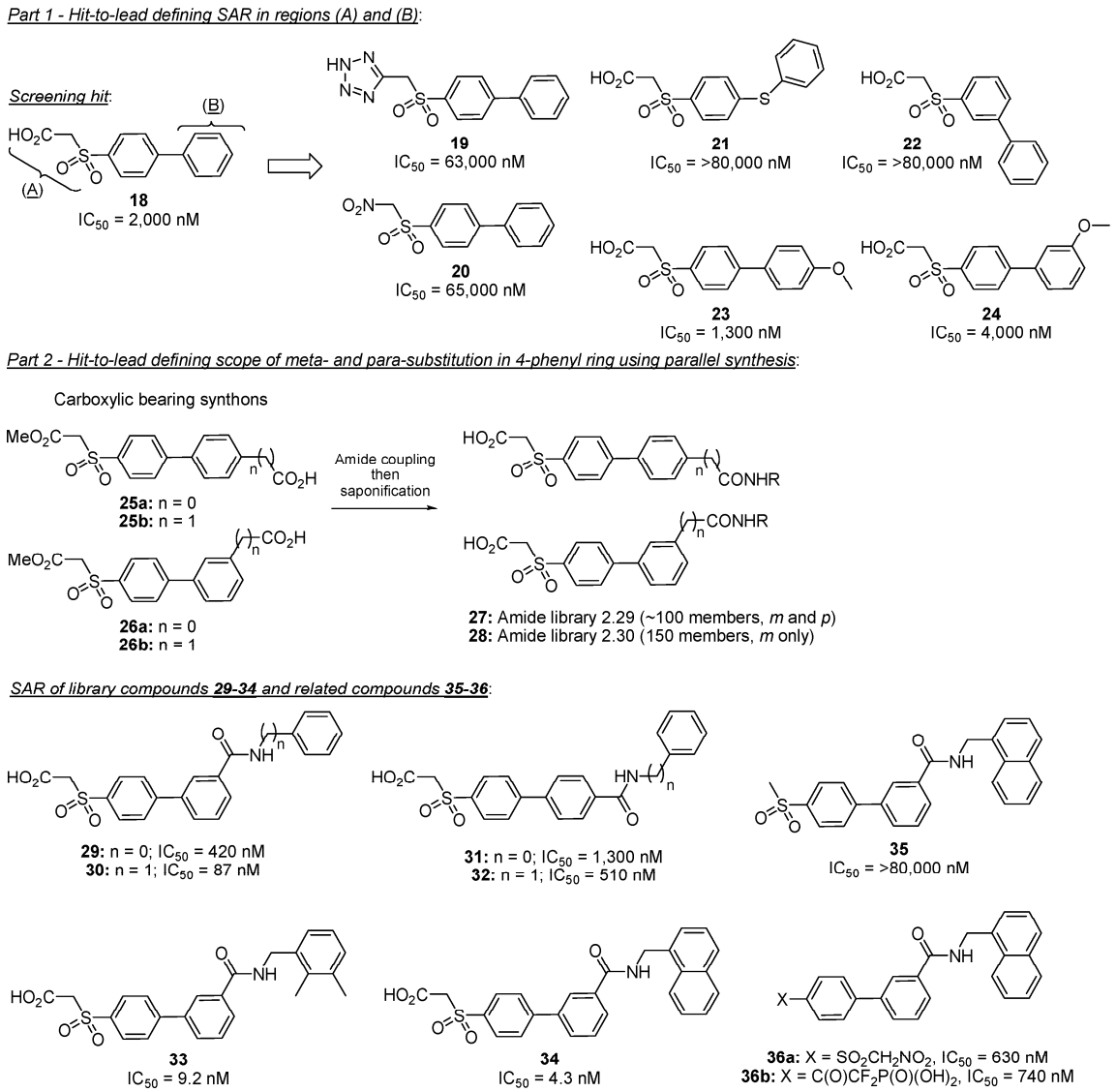


Figure 3. Hit-to-lead for HPV6 E1 helicase inhibitors.[124]

= 420 nM) versus **31** (IC_{50} = 1300 nM) and **30** (IC_{50} = 87 nM) versus **32** (IC_{50} = 510 nM). Continued focused library synthesis of ~150 additional *meta*-substituted analogues (library 2.30 (**28**)) furnished compounds **33** (IC_{50} = 9.2 nM) and **34** (IC_{50} = 4.3 nM), with the latter analogue demonstrating a 500-fold improvement in potency versus the screening lead **18**. One issue with the series was the lack of cell potency and the propensity for the sulfonylacetic acid to decarboxylate to the inactive methyl sulfone **35**. For this reason, sulfonacetic acid surrogates were revisited using **34** as a starting point. Unfortunately, none could be identified which maintained nanomolar potency. Two moderately active surrogates synthesized were **36a** (IC_{50} = 630 nM) and **36b** (IC_{50} = 740 nM). Neither of these compounds demonstrated whole-cell-based activity.

Affinity Selection-Mass Spectrometry: Identification of DHFR and *β*-Secretase Inhibitors. NeoGenesis reported an optimized automated process for identifying small molecule ligands from mass-encoded libraries on the basis of affinity selection-mass spectrometry (AS-MS; Figure 4).[9] In this process, soluble protein (enzyme, receptor) is incubated with a compound library. The mixture is subjected to automated microscale size-exclusion chromatography (SEC) conducted at 4 °C in less than 30 s, separating any newly formed protein−ligand complex(es). The combination of speed and low temperature maintains the integrity of the protein−ligand complex, even for weakly bound ligands (K_d < 10 μM) and moderate off rates (k_{off} < 0.1 s^{-1}). The separated complex is directly routed to a reversed-phase chromatography column (60 °C, pH <2) where protein−ligand dissociation occurs. The unbound ligand is then eluted into an electrospray HRMS for analysis. Because the libraries are constructed to minimize isobaric compounds by judicious choice of building blocks, data-searching algorithms can be used to identify the ligand by its molecular weight. Final confirmation of ligand structure is secured by independent synthesis of the ligand. If positional isomers exist (mass redundancy), then a sublibrary of ligands is synthesized. Highlights of the process include (1) no foreknowledge of the structure or biochemistry of the protein target is required; (2) immobilization or modification of the protein is unnecessary; (3) only submilligram amounts of purified, soluble protein is consumed (<1 μg protein per 2500 compounds); and (4) screening can be conducted at a rate of >250 000

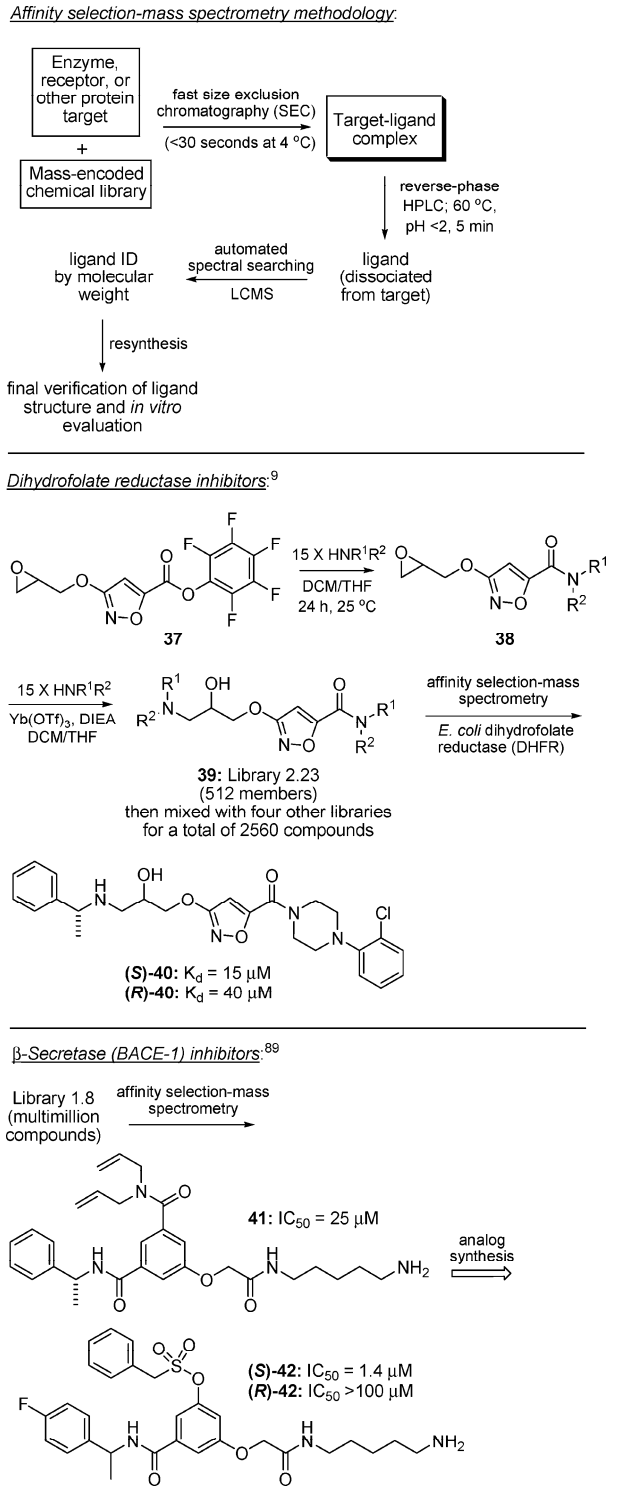


Figure 4. NeoGenesis's affinity selection-mass spectrometry method for ligand identification.[9]

compounds/day employing mixture libraries prepared by solid- or solution-phase chemistry.

By way of showcasing the AS-MS process, a 2560-member library was screened against *Escherichia coli* dihydrofolate reductase (DHFR). The library consisted of five 500-member libraries, including library 2.23 (**39**), prepared from bifunctional template **37** via acylation then epoxide ring opening (**37** → **38** → **39**) with 15 amines (same inputs, twice). The AS-MS process was conducted by incubating the 2560-member library at a 2.5 mM cumulative compound concentration with 5 μM DHFR (2 μL final volume, pH 7.5, phosphate buffer containing 2.5% DMSO, 100 mM NaCl) for 30 min at 37 °C, then chilled to 4 °C for SEC separation and further processing. In this way, 2 pmol of each library member (at 1.0 μM/component) and 10 pmol (0.18 μg) of protein were used in the analysis. Screening yielded a single monochlorinated DHFR ligand at *m*/*z* 515.24. The ligand corresponded to **(*R*,*S*)-40** or its positional isomer. These were the only two ligands in the 2560-member library that came within 0.05 amu of the measured molecular weight. Compound **(*R*,*S*)-40** and its positional isomer were individually synthesized employing the same experimental method used to produce the library. By comparison of the molecular fragmentation patterns of the authentic samples versus the isolated ligand, the structure of the DHFR ligand was determined to be the structure, as indicated. The *R*- and *S*-isomers were then separated by chiral HPLC. **(*S*)-40** was found to be the more active compound ($K_d = 15$ μM) versus its antipode **(*R*)-40** ($K_d = 40$ μM). **(*S*)-40** inhibited the growth of *E. coli* at an IC_{50} of 29 μg/mL.

In collaboration with NeoGenesis, Merck applied the AS-MS technology in a screening campaign to identify novel leads against β-secretase (BACE-1).[89] This resulted in the identification of structure **41** as the *only* compound emerging from a multimillion-compound library 1.8 (generic library structure was not defined). The nonpeptide BACE-1 inhibitor ($IC_{50} = 25$ μM) was subjected to a round of optimization. Replacement of the *N*,*N*-diallylcarboxamide with a benzyl sulfonate (**41** → **42**) resulted in a ~17-fold increase in enzyme affinity. The stereochemistry present in **42** was critical for activity: **(*S*)-42**, $IC_{50} = 1.4$ μM versus **(*R*)-42**, $IC_{50} > 100$ μM. An X-ray crystal structure of the corresponding enzyme−inhibitor complex revealed that **(*S*)-42** occupies the enzyme's S_4-S_1 subsites. Interestingly, the inhibitor makes no direct contact with the catalytic aspartic acid residues, but rather, its oxyacetamide NH forms a hydrogen bond with a catalytic water molecule situated between the aspartyl triad.

Positive Allosteric Modulators for mGluR5. The binding of glutamate and subsequent activation of the metabotropic glutamate receptor 5 (mGluR5) is coupled to increased function of the NMDA receptor. Suboptimal functioning of the NMDA receptor is associated with psychosis, including schizophrenia. Compounds that potentiate the binding of glutamate to mGluR5, that is, positive allosteric modulators, may therefore restore hypofunctioning NMDA receptors, leading to a new class of antipsychotic agents. A high-throughput FLIPR assay was developed at Merck to identify compounds with this biological profile.[243] One compound to emerge from the screen was phthalimide **43**: $EC_{50} = 740$ nM (Figure 5). This compound demonstrated a 6-fold potentiation of the response of CHO cells transfected with human mGluR5 to a low concentration of glutamate, the native agonist. The compound did not display agonist activity in the absence of glutamate, further confirming it as a positive allosteric modulator of the receptor. Lindsley led the effort to develop a SAR. In this regard, an iterative library approach to analogue synthesis was carried out, and some 1000 analogues (library 3.19) were reportedly prepared. Despite

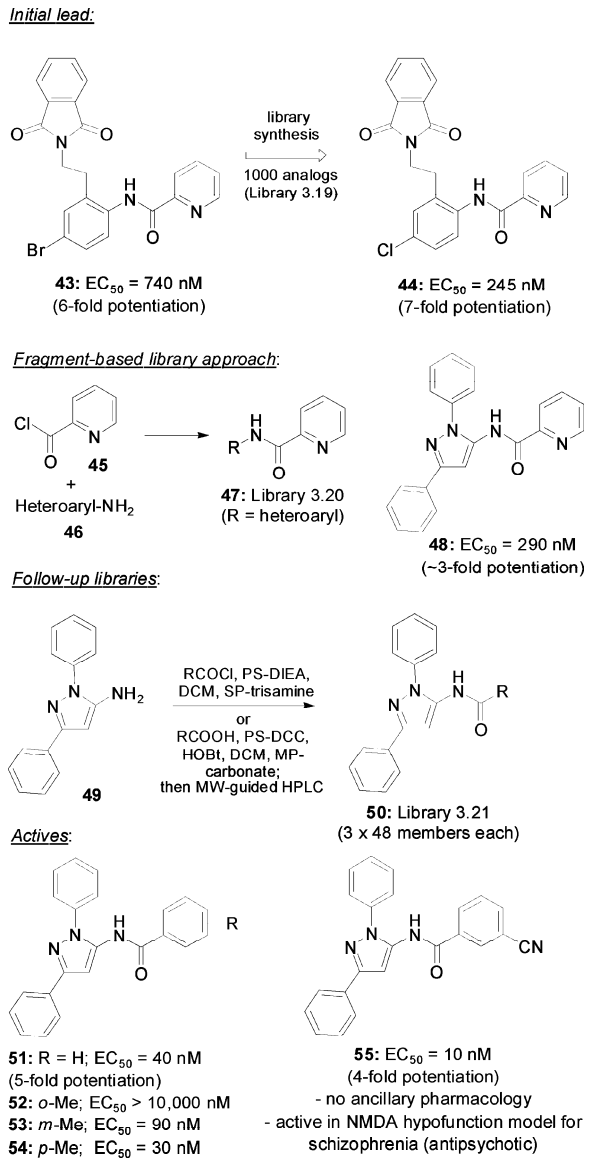


Figure 5. Positive allosteric modulators for mGluR5.[243]

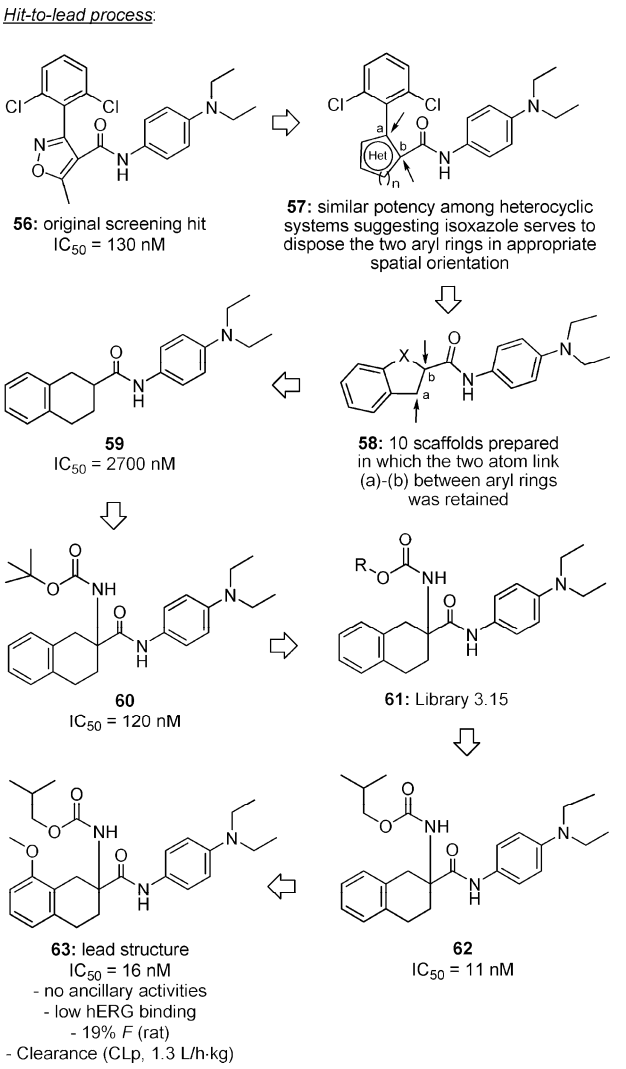


Figure 6. Abbott's growth hormone secretagogue receptor antagonists.[448]

the large number of analogues, the screening hit proved intractable. Compound **44**, in which chlorine conservatively replaced bromine in **43**, was one of only two structures (the other compound in which 2-pyridyl was replaced with 2,2-hydroxyphenyl) that retained a reasonable level of potentiation. A new lead structure was required. To this end, a fragment-base library approach in which the picolinoyl amide was retained was adopted. Picolinoyl chloride **45** was then reacted with a diverse set of commercially available and in-house heterocyclic amines **46** to give library 3.20 (**47**). The size of the library was not disclosed. This exercise led to the discovery of a new lead, 1,3-diphenylpyrazole **48**: EC_{50} = 290 nM, ~3-fold potentiation. Three focused libraries (**50**) were then prepared. Commercially available 5-amino-1,3-diphenylpyrazole **49** was derivatized with a range of carboxylic acids and chlorides. It was found that the phenyl derivative **51** was 7-fold more potent than **48**. Activity was dependent on the substituent pattern in the phenyl ring (EC_{50}'s for *ortho*- (**52**), *meta*- (**53**), and *para*-toluyl (**54**) were >10 000, 90, and 30 nM, respectively). Analogue **55** (EC_{50} = 10 nM, 4-fold potentiation) was selected for further evaluation. It was devoid of ancillary activity against a panel of kinases and receptors. The mGluR5 potentiator readily diffused into the CNS as measured by selected brain penetration experiments. In a critical in vivo proof-of-concept study, **55** dose-dependently reversed the rodent acoustic startle response following amphetamine administration. This is a well-characterized animal behavior model of sensorimotor gating in which antipsychotic drugs are similarly effective.

Growth Hormone Secretagogue Receptor (GHS-R) Antagonists. Administration of a peptide antagonist of GHS-R results in reduction of food intake and body weight gain in diet-induced obese mice, suggesting that GHS-R antagonists may be useful therapeutics for treating obesity. Isoxazole **56** was identified from a high-throughput screening campaign for GHS-R ligands at Abbott Laboratories (Figure 6).[448] This attractive hit was a rather potent antagonist possessing an IC_{50} = 130 nM against the receptor. Although extensive SAR led to more potent analogues, as a class, these displayed poor pharmacokinetics and were largely devoid of oral activity, the desired route of administration. Part of the problem was thought to be facile hydrolysis of the amide group in vivo. The isoxazole ring was replaced with a variety

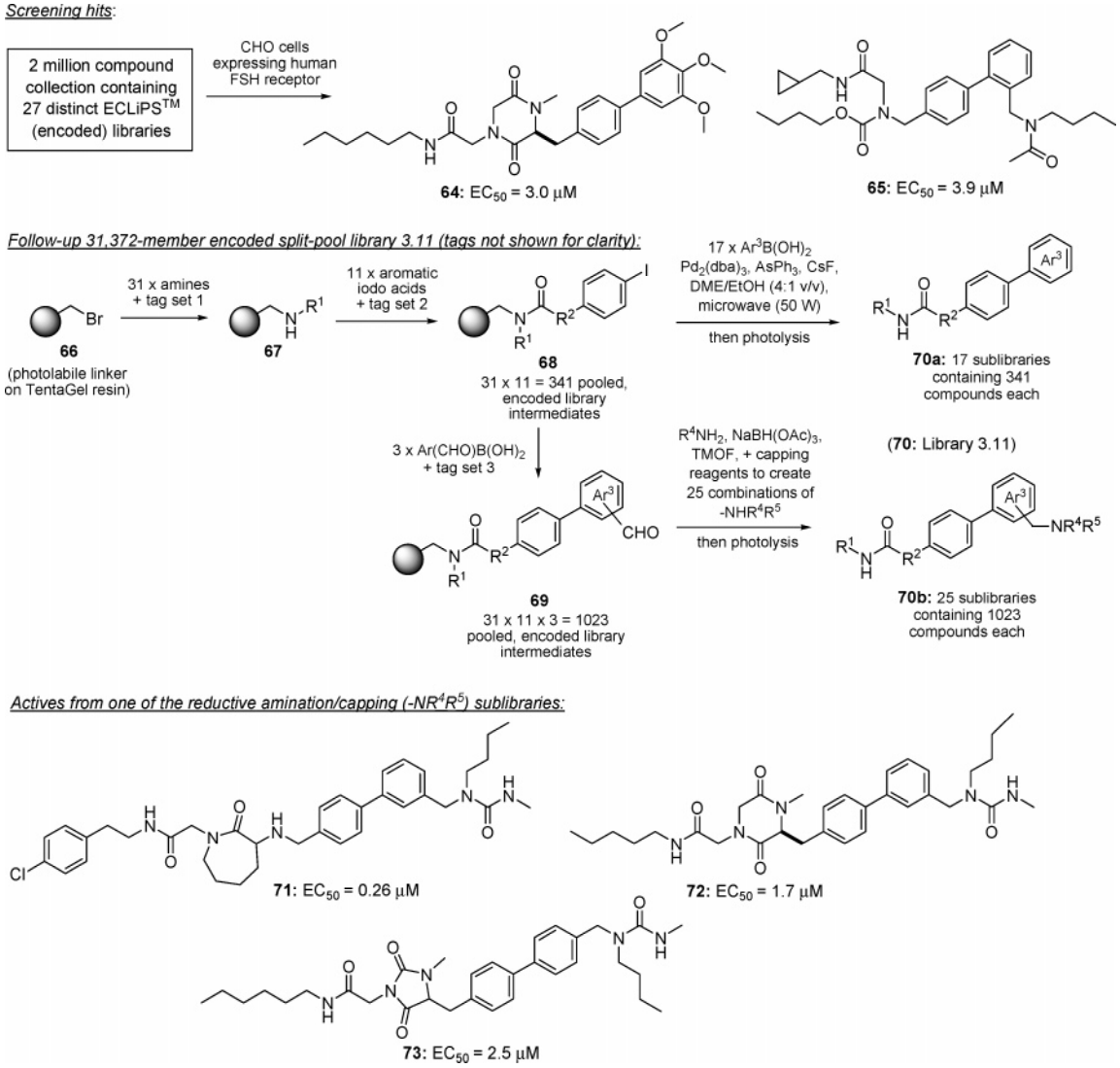


Figure 7. Pharmacopeia's FSH receptor agonists.[153]

of aryl and heteroaryl rings (**56** → **57**). On balance, these analogues retained receptor affinity. This led to the hypothesis that the isoxazole ring served as a spacer element providing a preferred distance and dihedral angle between the aryl rings in **56**. Ten scaffolds **58** were synthesized to test the hypothesis, and a new tetralin template, exemplified by **59**, was found. The IC_{50} of **59** was 200-fold less potent (IC_{50} = 2700 nM) versus the original hit (130 nM). Amide hydrolysis (metabolic instability) was still of concern in the new structure, and thus, the carbon atom α to the amide was quaternized by introducing alkyl, carboxylic, and assorted amine derivatives. This afforded the Boc-protected α-amino analogue **60**, restoring receptor affinity of the original hit. Library 3.15 (**61**) was then prepared to uncover isobutyl as the optimal carbamate: **62**, IC_{50} = 11 nM. Further SAR studies led to 7-methoxy analogue **63**, IC_{50} = 16 nM. Importantly, compound **63** was orally bioavailable in the rat (F = 19%), with reasonable clearance, and displayed excellent specificity (no off-target activity) and low hERG channel binding. Tetralin **63** was a functional antagonist of GHS-R. Receptor affinity of the enantiomers was not reported, nor was **63**'s ability to elicit reduction of food intake in an in vivo model of obesity.

Encoded Libraries and the Discovery of Follicle-Stimulating Hormone (FSH) Receptor Agonists. FSH is 38-kD heterodimeric protein which binds to FSH receptor, a G-protein-coupled receptor (GPCR), setting in motion a signaling cascade leading to the growth of ovarian follicles and improved fertility. Purified or recombinant FSH is a biopharmacetical used to treat low fertility in women. FSH must be administered by subcutaneous or intramuscular injection, and an orally active agent is highly desirable. Because the binding of FSH with its receptor is in essence a protein−protein interaction, the discovery of small molecules is a challenge. This past year, research groups at Pharmacopeia[153,154] and Affymax[258] independently reported potent nonpeptide FSH receptor agonists. In both instances, screening hits came from large chemically encoded libraries.

Guo and co-workers at Pharmacopeia collaborated with scientists at Organon to discover FSH agonists (Figure 7).[153] Two million compounds constituting 37 structurally distinct ECLiPS libraries (split−pool libraries encoded with electrophoric tags) were evaluated in a high-throughput screen using a CHO cell line expressing human FSH receptor and the cAmp-response-element (CRE)-luciferase-reporter con-

struct. One of the 37 ECLiPS libraries may perhaps have contained the privileged biaryl motif and, hence, yielded **(*S*)-64** and **65** as micromolar hits. A follow-up encoded library was synthesized to expand the nascent SAR. Thirty-one reaction vessels containing TentaGel resin **66** modified with the photolabile linker and encoded with a set of electrophoric halogenated tags were reacted with one of 31 primary amine inputs. Resin **67** so obtained was pooled and divided into 11 reaction vessels and acylated with one of 11 iodoaryl carboxylic acids and then tagged to give acylated resin, **68**. It was subsequently pooled and mixed, and approximately one-third of the resin was divided into 17 portions and subjected to Suzuki coupling with one of 17 arylboronic acids, yielding 17 sublibraries of 341 compounds (**70a**). The remaining two-thirds portion of resin was divided thrice; coupled to *o*-, *m*-, and *p*-formylphenylboronic acids; tagged; pooled; mixed; and split into 25 reaction vessels, **68** → **69**. Final resin treatment included a combination of reductive amination and N-capping, generating 25 sublibraries of 1023 members each (**70b**). The total number of library 3.11 compounds = 31 372. Compounds were cleaved from resin by photolysis after bead arraying. The structure identity of any given active was determined by ECGC analysis of the haloaromatic alcohol tags detached from beads in a separate tag-reading step and then confirmed by compound resynthesis. It was reported that 72 distinct structures with an EC_{50} < 10 μM were found. One of the reductive amination sublibraries contained 25 actives and was analyzed with respect to distribution frequency of synthons. Interestingly, this analysis revealed a remarkable *combinatorial* dependence on synthon pairs R^3-R^2 and R^3-R^1. The frequency of R^3-*ortho*-compounds was tightly paired with acylic carbamates, as found in **65**. The frequency of R^3-*meta*-compounds were coupled with the cyclic scaffolds, represented by azepinone **71** and diketopiperazine **72**. Last, R^3-*para*-compounds were nearly exclusively associated with the hydantoin scaffold, represented by **73**.

The diketopiperazine biaryls **64** and **72** obtained from the ECLiPS collection and follow-up library 3.11 were subjected to a second optimization step (Figure 8).[154] Parallel synthesis was used to prepare an additional ~300 compounds (library 3.12). Chemistry was developed to permit intracyclative cleavage of resin-bound Boc-protected amino esters to give the desamide biaryl diketopiperiazines that were not contained in the original ECLiPS library due to the synthetic strategy employed. The desamides **74** ((2*S*, 5*S*); EC_{50} = 13 nM) and **75** ((2*S*, 5*R*,*S*); EC_{50} = 1.2 nM) gave leads with greatly enhanced (>150-fold) potency over the original screening hit **64**.

In the Affymax study led by Maclean and Holmes,[258] broad screening of the Affymax libraries afforded thiazolidinone **76** (EC_{50} = ~5 μM) as a hit structure (Figure 9). An encoded split−pool library 3.10 (**77**), employing alkylamine-based tags, was prepared. The library was composed of 35 R^1 amino acids × 35 R^2 aldehydes × mercaptosuccinic acid × 35 HNR^3R^4 amines. The last step was not pooled, but kept as separate sublibraries. The total number library compounds was nominally 42 875, but is significantly much larger, considering that it is a mixture of diastereomers. In-process

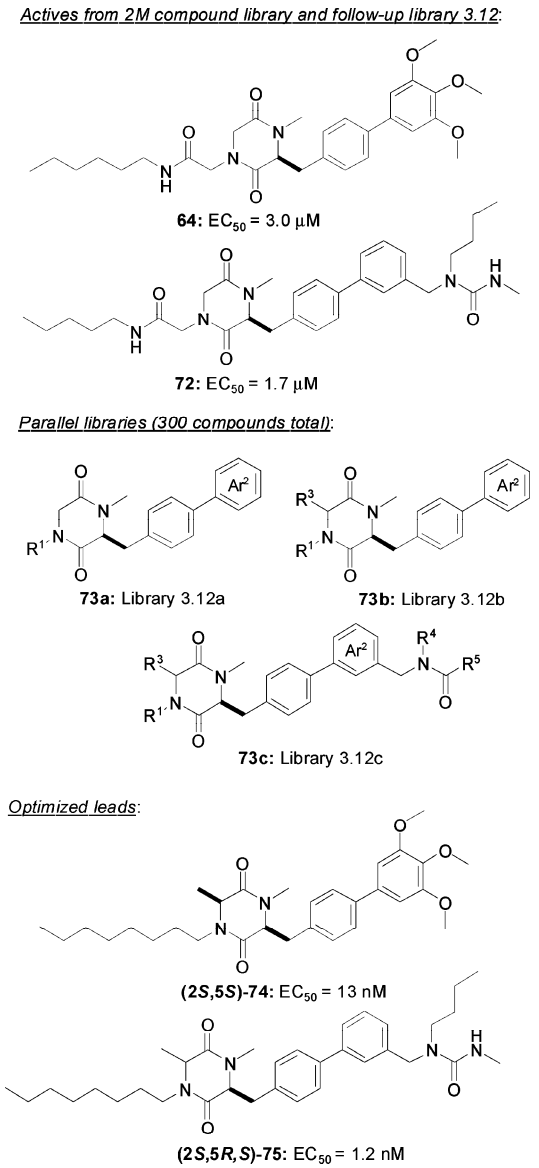


Figure 8. Optimization of Pharmacopeia's FSH receptor agonists.[154]

and final library quality control indicated a synthesis success rate of 96%. The library was designed to be in part a follow-up on **76** and in part random for screening against future molecular targets. As a result, only 10 building blocks per input set were either identical or closely matched functionality in **76**. The remaining 25 building blocks per input set were randomly selected, in part, on the basis of their expected chemical performance. Hence, only ~2% of the library contained direct analogues of **76**.

Library 3.10 (**77**) was initially surveyed to identify active sublibraries. This was done by arraying the entire library, 35 sublibraries, in 96-well plates at 30 beads per well in DMSO, followed by full photolysis (1 h, 365 nm) and screening (FSH receptor reporter assay). Two active sublibraries were found. Two screening strategies were then employed to identify biologically active single beads. In the first strategy, so-called tiered release, 0.75 library equivalents (defined as the number of library beads equal to the number of compounds in the library) was arrayed at 10 beads per well (96-well plate) and briefly photolyzed (2 min, 365 nm)

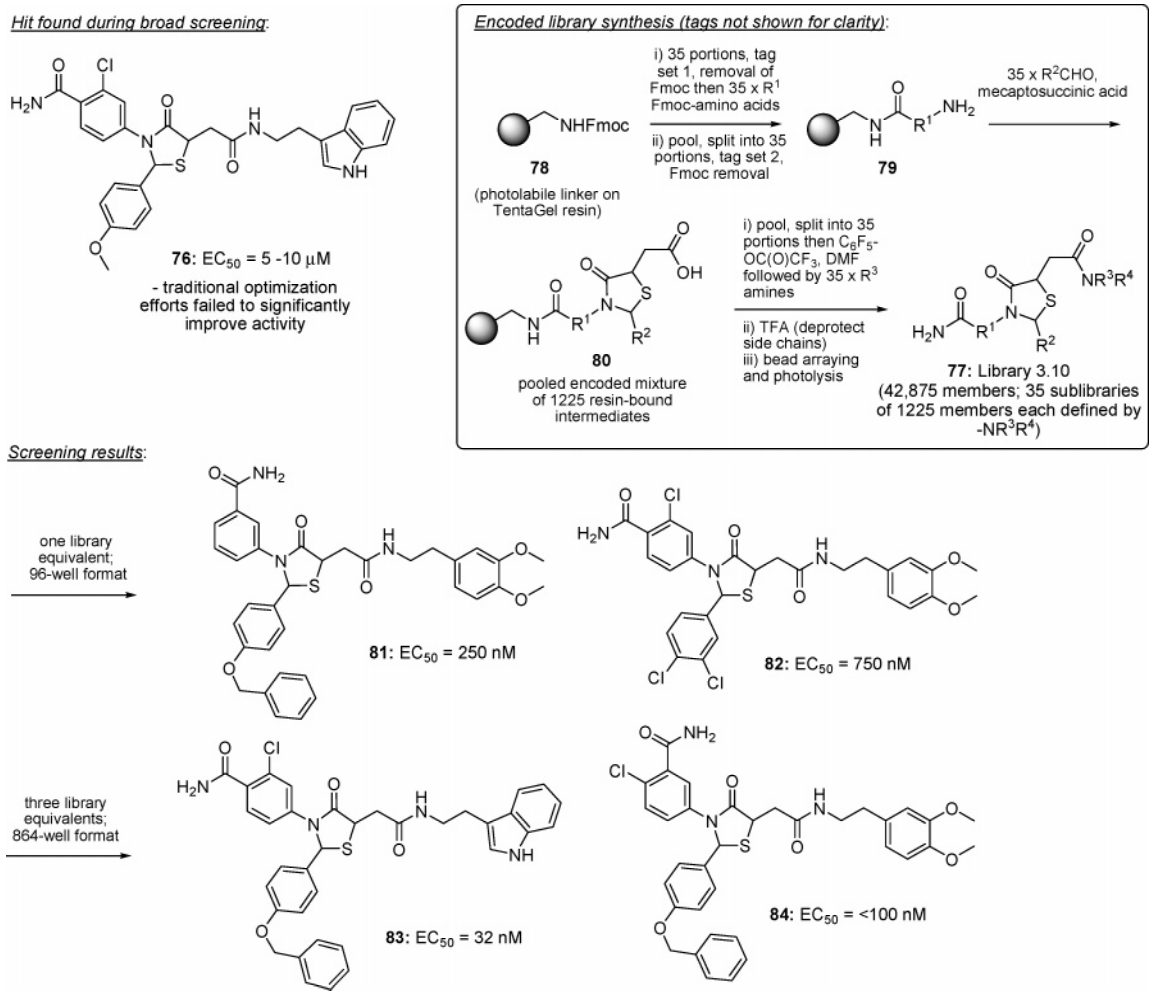


Figure 9. Affymax FSH receptor agonists: library synthesis.[258]

to release half of the compound from the bead. Only one of the two sublibraries confirmed activity. The beads from the active sublibrary were rearrayed as single beads per well and subjected to a second photolysis treatment, releasing the rest (remaining half) of the compound. Following screening and decoding, the structures of submicromolar FSH agonists were revealed as **81** and **82**.

In the second screening strategy, 3 library equivalents of just the confirmed active sublibrary was arrayed in six 864-well plates (high-density format) as single beads. Full photolysis and screening gave 63 active wells out of 5000 wells. Structures of the active wells were decoded, affording compounds **83** (EC_{50} = 32 nM) and **84** (EC_{50} < 100 nM), the former compound being significantly more potent than the original hit **76**. Compound **83** differs from **76** only by a benzyl versus methyl substituent in the aryl ring. Interestingly, the original hit **76** was not found by either screening strategy. It was subsequently shown that **76** was sensitive to TFA used in the final library treatment (R^1 amino acid side chain deprotection). Surprisingly, **83** was apparently insensitive to TFA. Omitting this TFA-cleavage step, **76** was found upon screening 2 library equivalents of the appropriate sublibrary in high-density format. This report aptly highlights the advantages and pitfalls of screening large, chemically encoded libraries.

Small Molecule Library for GPCRs Activated by Positively Charged Peptides. GPCRs for melanocortins, gonadotropin releasing hormone, bradykinin, melanin concentrating hormone, vasoactive intestinal peptide, galanin, orexin, and selected chemokines continue to receive much attention in the pharmaceutical industry. This is due to their involvement in a range of pathophysiological conditions, including reproductive disorders, pain, and obesity. These receptors constitute a subclass of GPCRs that are all activated by peptide ligands carrying an obligatory positively charged residue. Saunders and co-workers at Neurocrine Biosciences designed a non-peptide library test set (library 3.18 (**93**)) of 2024 members targeting this subclass of GPCRs (Figure 10).[227] They first defined the 5-dimensional space occupied by 81 560 biologically active compounds, including marketed drugs, by calculating their BCUT metrics (DiverseSolutions software) for H-bond donor and acceptor, two metrics of polarizability and charge. Relying on cell-based methodology, each of the 5 axes was divided into 10 bins, partitioning the entire drug space into 100 000 individual cells. The actual number of cells occupied by the 81 560 ligands was 8506 cells, or ~8% of the total. At this juncture, Saunders introduced the concept of analyzing neighboring cells. Experience had taught that although potent compounds reside in a few cells or a single cell, progressively less active

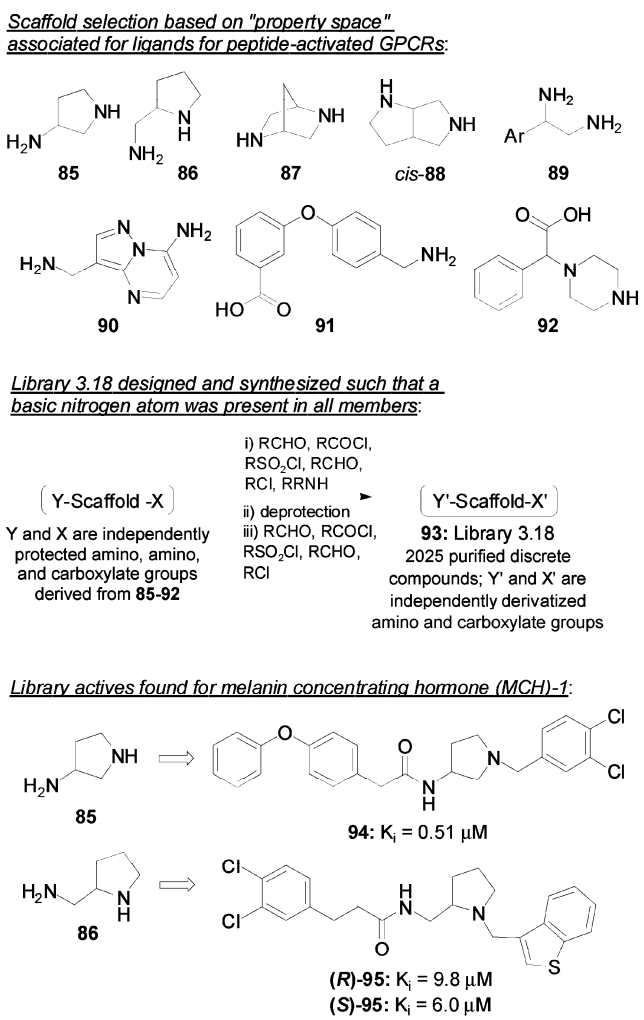


Figure 10. GPCR screening library.[227]

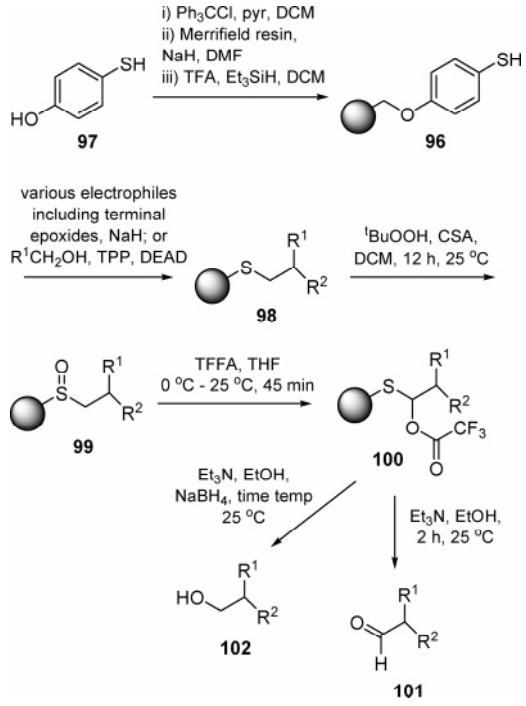


Figure 11. Safety-catch linker cleaved by Pummerer rearrangement.[358]

compounds are layered in neighboring cells. In 5-dimensional space, each occupied cell has $3^5 - 1 = 242$ neighbors, and for the 81 560 ligands, raising the total number of cells populated to 91 080 cells, or 91%. A similar analysis was carried out on 111 known nonpeptide ligands for positively activated GPCRs. Mapping the results showed that only 6% of the drug space (6437 cells) was occupied, including nearest neighbor cell count, which projected into three of five dimensions. With this analysis in hand, 19 scaffolds containing at least one basic nitrogen atom were subjected to virtual library derivatization and enumeration. A virtual collection of 90 000 000 compounds resulted, each possessing a basic nitrogen atom within the scaffold as the key pharmacophoric element. The five BCUT metrics were calculated for each virtual compound to assess its location relative to the space occupied by the 111 known nonpeptide ligands. Seven of the scaffolds, **85**−**92**, were selected for actual library synthesis. The scaffolds were derivatized employing acylation, sulfonylation, ureidoation, reductive amination, alkylation, and amidation reactions. This furnished library 3.18 (**93**) containing 2025 discrete compounds. Evaluation of **93** against three GPCRs, melanocortin-4 receptor (MC4-R), gonadotropin-releasing hormone receptor (GRH-R), and melanin-concentrating hormone receptor (MCH-R), resulted in a 4.5- to 61-fold increase in hit rate, as compared to a random library set of comparable size. The structures and K_i's of several hits, for example, **94** and **95**, were revealed for MCH-R. In addition, the computational analysis suggested that ∼7000 compounds would be necessary to establish the boundaries of this GPCR subclass and provide a comprehensive targeted screening library.

New Linker Chemistry. Li and co-workers developed a new safety-catch linker **96** cleaved by Pummerer rearrangement, releasing aldehydes and alcohols (Figure 11).[358] 4-Hydroxythiophenol **97** was coupled to Merrifield resin in a high loading routine 3-step reaction sequence: S-tritylation, resin etherification, and S-trityl deprotection (**97** → **96**). The safety-catch linker **96** reacts with various electrophiles, such as halides and sulfonate esters (NaH is required as the base) and epoxides (Et_3N as the base), or alcohols under Mitsunobu conditions, yielding a sulfide resin **98**. The sulfide linkage is stable to a wide range of reaction conditions. To cleave the linker, resin **98** is first oxidized to the sulfoxide **99**. A survey of oxidants found *t*-BuOOH/10-camphorsulfonic acid in DCM was optimal (12 h, 25 °C), avoiding overoxidation to the corresponding sulfone. The oxidation reaction was conveniently monitored by magic angle spinning gel-phase NMR. Initial attempts to effect Pummerer rearrangement with sodium acetate/acetic anhydride proved too harsh, because the high temperature required was incompatible with the polystyrene bead. Switching to trifluoroacetic acid anhydride (TFAA) solved this problem, leading to the α-trifluoroacetoxythioacetals **100** in high yield at ambient temperature (THF, 0 → 25 °C, 45 min). Treatment of **100** with Et_3N in EtOH (2 h, 25 °C) released the aldehydes **101**. By adding $NaBH_4$ to the cleavage cocktail, a one-pot procedure was developed to yield alcohols **102** directly.

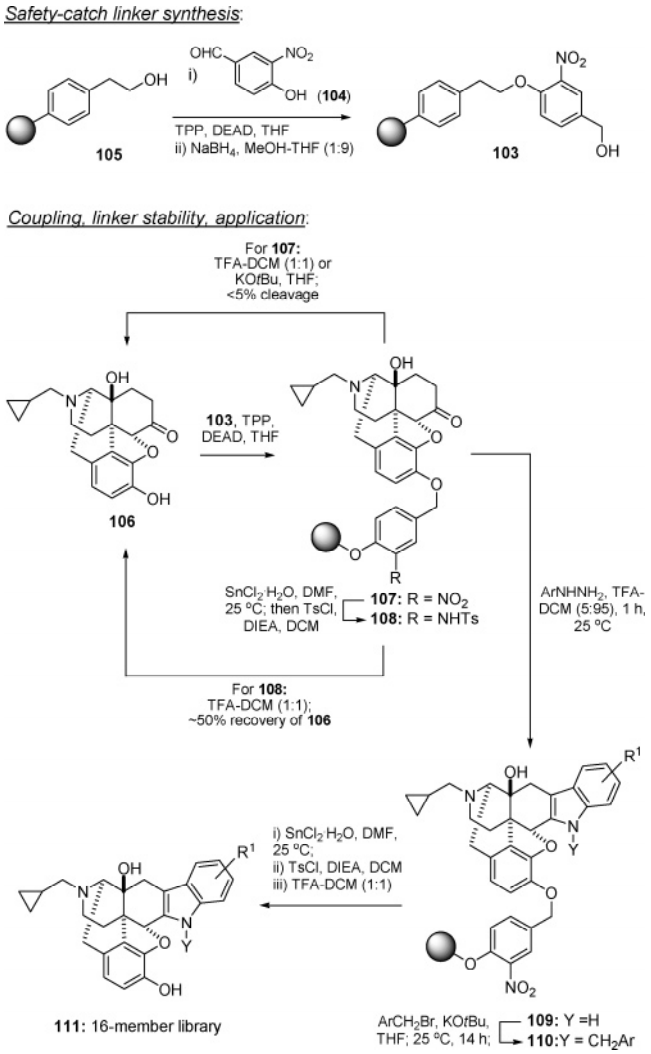


Figure 12. New 3-nitrobenzyl safety-catch linker.[293]

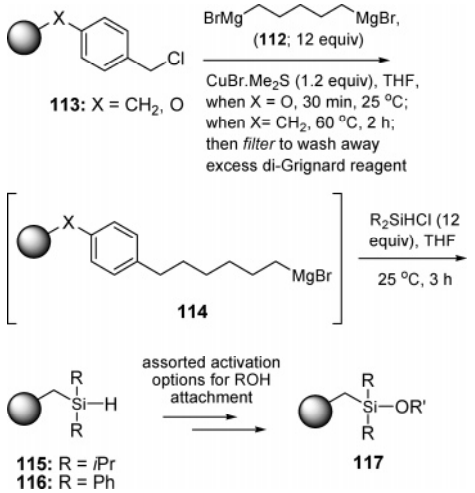


Figure 13. Formation of silyl linker via di-Grignard chemistry.[110]

Nitrobenzyl linker **103** was conceived as a new safety-catch linker for solid-phase synthesis possessing both acid and base stability (Figure 12).[293] This is a Wang-type resin whose acid stability is dramatically improved by virtue of the nitro substituent. It is activated by reduction of the nitro group to the corresponding aniline, followed by acylation or sulfonylation. Products are released upon exposure to mild acid. Linker **103** was prepared upon Mitsunobu coupling of

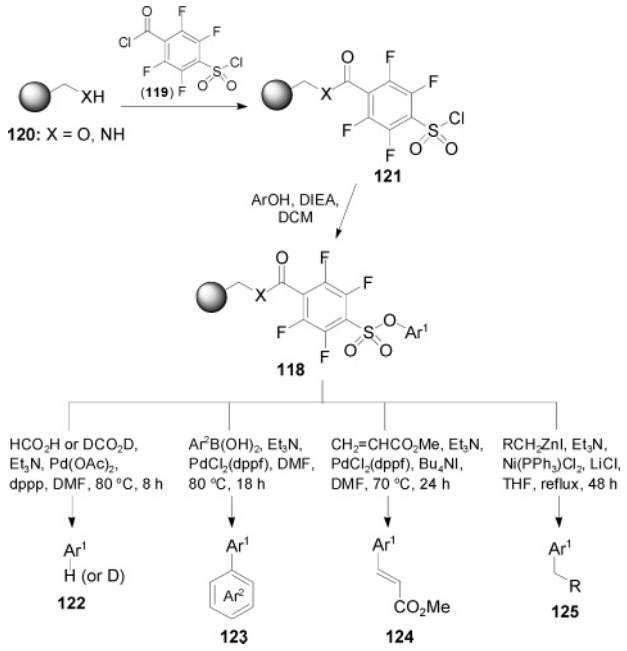


Figure 14. Perfluoroarylsulfonate linker for cross-coupling.[62,323]

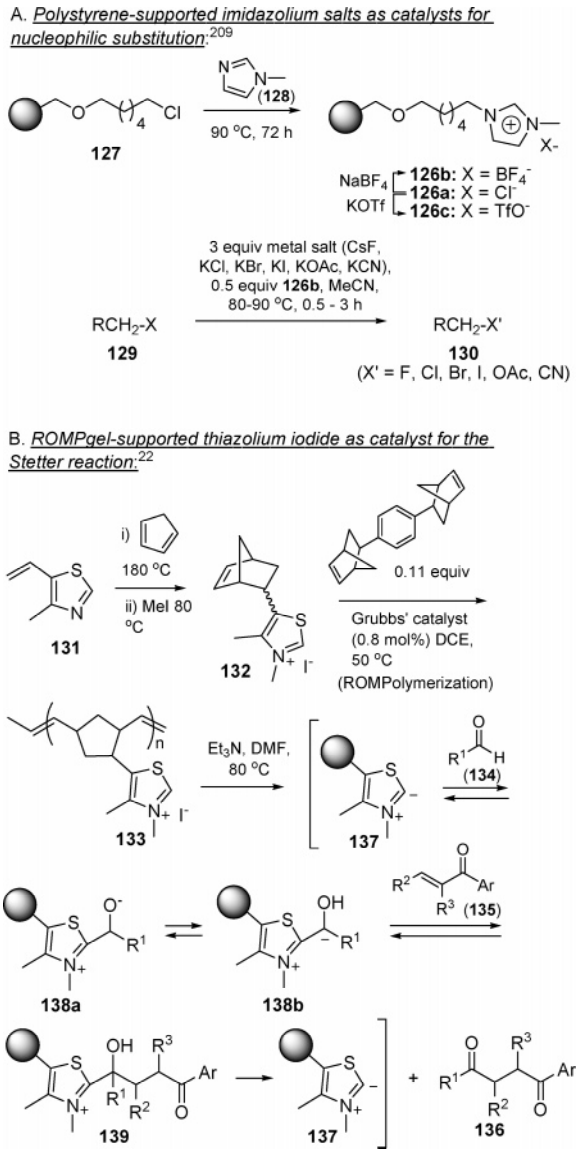


Figure 15. Polymer-supported ionic catalysts.

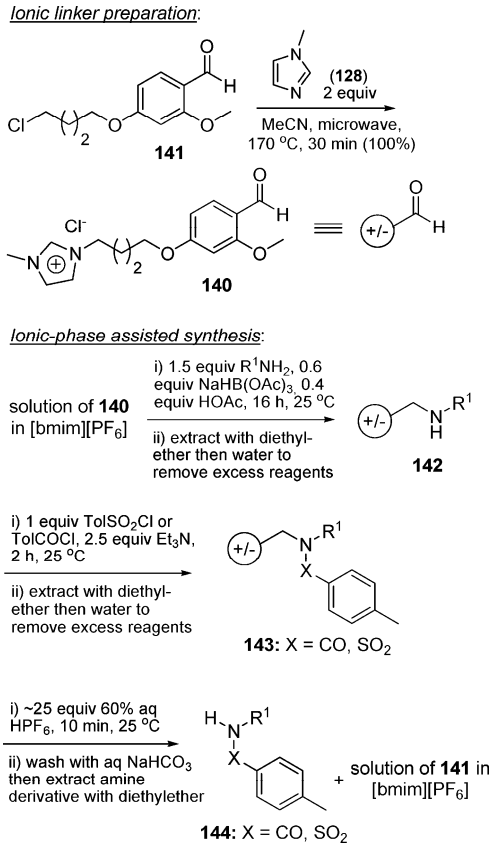


Figure 16. Acid-labile ionic linker.[102]

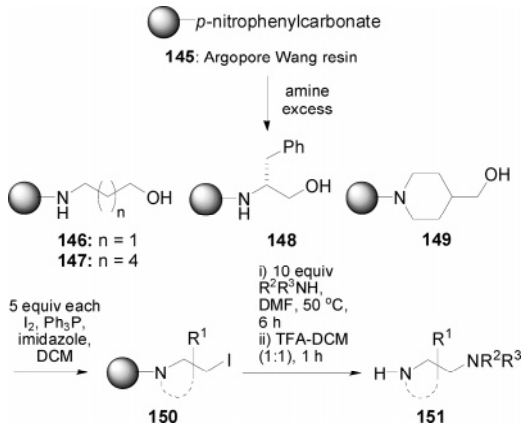


Figure 17. Solid-phase synthesis of secondary and tertiary amines.[297]

4-hydroxy-3-nitrobenzaldehyde **104** to 2-hydroxyethylpolystyrene **105** followed by aldehyde reduction with $NaBH_4$ in MeOH−THF (1:9). Resin loading (determined by elemental analysis of **103**) was reasonable at ∼1 mmol/g. To demonstrate the linkers's robustness to acid, naltrexone **106** was coupled to **103** (Mistunobu reaction conditions) to give resin-bound phenol **107**. Exposure of **107** to TFA−DCM (1:1) or *t*-BuOK in THF resulted in <5% cleavage of naltrexone.Nitro group reduction was readily carried out under standard reaction conditions using $SnCl_2 \cdot H_2O$. Sulfonylation of the anilino group rather than acylation (to avoid competing O-acylation) gave activated resin **108**. The linker was cleaved (TFA−DCM (1:1)), resulting in 50% recovery of **106**. In a further demonstration of the utility of the safety-catch linker, resin-bound naltrexone **107** was subjected to Fisher indole synthesis (4 × arylhydrazines, TFA−DCM (5:95), 25 °C, 1 h) and N-alkylation (4 × $ArCH_2Br$, *t*-BuOK, THF, 25 °C, 14 h; **107** → **109** → **110**). Tin-mediated nitro reduction, N-sulfonylation, and acid cleavage produced the 16-member library **111**. The chemistry was performed by the directed sorting split−pool method with IRORI MicroKans. Final products were purified by preparative reversed-phase HPLC to remove *N*,*O*-dialkylated byproducts generated during the *t*-butoxide alkylation step.

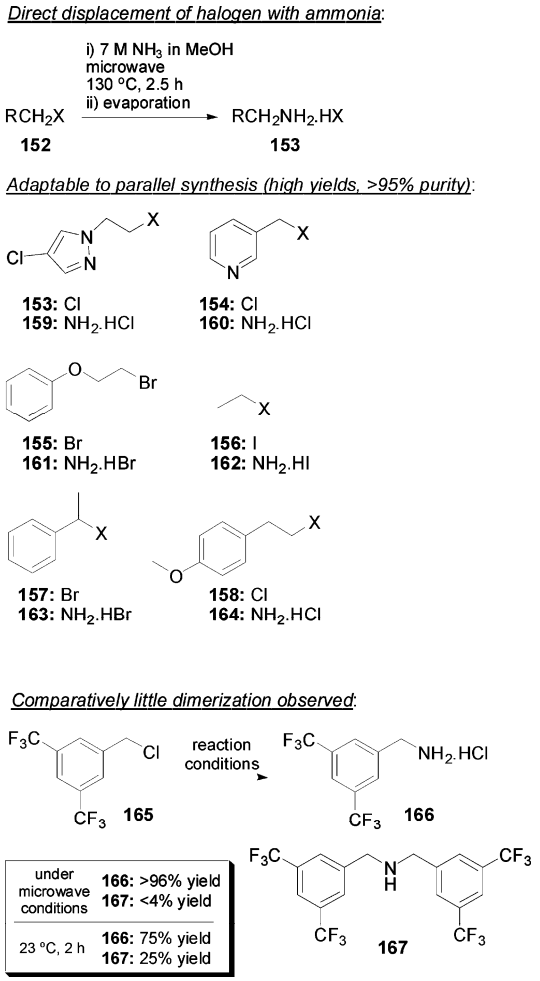


Figure 18. Microwave-assisted primary amine synthesis.[341]

Silyl linkers have broad appeal in solid-phase synthesis. Encoded diversity-oriented synthesis (DOS) libraries originating from the Schreiber group rely almost exclusively on immobilizing alcohol building blocks via the silyl ether. The linker supports aryls where the silicon−aryl bond is subject to *ipso* substitution to yield traceless cleavage products. Cleavage conditions are tunable, depending upon the type of alkyl substituents present on the silicon atom. Takahashi and co-workers reported an efficient synthesis of a range of polymer-supported silyl linkers employing di-Grignard chemistry (Figure 13).[110] Pentane-1,5-di(magnesium bromide) **112** (12 equiv) was coupled to benzyl chloride-bearing resins (**113**), including Merrifield, Argogel-Cl, Wang-Cl, and Argogel Wang-Cl, in the presence of $CuBr \cdot Me_2S$. The bulky nature of the resin permitted selective monoalkylation of **113**. After filtration to remove excess **112**, the reactive intermediate Grignard resin **114** was further treated with solutions of chlorodiisopropylsilane and chlorodiphenylsilane, affording **115** and **116**, respectively. For the Wang-type resins, the

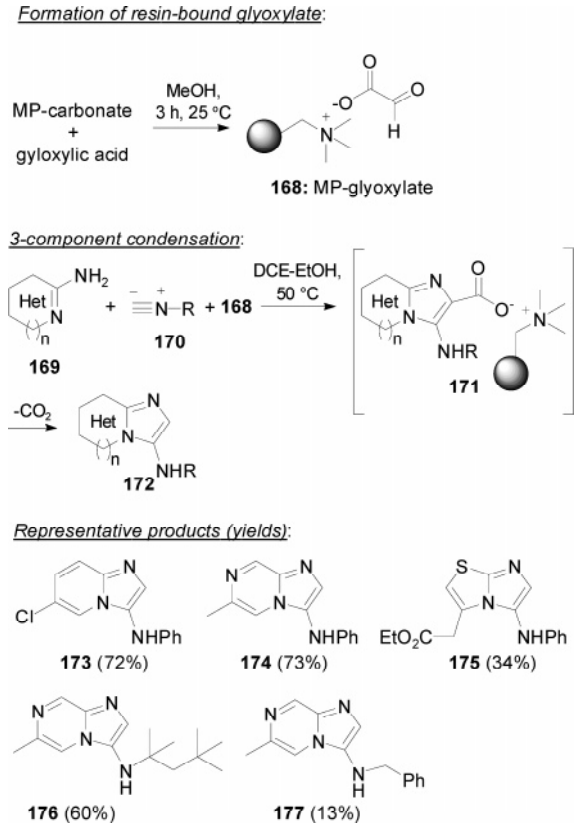


Figure 19. Formaldehyde equivalent in 3-component condensation.[256]

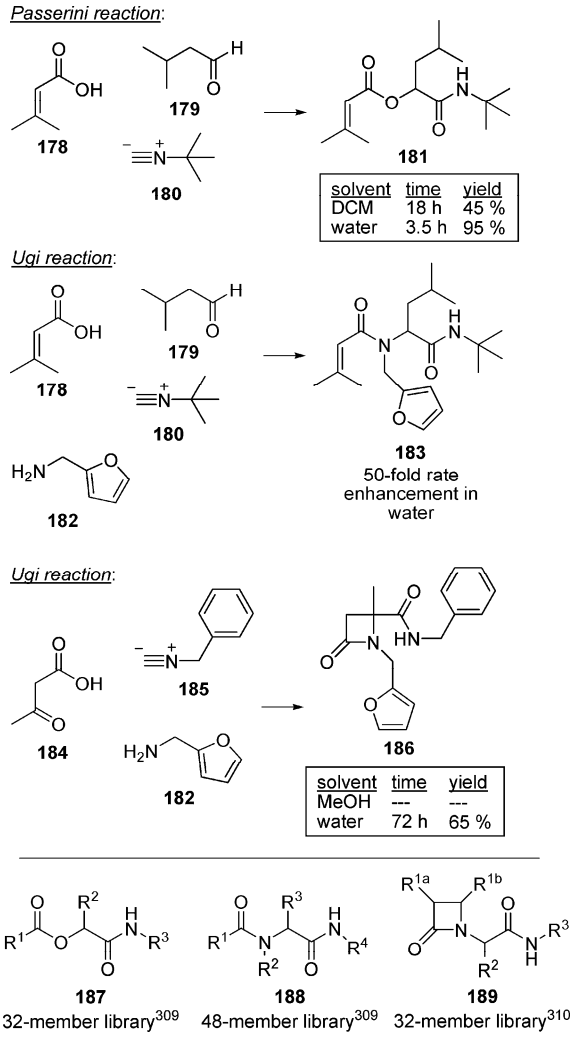


Figure 20. Multicomponent reactions in water.[309,310]

sequential reactions proceeded at room temperature. Resin loading was established by the Fmoc cleavage test via chlorination (SiH → SiCl) and attachment of *N*-Fmoc-2-aminoethanol. Loading was adequate, averaging 50−75% of the initial loading. The silane resins were activated to the corresponding silyl chloride and silyl triflate resins using standard methodology for the attachment of alcohol substrates and formation of silyl ethers **117**. A novel one-step dehydrosilation method was also developed to attach alcohols directly to the diisopropylsilane resin **115** using $B(C_6F_5)_3$.

Two research groups, one led by Cammidge[62] and the other by Ganesan,[323] independently developed perfluoroarylsulfonate linker **118** (X = O or NH) as a polymer-supported "triflate" equivalent (Figure 14). Their research disclosures appeared as back-to-back communications in *Chemical Communications.* The readily available acid chloride **119** was coupled to resin **120** via an ester or amide linkage, affording sulfonyl chloride resin **121**. Resin **121** smoothly reacted with a series of phenols in high yield to give resin-bound sulfonate esters **118**. Both research groups demonstrated the opportunities for Pd-catalyzed traceless cleavage. For example, the reductive cleavage by transfer hydrogenation gives deoxygenated products **122**. Site-specific isotopic labeling of aromatic compounds was achieved by substituting formic acid with deuterium-labeled formic acid in the reaction. Ganesan reported a ~10% higher yield of products **122** using amide versus ester linked tetrafluorosulfonate.[323] Resin **118** also performed well in the Suzuki−Miyaura (**118** → **123**), Mizoroki−Heck (**118** → **124**), and Negishi (**118** → **125**) cross-coupling reactions. Perfluoroarylsulfonate resins have excellent shelf stability.

Polymer-Supported Ionic Catalysts and Ionic Linkers. Examples of polymer-supported ionic catalysis and ionic liquid-based linkers representing a new and potentially burgeoning family of reagents for high-throughput synthesis were described in 2004. Ionic liquids are recognized as alternative reaction media for conducting a variety of chemical transformations. They are documented to accelerate chemical reactions; act as catalysts; and in some instances, provide cleaner reaction products with reduced byproduct formation. Nucleophilic substitution reactions with alkali-metal salts proceed with greater efficiency in ionic liquids containing imidazolium cations. Due to the difficulty in extracting polar products from such reaction media, Chi and co-workers investigated polymer-supported imidazolium salts **126a**−**c** as catalysts for this reaction class (Figure 15A).[209] The polystyrene-based ionic-liquid system **126a** was synthesized by simply heating the chloroalkyl ether resin **127** with *N*-methylimidazole **128** (neat, 90 °C, 72 h). Counterion exchange afforded resin-bound imidazolium salts **126b** and **126c**. A survey of the new resins in a representative fluorination reaction identified **126b** as the superior reagent, which could be used catalytically. Displacement of a primary mesylate with CsF in acetonitrile in the presence of **126b**

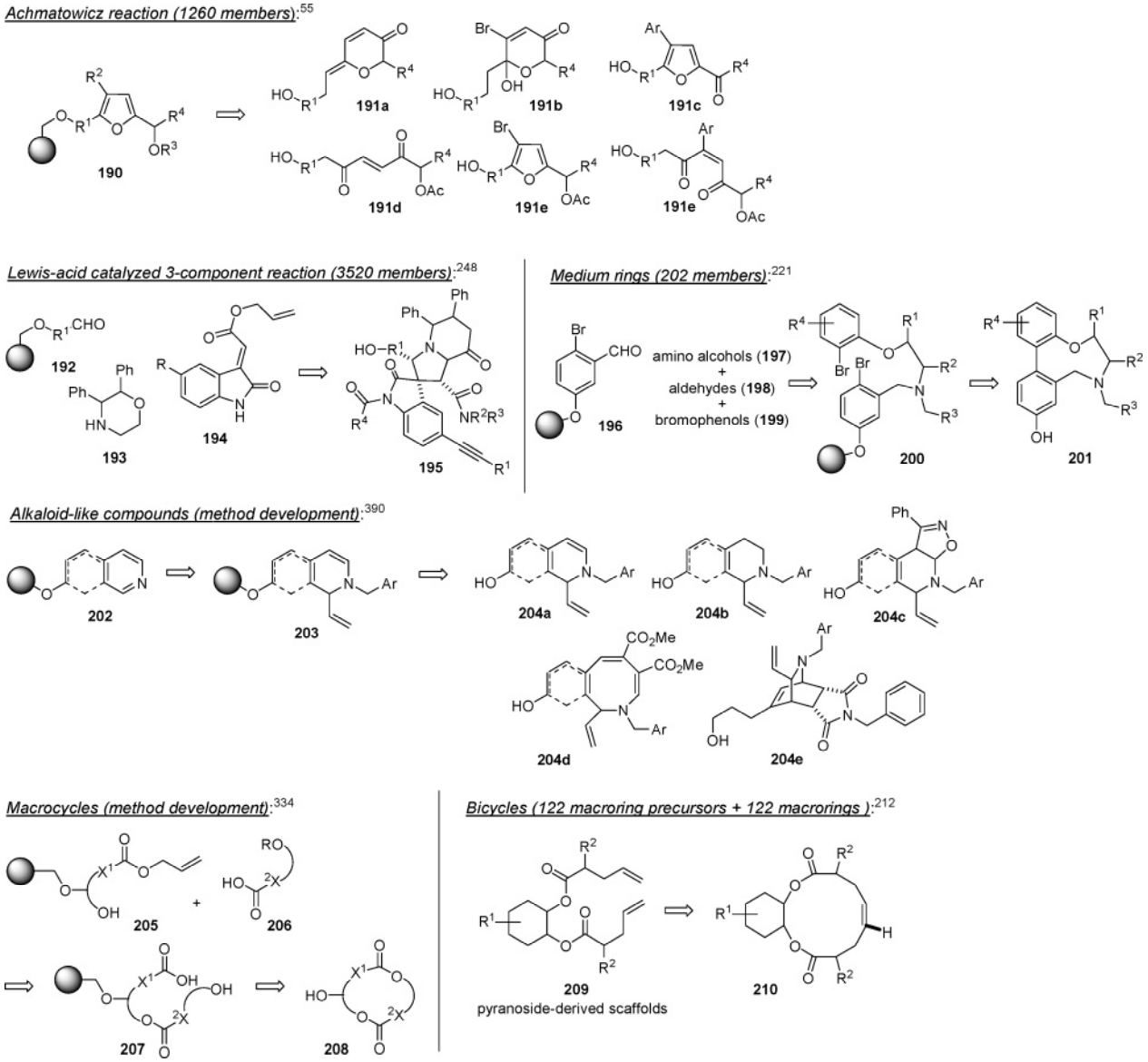


Figure 21. Schreiber's diversity-oriented synthesis (DOS) libraries.

(0.5 equiv) gave 100% conversion in 2 h at 100 °C versus <5% product formation without **126b**. Ionic resin **126b** also catalyzed the S_N2 reaction using a range of nucleophiles (**129** → **130**).

High-loading ROMPgel-supported thiazolium iodide **133** was developed by Barrett (Figure 15b).[22] This ionic ROMPgel proved to be an effective catalyst in the Stetter reaction, the umpolung condensation of aldehydes **134** with, in this case, an α,*β*-unsaturated aryl ketone **135**, to give 3-oxoketones **136**. Triethylamine was the preferred base to generate the ionic catalytic species **137**. The catalyst was recovered up to four consecutive times without compromising its activity. Some 17 condensations were reported. The yields ranged from 68% to 99%, and product purity was excellent.

Ionic liquids have extremely low vapor pressure, are stable to heat, and form a separate phase in the presence of both aqueous and organic solvents. It was this latter physical property that led de Kort and co-workers to prepare the ionic AMEBA-type linker **140** (Figure 16).[102] Microwave heating **141** with *N*-methylimidazole **128** furnished imidazolium salt **140** in quantitative yield. Linker **140** formed a homogeneous solution in the ionic liquid, [bmim][PF_6], and underwent sequential reductive amination and acylation/sulfonylation employing standard reaction conditions (**140** → **142** → **143**). Taking advantage of ionic-phase assisted extraction, excess reagents were removed after each step by washing the reaction solution with Et_2O, then water; intermediates **142**/**143** remained in the ionic liquid. Linker cleavage was carried out using 60% aqueous HPF_6 (10-min exposure). Although cleavage occurred readily with TFA, HPF_6 was the preferred acid to avoid generating mixed counterions of the ionic liquid. Amide derivatives **144** were obtained upon quenching the cleavage reaction with saturated aq $NaHCO_3$ and extraction with organic solvent. Product yields were comparable to those obtained using AMEBA resin.

Amine Synthesis. As part of a broader research effort to develop an expedient solid-phase synthesis of polyamines, Franzyk investigated the synthesis of secondary and tertiary amines via direct displacement of resin-bound halides (Figure 17).[197] Initial attempts focused on the displacement of

polystyrene *N*-trityl-linked 1-iodopropylamine with primary amines. The approach was abandoned when issues with on-resin halide formation and cross-linking during the S_N2 reaction surfaced, this despite the use of lower loading strategies. Ultimately, a protocol was worked out whereby primary and secondary amino alcohols, immobilized via a *N*-carbamate on Argopore Wang resin (**145** → **146**−**149**), were efficiently converted to iodides 150 (I_2/Ph_3P) and displaced with a variety of amines, including unprotected amino alcohols (10 equiv of a 1.0 M solution of amine in DMF, 50 °C, 6 h). Following resin cleavage, diamines **151** were isolated in good yield (50−88%) with purities >90%.

An atom economical synthesis of primary amine salts **153** from halides, tosylates and mesylates **152** was achieved by Saulnier using simple microwave irradiation of their solutions in methanolic ammonia (Figure 18).[341] The optimal substrate concentration was established as 0.04 M (0.25 mmol of substrate in 6.25 mL of 7 M ammonia in methanol) and irradiation at 100−130 °C from 0.25 to 2.5 h. Some 20 different substrates were studied, represented by **153**−**164**. The yields of the amine salts were in excess of 90%; secondary amine byproducts were typically <4%. Workup requires only solvent evaporation. Lower concentrations of ammonia led to an increase in secondary amine byproducts. In one specific example studied, substrate **165** gave 96% yield of the amine salt **166** using the microwave-assisted conditions (100 °C, 15 min) with <4% dimer **167** formation. Conducting the same reaction at room temperature resulted in complete conversion of substrate to ∼75% yield of **166** and ∼25% yield of **167**. Volatile primary amines, for example, **156** → **162**, are accessible because it is their nonvolatile salts that are isolated from the displacement reaction.

Multicomponent Condensations. The application of multicomponent condensation reactions in combinatorial library synthesis is well-known,[472] dating back to the pioneering work of Armstrong.[473] This remains a very active area of research. The 3-component condensation (3-CC) of 2-aminoazines, aldehydes, and isonitriles yields 2-substituted 3-amino-imidazoheterocyles. Such heterocyclic systems are found in biologically active compounds, including marketed drugs. Kercher and Lyon at Array Biopharma[256] found that glyoxylic acid, in solution or immobilized on macroporous polystyrene resin, MP-glyoxylate **168**, serves as a formaldehyde equivalent in this 3-CC, affording 2-*un*substituted-3-amino-imidazoheterocyles (Figure 19). In solution, the 3-CC/decarboxylation proceeds at room temperature. Using reagent **168**, the reaction is conducted at 50 °C in dichloroethane (DCE)−MeOH. A Lewis-acid catalyst is not required. The scope of the 3-CC reaction was investigated using a variety of 2-aminoazines (**173**−**177** as representative products). 2-Aminopyridines and 2-aminopyrazines were preferred inputs in terms of yield and purity of isolated reaction products.

The rate of multicomponent condensation reactions is profoundly influenced by solvent. In an elegant study of the Passerini reaction, Pirrung and Sarma[309] showed that substituting water for organic solvent resulted in a rate acceleration of 18-fold (**178** + **179** + **180** → **181**; Figure 20). Further rate enhancements were seen with LiCl and glucose as additives. The reaction in water proceeds faster at 4 °C versus 50 °C. The hydrophobic effect and cohesive energy density of water are thought to be factors contributing to rate acceleration. Similar rate enhancements were observed in the Ugi reaction (**178** + **179** + **180** + **182** → **183**). The condensation of the β-ketoacid **184**, amine **182**, and isonitrile **185** in water yielded a β-lactam **186** (72 h, 65%). This reaction does not proceed in organic solvent. A small demonstration library of Passerini products **187** ($4 \times 4 \times 4 = 32$ members) was prepared by stirring an acid (10% excess) and equimolar amounts of aldehyde and isonitrile in water for 3−6 h at 25 °C. Solid products were isolated by simple filtration, while liquid products were isolated by extraction. The average yield and purity of the library was 87%. Libraries of Ugi products **188** and β-lactams **189**[310] were similarly prepared using water as the reaction solvent.

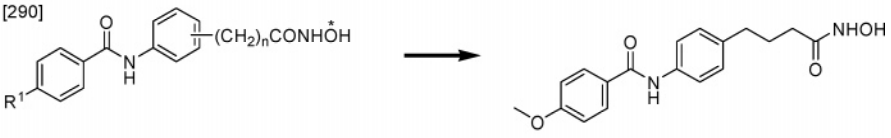
DOS Libraries. Library synthesis in Schreiber's laboratories at Harvard continues to emphasize design strategies that furnish collections of skeletally and stereochemically diverse small molecules (Figure 21). Complexity-generating reactions coupled with appending chemistries are represented by the encoded furan-derived library (**190** → **191a**−**e**),[55] based, in part, on the Achmatowicz reaction, the encoded spirooxindole library **195**,[248] utilizing a 3-component reaction, and parallel libraries of nine-membered biaryl rings **201**[221] and pyranoside-derived bicycles **210**.[112] In the library collection **191**, substrates possessing pre-encoded skeletal information, termed σ-elements,[470] were combined combinatorially under a common set of reaction conditions. All possible combinations of building block and stereochemical and skeletal diversity were efficiently assembled. This is analogous to the process of protein folding in which primary amino acid sequences ("σ-elements") are transformed into diverse 3-dimensional structures. Synthetic methodology was described for constructing libraries of alkaloid-like compounds **204a**−**e**[390] and macrocycles **208**.[334] Skeletal diversity in **204** was achieved by manipulating resin-bound reactive dihydroisoquinoline and dihydropyridine intermediates. Statistical and computational analyses were carried out to understand the relationship between structure and cell activity.[212,469] No other research group worldwide is operating at this level of sophistication with regard to library design, synthetic intricacy, and assembly. Other reports of DOS methodology and libraries include 4-oxo- and 4-chloropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones,[464] 1,2-disubstituted and 1,2,5-trisubstituted pyrroles,[158] tetrasubstituted olefins,[458,459] C1-nitrogen iminocyclitols,[244] azaspirocycles,[421] polysubstituted spirotriones,[460] sulfotransferase inhibitors,[34] and tetrahydro-1,2-oxazines.[433]

Acknowledgment. The author is indeed indebted to the continued support and dedication of Karen Rivera who rendered the extensive chemical structure drawing of structures found in the tables. Appreciation is expressed to Paul Tuthill who assisted in organizing and editing portions of this year's manuscript.

Table 1. Chemical Libraries Targeting Proteases[a]

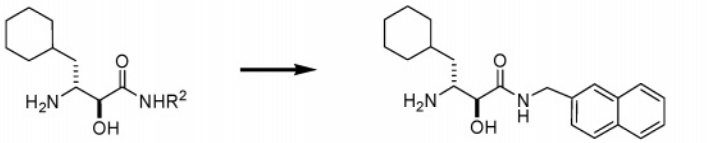
Metallo-proteases

Library: 1.1
Name: Hydroxamic acid
Size: 10 members
Reference: Ockey, D. A.; *et al.* [290]



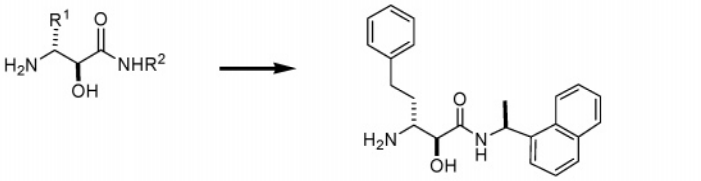
Enzyme: Stromelysin
Activity: IC_{50} = 200 μM

Library: 1.2
Name: 3-Amino-2-hydroxyamide
Size: >500 members
Reference: Sheppard, G. S.; *et al.* [361]



Enzyme: Methionine aminopeptidase-2
Activity: IC_{50} = 160 nM

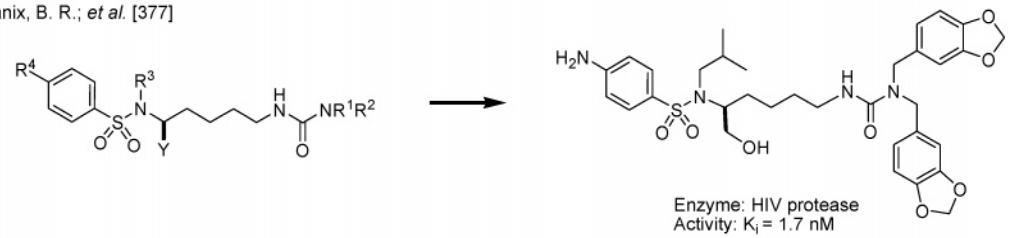
Library: 1.3
Name: 3-Amino-2-hydroxyamide
Size: *ca.* 90 members
Reference: Sheppard, G. S.; *et al.* [361]
Note: Follow-up to Library 1.2



Enzyme: Methionine aminopeptidase-2
Activity: IC_{50} = 20 nM

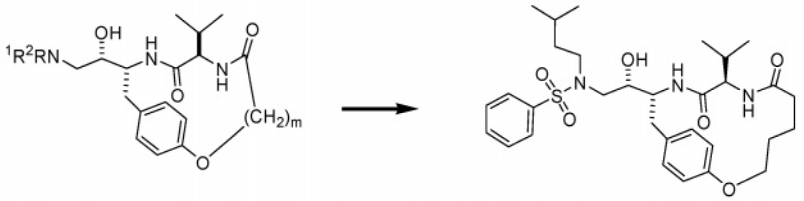
Aspartyl proteases

Library: 1.4
Name: Sulfonamide
Size: Not defined
Reference: Stranix, B. R.; *et al.* [377]



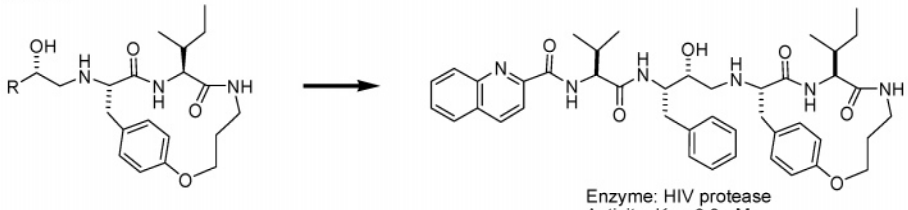
Enzyme: HIV protease
Activity: K_i = 1.7 nM

Library: 1.5
Name: Cyclopeptide mimetic
Size: Not defined
Reference: Reid, R. C.; *et al.* [322]



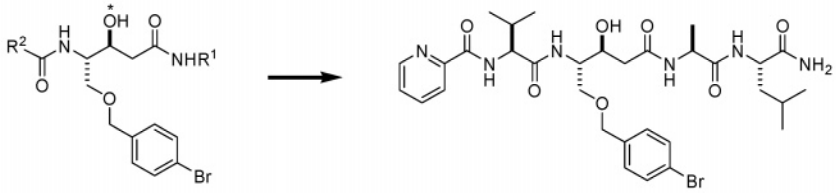
Library: 1.6
Name: Cyclopeptide mimetic
Size: Not defined
Reference: Reid, R. C.; *et al.* [322]

Enzyme: HIV protease
Activity: K_i = 4 nM



Enzyme: HIV protease
Activity: K_i = 0.3 nM

Library: 1.7
Name: Statine
Size: *ca.* 40 members
Reference: Johansson, P.-O.; *et al.* [194]
Note: Series of small libraries optimizing R^1 and R^2.

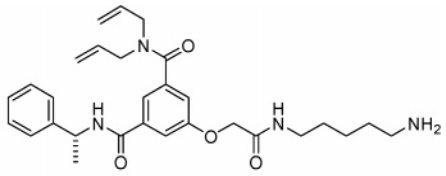


Enzyme: Plasmepsin I and II (*Plasmodium falciparum*)
Activity: K_i = 0.5 nM, Plm I; K_i = 2.2 nM, Plm II

Table 1. (Continued)

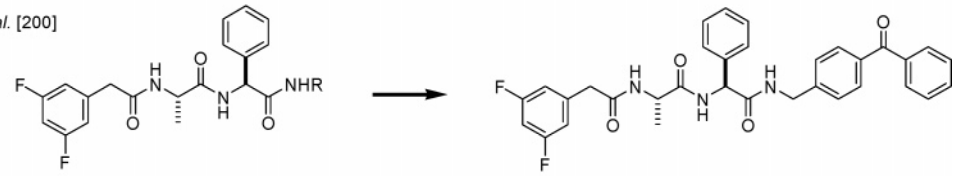
Library: 1.8
Name: (composition unknown)
Size: Multimillion members
Reference: Coburn, C. A.; *et al.* [89]
Note: NeoGenesis's affinity selection-mass spectrometry method for the identification of small molecule ligands from self-encoded combinatorial libraries.

Library composition not defined



Enzyme: β-Secretase (BACE-1)
Activity: IC_{50} = 25 μM

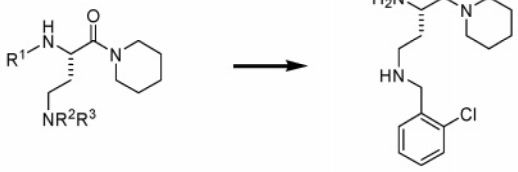
Library: 1.9
Name: DAPT analog
Size: 15 members
Reference: Kan, T.; *et al.* [200]



Enzyme: γ-Secretase
Activity: IC_{50} = *ca.* 2 nM

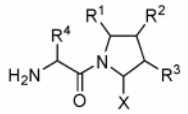
Serine proteases

Library: 1.10
Name: 2,4-diaminobutanoyl-piperidine
Size: 22 members
Reference: Senten; K.; *et al.* [350]

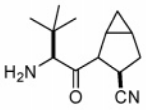


Enzyme: Dipeptidyl peptidase II
Activity: IC_{50} = 0.23 μM

Library: 1.11
Name: Methanoproline
Size: Not defined
Reference: Magnin, D. R.; *et al.* [261]

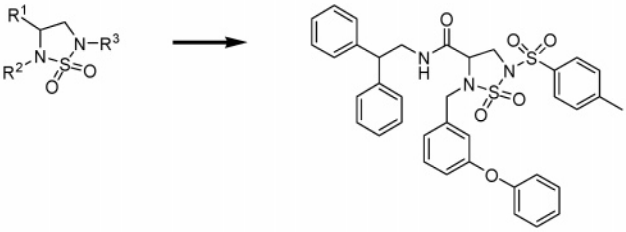


((R^1 + R^2) or (R^2 + R^3) taken together to form cyclopropyl)



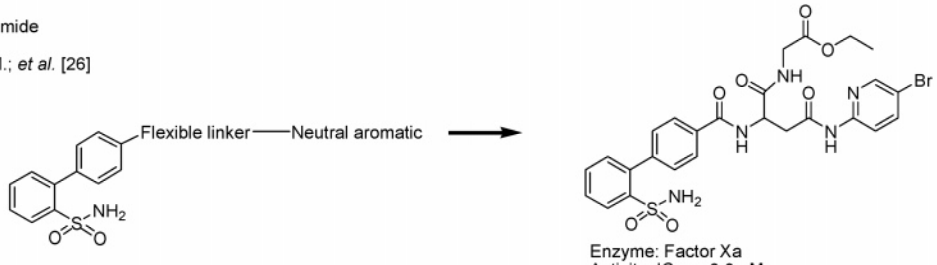
Enzyme: Dipeptidyl peptidase IV
Activity: K_i = 7 nM

Library: 1.12
Name: Cyclosulfonamide
Size: *ca.*19 members
Reference: Zhong, J.; *et al.* [450]



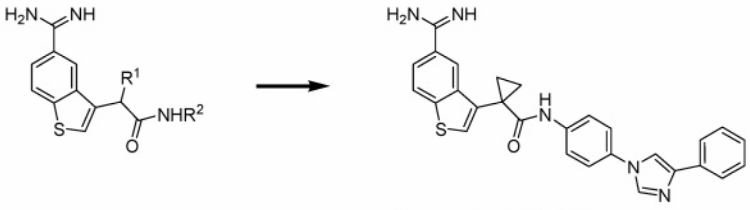
Enzyme: Elastase (human leukocyte)
Activity: K_i = 18 μM

Library: 1.13
Name: Biphenylsulfonamide
Size: Not defined
Reference: Bauer, S. M.; *et al.* [26]



Enzyme: Factor Xa
Activity: IC_{50} = 3.3 nM

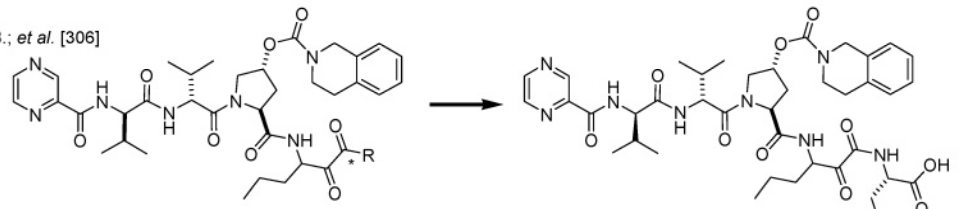
Library: 1.14
Name: Amidinobenzothiophens
Size: Not defined
Reference: Qiao, J. X.; *et al.* [316]



Enzyme: Factor Xa (fXa)
Activity: K_i = 22 nM, fXa; K_i = 4900 nM, fIXa

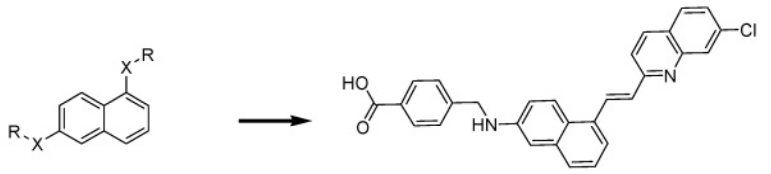
Table 1. (Continued)

Library: 1.15
Name: α-Ketoamide
Size: Not Defined
Reference: Perni, R. B.; *et al.* [306]



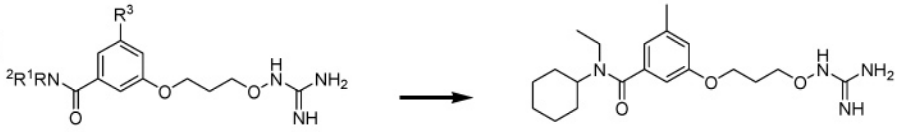
Enzyme: HCV N53-4A protease
Activity: K_i = 30 nM

Library: 1.16
Name: Naphthalene derivatives
Size: Not defined
Reference: Gopalsamy, A.; *et al.* [145]



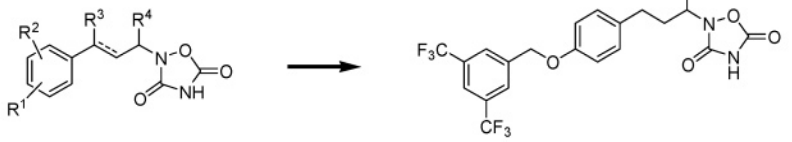
Enzyme: Human cytomegalovirus (HCMV) protease
Activity: IC_{50} = 2.7 μM

Library: 1.17
Name: Oxyguanidine
Size: >50 members
Reference: Lu, T.; *et al.* [253]



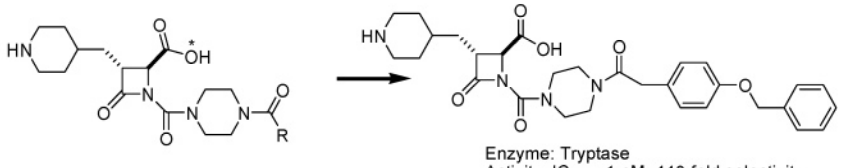
Enzyme: Thrombin
Activity: K_i = 6 nM

Library: 1.18
Name: Oxadiazolidine
Size: Not defined
Reference: Gopalsamy, A.; *et al.* [144]



Enzyme: Tissue plasminogen activator
Activity: IC_{50} = 0.39 μM

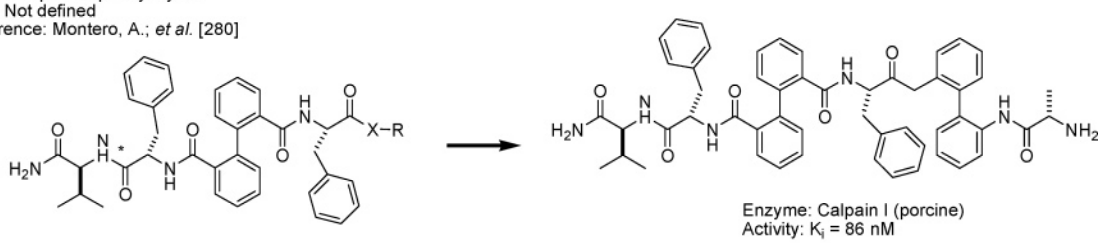
Library: 1.19
Name: Azetidinone
Size: *ca.* 42 members
Reference: Sutton, J. C.; *et al.* [382]



Enzyme: Tryptase
Activity: IC_{50} = 1 nM; 440-fold selectivity versus trypsin

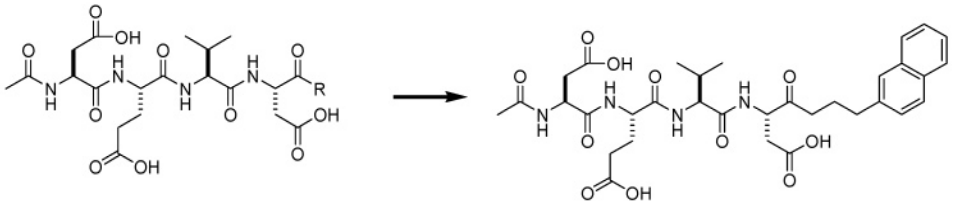
Cysteine proteases

Library: 1.20
Name: Peptide-biphenyl hybrid
Size: Not defined
Reference: Montero, A.; *et al.* [280]



Enzyme: Calpain I (porcine)
Activity: K_i = 86 nM

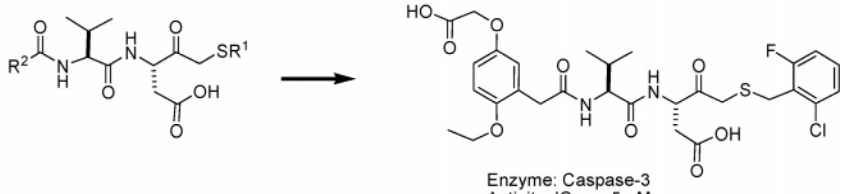
Library: 1.21
Name: α-Ketoamide
Size: Not Defined
Reference: Grimm, E. L.; *et al.* [150]



Enzyme: Caspase-3
Activity: IC_{50} = 0.1 nM

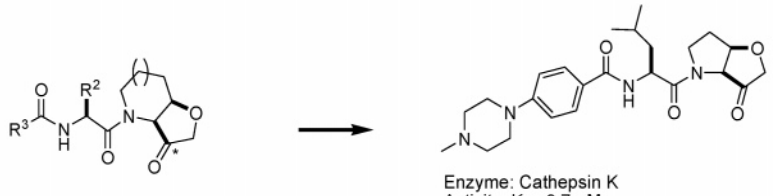
Table 1. (Continued)

Library: 1.22
Name: Dipeptidyl ketone
Size: 100 members
Reference: Han, Y.; *et al.* [157]
Note: Prepared by split-pool protocol using IRORI Macro Kan



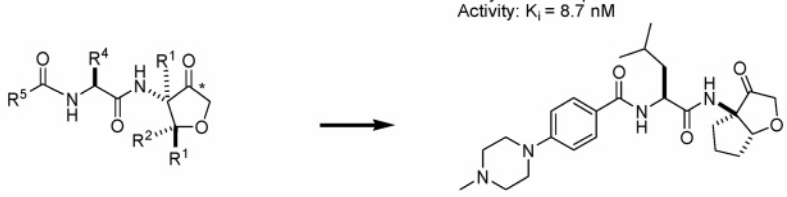
Enzyme: Caspase-3
Activity: IC_{50} = 5 nM

Library: 1.23
Name: Bicyclic ketone
Size: *ca.* 13 members
Reference: Quibell, M.; *et al.* [319]



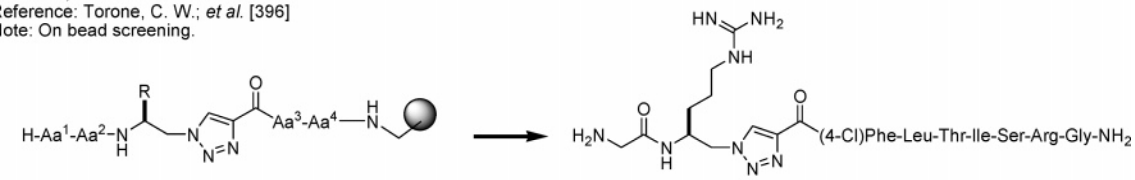
Enzyme: Cathepsin K
Activity: K_i = 8.7 nM

Library: 1.24
Name: Aminotetrahydrofuranone
Size: Not defined
Reference: Watts, J.; *et al.* [416]



Enzyme: Cathepsin K
Activity: K_i = 1.8 μM

Library: 1.25
Name: Peptidotriazole
Size: 400,000 members
Reference: Torone, C. W.; *et al.* [396]
Note: On bead screening.



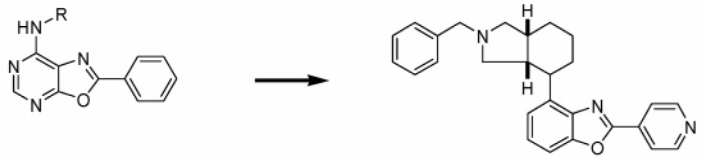
Enzyme: *L. mexicana* CPB2.8ΔCTE, cysteine protease
Activity: K_i = 76 nM

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

Table 2. Chemical Libraries Targeting Nonproteolytic Enzymes[a]

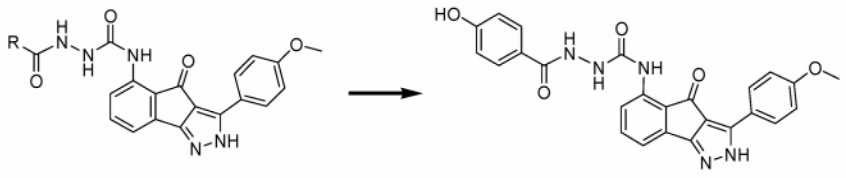
Kinases

Library: 2.1
Name: Oxazolo-pyrimidine
Size: 100 members
Reference: Bauser, M.; *et al.* [27]



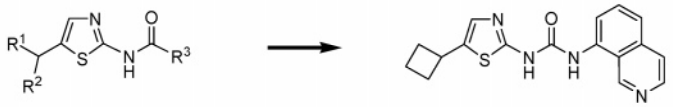
Enzyme: Adenosine kinase
Activity: IC_{50} = 1 nM

Library: 2.2
Name: Acylsemicarbazide
Size: 84 members
Reference: Nugiel, D. A.; *et al.* [289]



Enzyme: cdk2/E and cdk4/DI
Activity: IC_{50} = 9 nM, cdk2; IC_{50} = 5 nM, cdk4

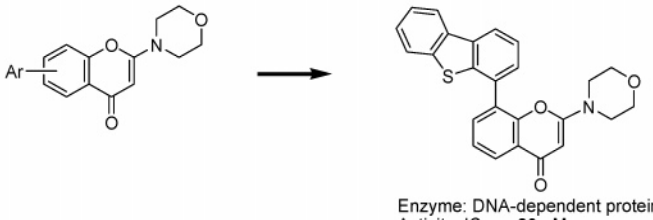
Library: 2.3
Name: Thiazole
Size: Not defined
Reference: Helal, C. J.; *et al.* [164]



Enzyme: Cyclin-dependent kinase 5/p25 (cdk5)
Activity: IC_{50} = 5 nM

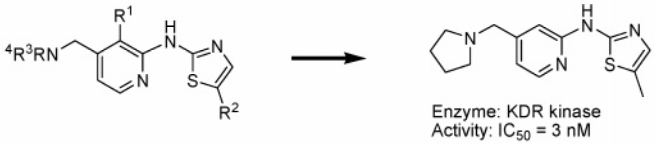
Table 2. (Continued)

Library: 2.4
Name: Chromenone
Size: 152 members
Reference: Leahy, J. J. J.; *et al.* [229]



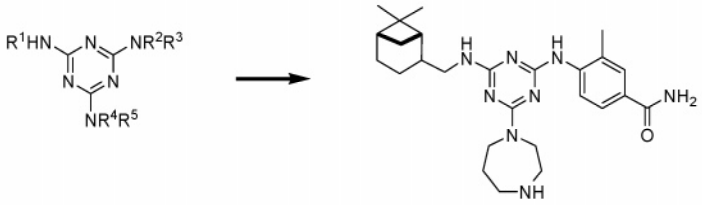
Enzyme: DNA-dependent protein kinase
Activity: IC_{50} = 20 nM

Library: 2.5
Name: (Thiazol-2-yl)aminopyridine
Size: 40 members
Reference: Bilodeau, M. T.; *et al.* [36]



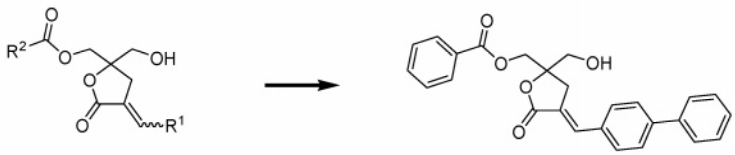
Enzyme: KDR kinase
Activity: IC_{50} = 3 nM

Library: 2.6
Name: Triazine
Size: Not defined
Reference: Leftheris, K.; *et al.* [461]
Note: Hit came from screening Pharmacopeia's ECLiPS compound collection which may have included this generic motif.



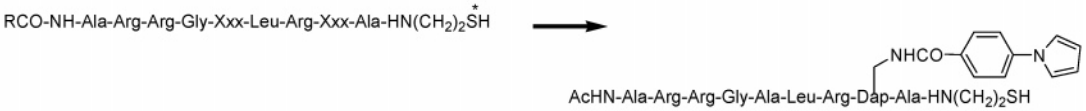
Enzyme: p38 MAP Kinase
Activity: IC_{50} = 1.4 μM

Library: 2.7
Name: Diaylglycerol lactone
Size: 9 members
Reference: Duan, D.; *et al.* [115]



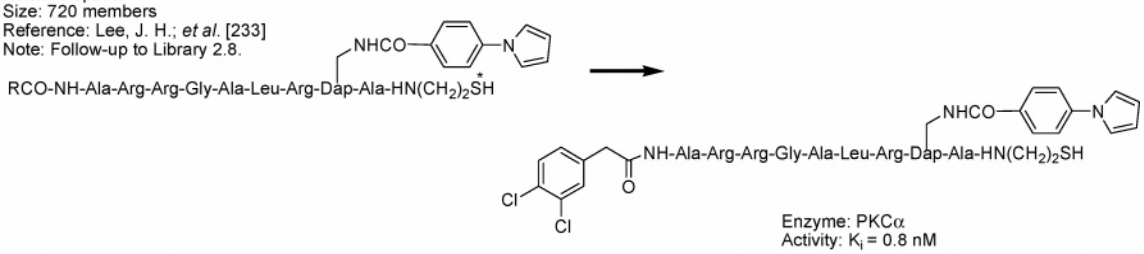
Enzyme: Protein kinase Cα (PKCα)
Activity: K_i = 14 nM

Library: 2.8
Name: Peptide
Size: 3 x 720 members
Reference: Lee, J. H.; *et al.* [233]



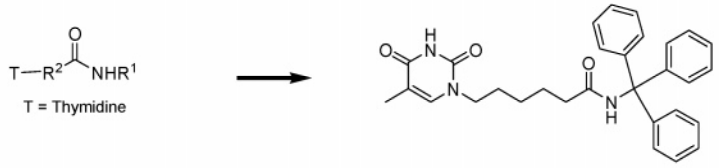
Enzyme: PKCα
Activity: K_i = 550 nM

Library: 2.9
Name: Peptide
Size: 720 members
Reference: Lee, J. H.; *et al.* [233]
Note: Follow-up to Library 2.8.



Enzyme: PKCα
Activity: K_i = 0.8 nM

Library: 2.10
Name: Thymidine carboxyamide
Size: *ca.* 15 members
Reference: Priego, E.-M.; *et al.* [314]

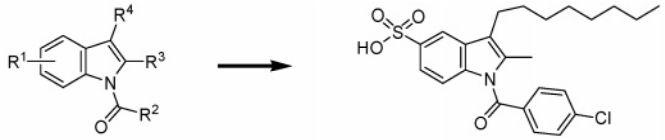


T = Thymidine

Enzyme: Thymidine kinase-2
Activity: IC_{50} = 19 μM

Table 2. (Continued)

Library: 2.11
Name: Indomethacin
Size: 197 members
Reference: Rosenbaum, C.; *et al.* [330]

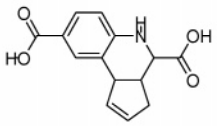


Enzyme: VEGFR-2 tyrosine kinase
Activity: IC_{50} = 9 μM

Phosphatases

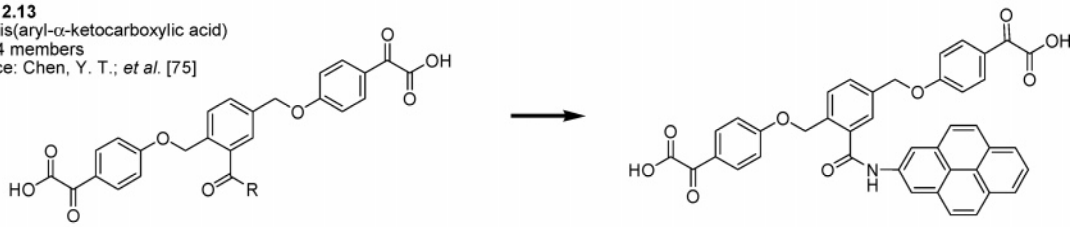
Library: 2.12
Name: Not defined
Size: 10,000 members
Reference: Brisson, M.; *et al.* [50]
Note: Commercial collection obtained from Chembridge, Inc.

Commercial library



Enzyme: Cdc25A phosphatase
Activity: IC_{50} = 2.5 μM

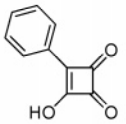
Library: 2.13
Name: Bis(aryl-α-ketocarboxylic acid)
Size: 104 members
Reference: Chen, Y. T.; *et al.* [75]



Enzyme: Protein tyrosine phosphatase (PTP-1b)
Activity: IC_{50} = 150 nM

Library: 2.14
Name: Transition state mimetic
Size: 19 members
Reference: Ockey, D. A.; *et al.* [291]
Note: Mostly aryls displaying a functional group interacting with the enzyme's active site cysteine.

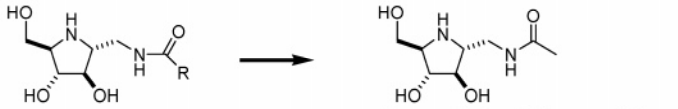
R-X
(X = CHO, COR, CN, $B(OH)_2$, halogen)



Enzyme: PTP-1b
Activity: IC_{50} = 60 μM

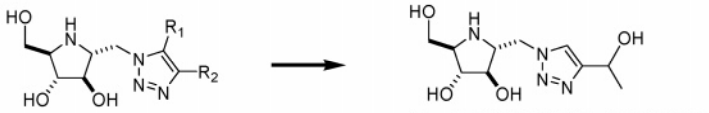
Alphabetical listing

Library: 2.15
Name: Iminocyclitol
Size: 23 members
Reference: Liu, J.; *et al.* [244]



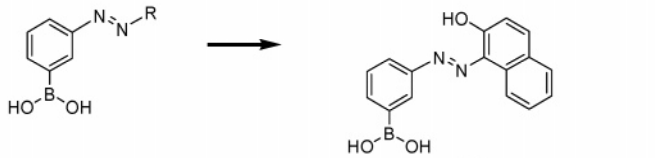
Enzyme: *N*-Acetyl-β-hexosaminidase
Activity: 92% inhibition at 25 μM

Library: 2.16
Name: Iminocyclitol
Size: 97 members
Reference: Liu, J.; *et al.* [244]
Note: Companion library to library 2.15.



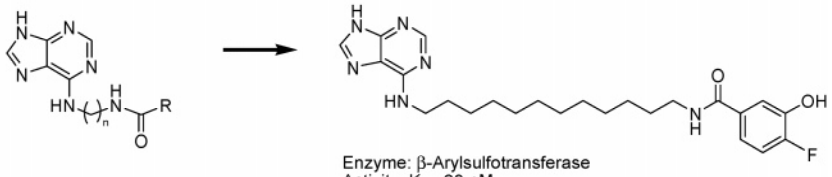
Enzyme: *N*-Acetyl-β-hexosaminidase
Activity: 26% inhibition at 25 μM

Library: 2.17
Name: Boronic acid
Size: *ca.* 12 members
Reference: Buzzoni, V.; *et al.* [57]



Enzyme: AmpC-β-lactamase (*E. coli*)
Activity: K_i = 0.3 μM

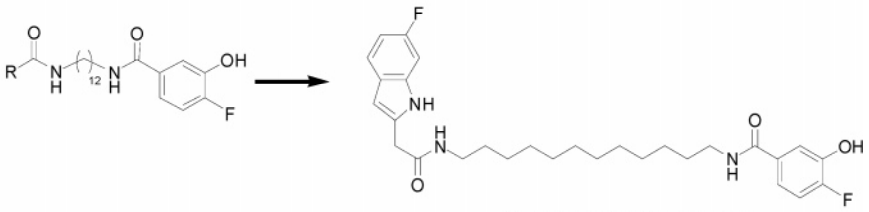
Library: 2.18
Name: Purine
Size: 80 members
Reference: Best, M. D.; *et al.* [34]



Enzyme: β-Arylsulfotransferase
Activity: K_i = 28 nM

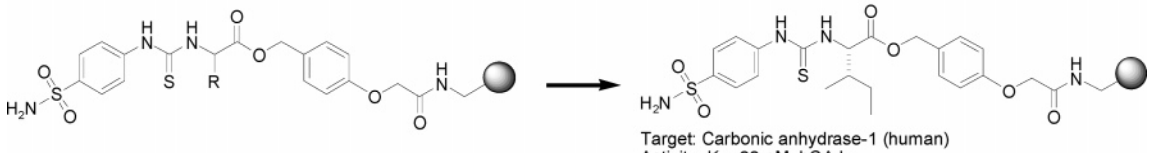
Table 2. (Continued)

Library: 2.19
Name: Substituted benzamide
Size: *ca.* 46 members
Reference: Best, M. D.; *et al.* [34]
Note: Follow-up to library 2.18.



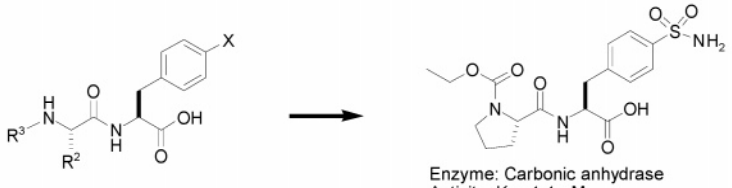
Enzyme: β-Arylsulfotransferase
Activity: K_i = 5 nM

Library: 2.20
Name: 4-Sulfamoylphenylthioureas
Size: 10 members
Reference: Innocenti, A.; *et al.* [181]
Note: On-bead screening.



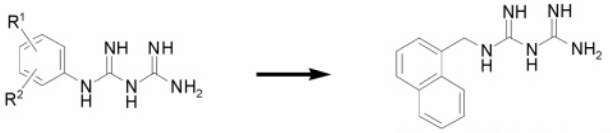
Target: Carbonic anhydrase-1 (human)
Activity: K_i = 22 nM, hCA I;
K_i = 4 nM, hCA II

Library: 2.21
Name: Dipeptide
Size: 8 members
Reference: Corbett, A. D.; *et al.* [93]
Note: Pseudodynamic combinatorial library combining irreversible library synthesis with an irreversible destruction step.



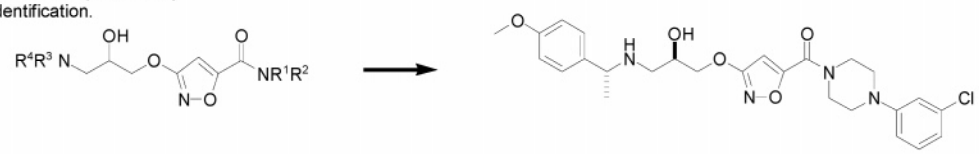
Enzyme: Carbonic anhydrase
Activity: K_i = 1.1 μM

Library: 2.22
Name: Biguanide
Size: 60 members
Reference: Mayer, S.; *et al.* [270]



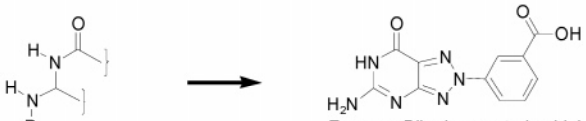
Enzyme: Dihydrofolate reductase (*E. coli*)
Activity: 45% inhibition @ 100 μM

Library: 2.23
Name: β-Aminoalcohol
Size: 512 members
Reference: Annis, D. A.; et al. [9]
Note: Affinity selection-mass spectrometry method for ligand identification.



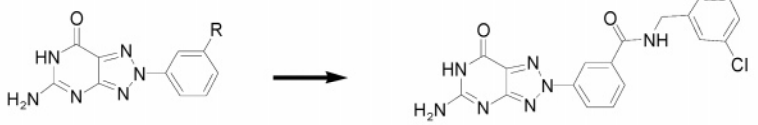
Enzyme: Dihydrofolate reductase (*E. coli*)
Activity:K_d = 15 μM

Library: 2.24
Name: 3-Point H-Bond motif
Size: ca. 1000 members
Reference: Sanders, W. J.; *et al.* [340]
Note: CrystaLEAD X-ray crystallographic high-throughput screening of 10,000 member random library identified the 3-point H-bond motif as the pharmacophore.



Enzyme: Dihydroneopterin aldolase
Activity: IC_{50} = 1.5 μM

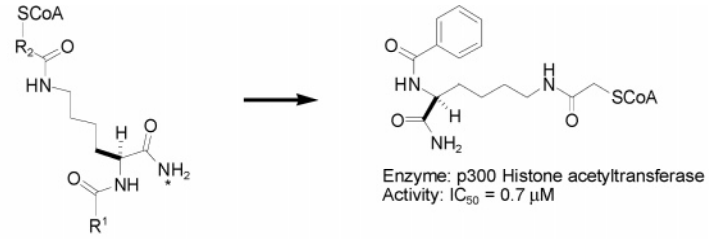
Library: 2.25
Name: Triazolopyrimidine
Size: Not defined
Reference: Sanders, W. J.; *et al.* [340]
Note: Follow-up to Library 2.24.



Enzyme: Dihydroneopterin aldolase
Activity: IC_{50} = 68 nM

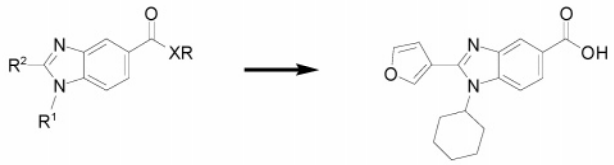
Table 2. (Continued)

Library: 2.26
Name: Lysine-CoA bisubstrate
Size: *ca.* 12 members
Reference: Sagar, V.; *et al.* [337]



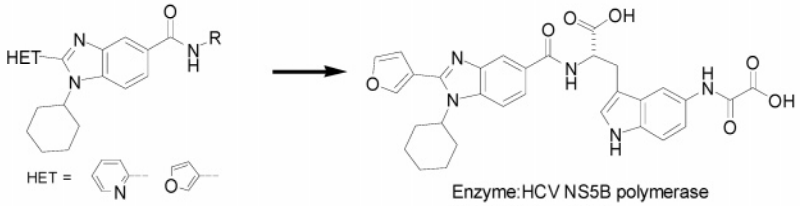
Enzyme: p300 Histone acetyltransferase
Activity: IC_{50} = 0.7 μM

Library: 2.27
Name: Benzimidazole
Size: Not defined
Reference: Beaulieu, P. L.; *et al.* [29]
Note: Multiple libraries produced by solution and solid phase methods.



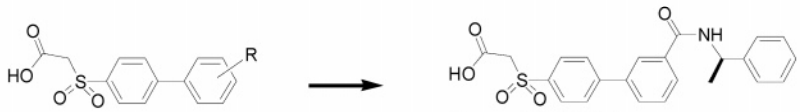
Enzyme: HCV NS5B polymerase
Activity: IC_{50} = 1.6 μM

Library: 2.28
Name: Benzamidazoles
Size: Not defined
Reference: Beaulieu, P. L.; *et al.* [30]



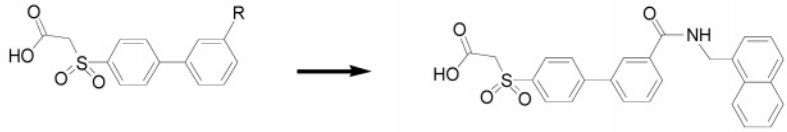
Enzyme:HCV NS5B polymerase
Activity: IC_{50} = 8 nM

Library: 2.29
Name: Biarylsulfone amide
Size: 100 members
Reference: Faucher, A.-M.; *et al.* [124]



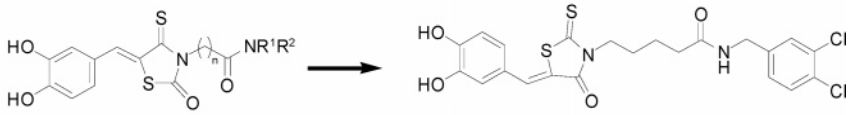
Enzyme: HPV E1 helicase
Activity: IC_{50} = 43 nM

Library: 2.30
Name: Biarylsulfonamide
Size: 150 members
Reference: Faucher, A.-M.; *et al.* [124]
Note: Follow-up to library 2.29.



Enzyme: HPV E1 helicase
Activity: IC_{50} = 4.3 nM

Library: 2.31
Name: Catechol
Size: 300 members
Reference: Sem, D. S.; *et al.* [349]

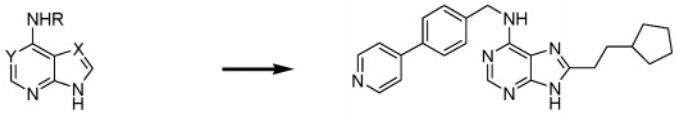


Enzyme: Lactate dehydrogenase
Activity: K_{is} = 42 nM

Library: 2.32
Name: Swainsonine analog
Size: 10 members
Reference: Fujita, T.,; *et al.* [455]

Enzyme: α-Mannosidase
Activity: IC_{50} = 0.25 μM

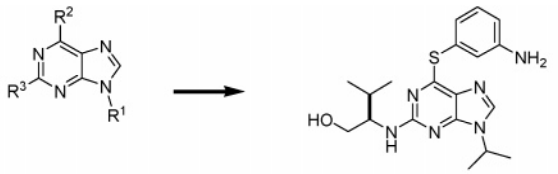
Library: 2.33
Name: Purine analog
Size: Not defined
Reference: Tedder, E. T.; *et al.* [391]
Note: Multiple libraries using chloro-heterocycles as templates.



Enzyme: MTA nucleosidase
Activity: K_i = 2.8 nM

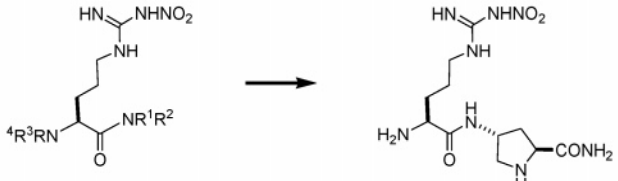
Table 2. (Continued)

Library: 2.34
Name: Purine
Size: 1561 members
Reference: Wignall, S. M.; *et al.* [420]
Note: Library composed of 128 purified compounds and 1433 compounds from a combinatorial library.



Enzyme: NQO1 (NADP- dependent oxidoreductase)
Activity: K_i = 1.7 μM

Library: 2.35
Name: Nitroarginine dipeptide
Size: 40 members
Reference: Gomez-Vidal, J. A.; *et al.* [143]

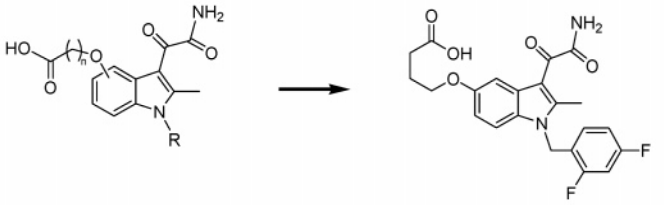


Enzyme: Neuronal nitric oxide synthase (nNOS)
Activity: K_i = 100 nM; >200-fold selective versus iNOS and eNOS

Library: 2.36
Name: Peptide chelator
Size: 1584 members
Reference: Chen, D.; *et al.* [70]
Note: Three libraries of 528 members each defined by X, a metal chelating group.

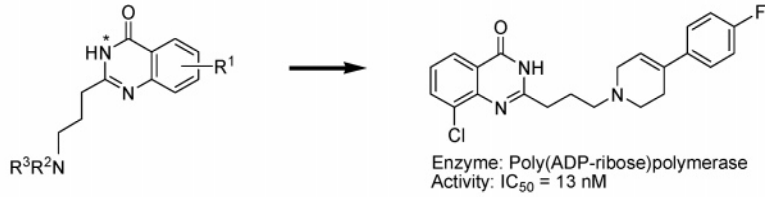
Enzyme: Peptide deformylase (*E. coli* Ni^{+2} enzyme)
Activity: K_i = 0.24 nM

Library: 2.37
Name: Me-Indoxam
Size: *ca.* 48 members
Reference: Smart, B. P.; *et al.* [368]



Enzyme: Phospholipase A_2 (hGX)
Activity: IC_{50} = *ca.* 1 μM

Library: 2.38
Name: Quinazolidone
Size: Not defined
Reference: Hattori, K.; *et al.* [159]



Enzyme: Poly(ADP-ribose)polymerase
Activity: IC_{50} = 13 nM

Library: 2.39
Name: Koji acid tripeptide
Size: 30 members
Reference: Kim, H.; *et al.* [210]

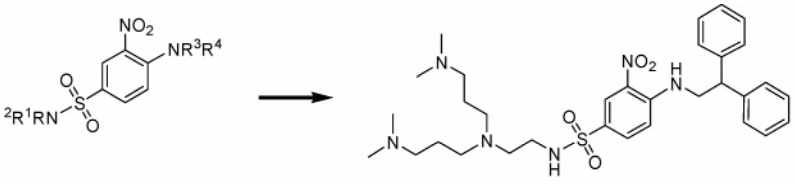
Enzyme: Tyrosinase
Activity: IC_{50} = 0.24 μM

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

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

Alphabetical listing

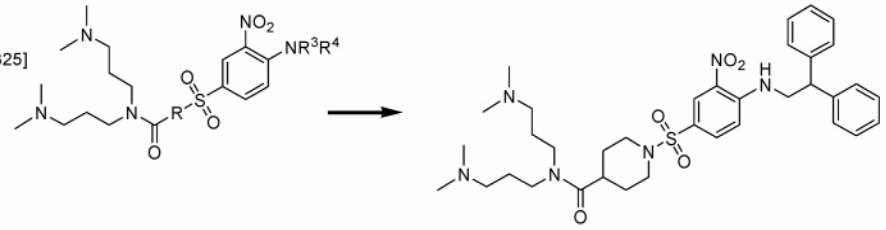
Library: 3.1
Name: Sulfamoylbenzamide
Size: 71 members
Reference: Ritchie, T. J.; *et al.* [325]



Receptor: Bradykinin-1 (BK-1)
Activity: K_i = 239 nM

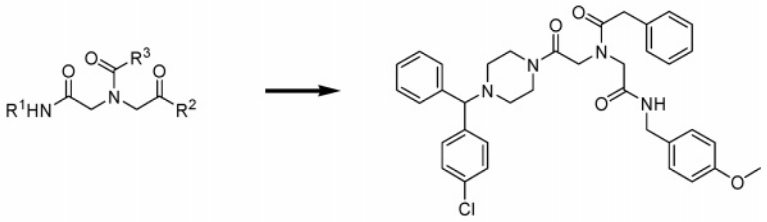
Table 3. (Continued)

Library: 3.2
Name: Sulfamoylbenzamide
Size: Not defined
Reference: Ritchie, T. J.; *et al*. [325]
Note: Follow-up to library 3.1.



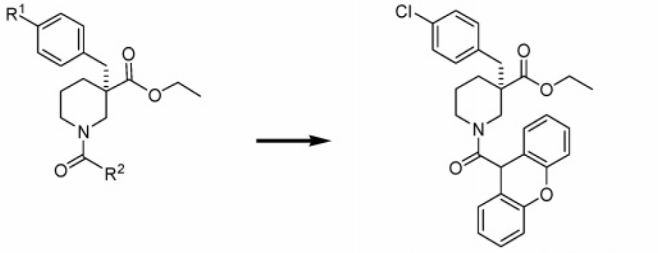
Receptor: BK-1
Activity: K_i = 18 nM

Library: 3.3
Name: Triamide
Size: 50 members
Reference: Kam, Y. L.; *et al*. [196]



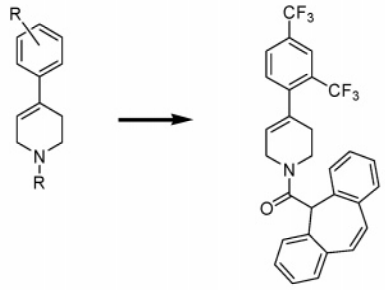
Receptor: Bradykinin-2 (BK-2; guinea pig)
Activity: IC_{50} = *ca*. 100 nM

Library: 3.4
Name: Substituted piperidine
Size: 83 members
Reference: Rogers-Evans, M.; *et al*. [329]



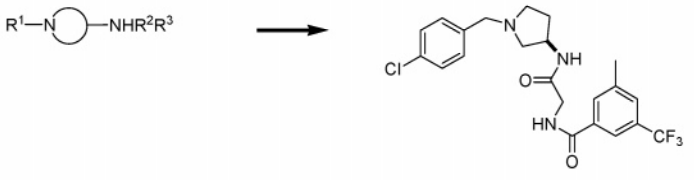
Receptor: Cannabinoid-1 (CB-1)
Activity: K_i = 2.0 μM

Library: 3.5
Name: 4-Aryltetrahydropyridine
Size: 83 members
Reference: Rogers-Evans, M.; *et al*. [329]



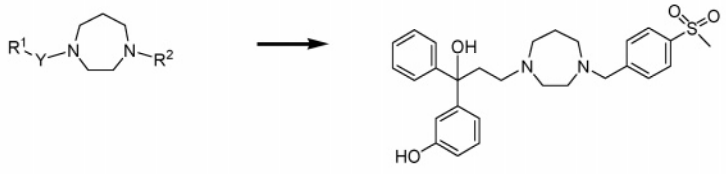
Receptor: CB-1
Activity: K_i = 0.3 μM

Library: 3.6
Name: Diamine
Size: Not defined
Reference: Moree, W. J.; *et al*. [281]



Receptor: Chemotactic cytokine-2b (CCR-2b)
Activity: IC_{50} = 180 nM; EC_{50} = 24 nM
(chemotaxis to MCP-1)

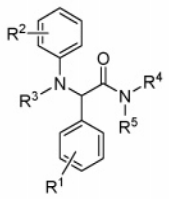
Library: 3.7
Name: Homopiperazine
Size: Not defined
Reference: Imai, M.; *et al*. [180]

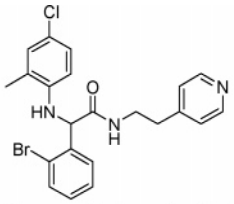


Receptor: CCR-2b
Activity: IC_{50} = 0.71 μM

Table 3. (Continued)

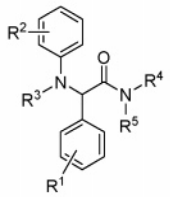
Library: 3.8
Name: N-phenylphenylglycine
Size: 174 members
Reference: Molteni, V.; *et al.* [278]

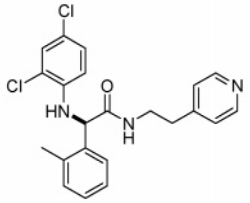




Receptor: Corticotropin releasing factor (CRF)
Activity: K_i = 1 μM (antagonist)

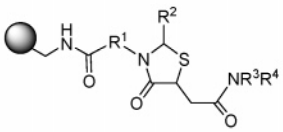
Library: 3.9
Name: N-phenylphenylglycine
Size: Not defined
Reference: Molteni, V.; *et al.* [278]
Note: Series of follow-up libraries to library 3.8.

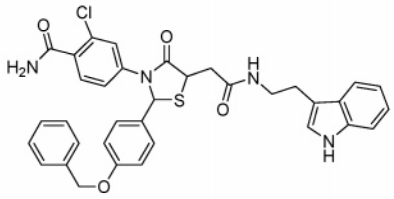




Receptor: CRF
Activity: K_i = 154 nM (antagonist)

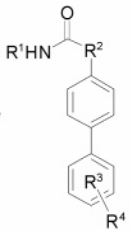
Library: 3.10
Name: Thiazolidinone
Size: 42,875 members
Reference: Maclean, D.; *et al.* [258]
Note: Encoded library of 35 pools of 1225 members each.

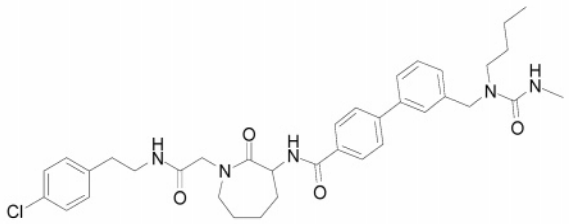




Receptor: Follicle stimulating hormone (FSH)
Activity: EC_{50} = 32 nM (agonist)

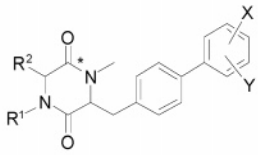
Library: 3.11
Name: Biaryl
Size: 31,372 members
Reference: Guo, T.; *et al.* [153]
Note: Encoded (ECLiPS™) library containing 17 sublibraries of 341 compounds and 25 sublibraries of 1023 compounds each.

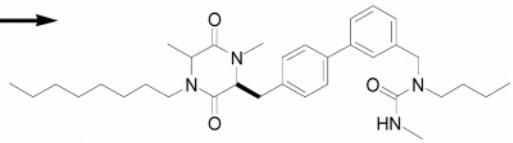




Receptor: Follicle stimulation factor (FSH)
Activity: EC_{50} = 0.26 μM

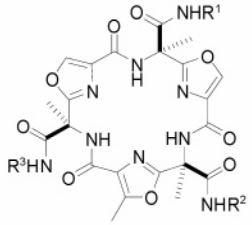
Library: 3.12
Name: Biaryl
Size: 300 members
Reference: Guo, T.; *et al.* [154]
Note: Comprised of three parallel library collections.

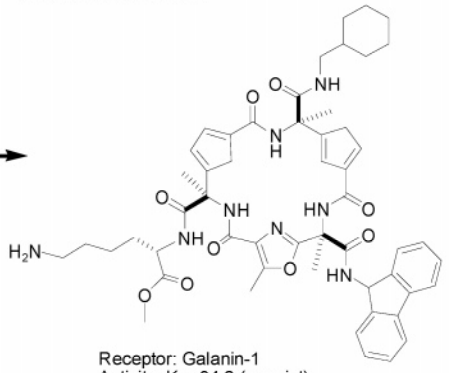




Receptor: FSH
Activity: EC_{50} = 1.2 nM (CHO-hFSH-luciferase assay)

Library: 3.13
Name: Cyclic tripeptidomimetic
Size: Not defined
Reference: Ceide, S. C.; *et al.* [67]

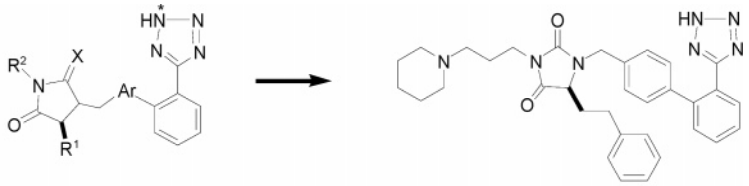




Receptor: Galanin-1
Activity: K_i = 34.2 (agonist)

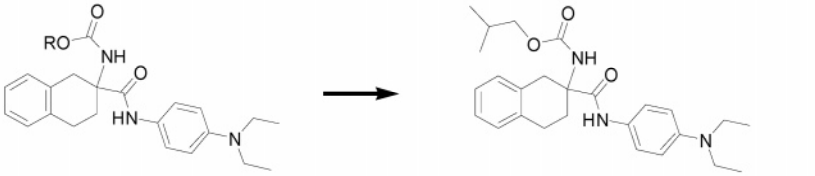
Table 3. (Continued)

Library: 3.14
Name: Biaryl
Size: Not defined
Reference: Severinsen, R.; *et al.* [352]



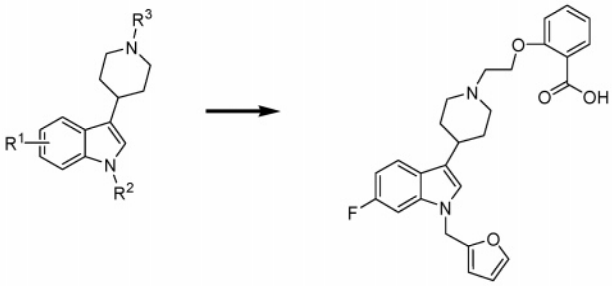
Receptor: Growth hormone secretagogue
Activity: IC_{50} = 0.6 μM

Library: 3.15
Name: Tetralin
Size: Not defined
Reference: Zhao, H.; *et al.* [448]



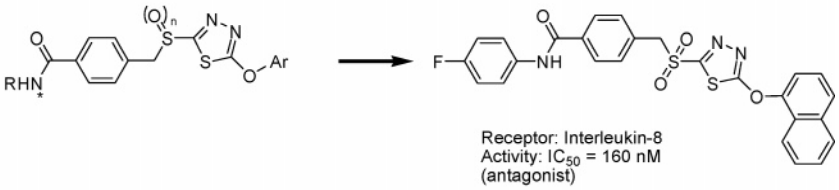
Receptor: Growth hormone secretagogue
Activity: IC_{50} = 11 nM

Library: 3.16
Name: Indolylpiperidine
Size: Not defined
Reference: Fonquerna, S.; *et al.* [127]



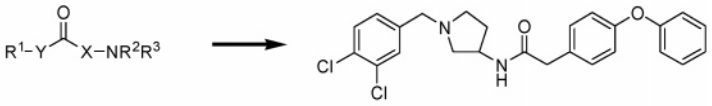
Receptor: Histamine H_1
Activity: IC_{50} = 37 nM

Library: 3.17
Name: Thiadiazole ether
Size: >100 members
Reference: Pernerstorfer, J.; *et al.* [305]
Note: IRORI Mini Kan technology.



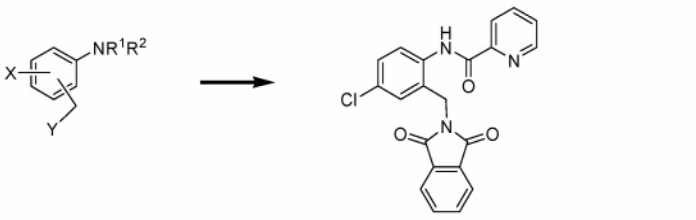
Receptor: Interleukin-8
Activity: IC_{50} = 160 nM
(antagonist)

Library: 3.18
Name: Amine
Size: 2025 members
Reference: Lavrador, K.; *et al.* [227]
Note: Seven unique amine-containing scaffolds were derivatized so that each compound contained a basic nitrogen atom.



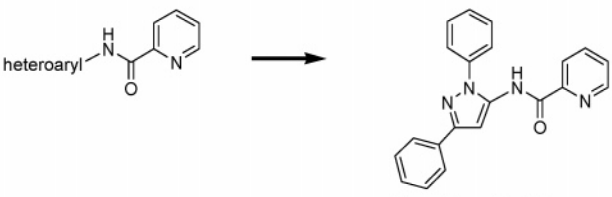
Receptor: Melanin concentrating hormone-1 (MCH-1)
Activity: K_i = 0.51 μM

Library: 3.19
Name: Substituted aryl
Size: *ca.* 1000 members
Reference: Lindsley, C. W.; *et al.* [243]



Receptor: Metabotropic glutamate receptor subtype 5 (mGluR5)
Activity: EC_{50} = 300 nM; ~7 fold potentiation

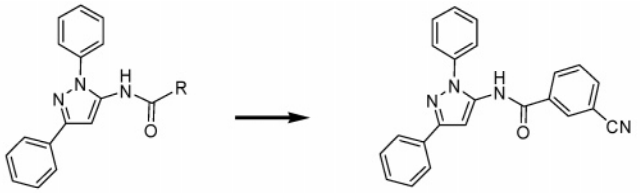
Library: 3.20
Name: Picolinoyl amide
Size: Not defined
Reference: Lindsley, C. W.; *et al.* [243]
Note: Follow-up to library 3.19.



Receptor: mGluR5
Activity: EC_{50} = 290 nM; ~3 fold potentiation

Table 3. (Continued)

Library: 3.21
Name: Pyrazole amide
Size: 144 members
Reference: Lindsley, C. W.; *et al.* [243]
Note: Three libraries of 48 members each. Follow-up to library 3.20.



Receptor: mGluR5
Activity: EC_{50} = 10 nM; ~4 fold potentiation

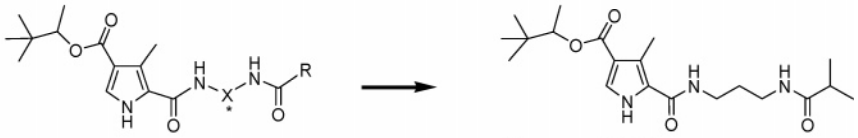
Library: 3.22
Name: Aryl-tetrazole
Size: *ca.* 172 members
Reference: Eastman, B.; *et al.* [116]

Receptor: mGluR5
Activity: IC_{50} = 108 nM

Library: 3.23
Name: Tetrazole
Size: > 10 members
Reference: Eastman, B.; *et al.* [116]
Note: Follow-up library to library 3.22.

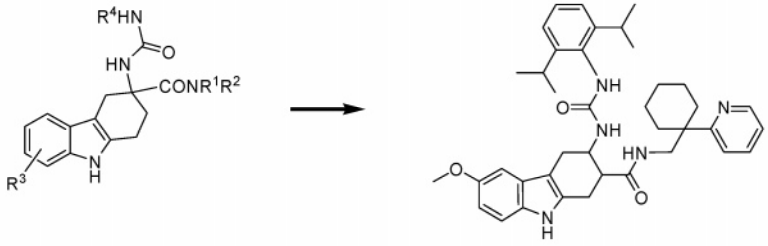
Receptor: mGluR5
Activity: IC_{50} = 28 nM

Library: 3.24
Name: Pyrrole
Size: 80 members
Reference: Micheli, F.; *et al.* [274]



Receptor: mGluR1
Activity: pIC_{50} = 6.53

Library: 3.25
Name: Tetrahydrocarbazole
Size: Not defined
Reference: Shuttleworth, S. J.; *et al.* [365]
Note: Three libraries sequentially targeting urea, amide and indole SAR.

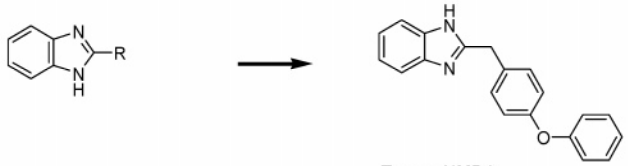


Receptor: Neuromedin β
Activity: IC_{50} = 29 nM, (+)-enantiomer (partial agonist)

Library: 3.26
Name: Cinnamide
Size: 225 members
Reference: Weber, C.; *et al.* [417]

Receptor: NMDA
Activity: IC_{50} = 225 nM

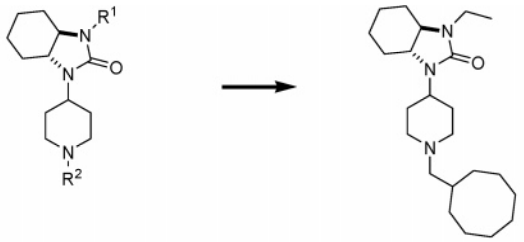
Library: 3.27
Name: Benzimidazole
Size: *ca.* 100 members
Reference: McCauley, J. A.; *et al.* [271]



Target: NMDA
Activity: K_i = 2 μM (NR2B-selective NMDA antagonist)

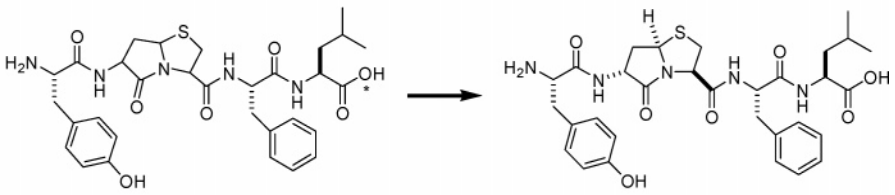
Table 3. (Continued)

Library: 3.28
Name: Octahydrobenzimidazolone
Size: 18 members
Reference: Chen, Z.; *et al.* [76]



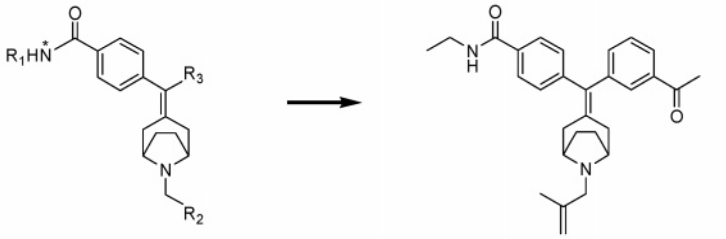
Receptor: Nociceptin/orphanin FQ (N/OFQ; also known as ORL-1)
Activity: K_i = 11 nM

Library: 3.29
Name: Bicyclic β-turn mimetic
Size: 4 members
Reference: Gu, X.; *et al.* [152]



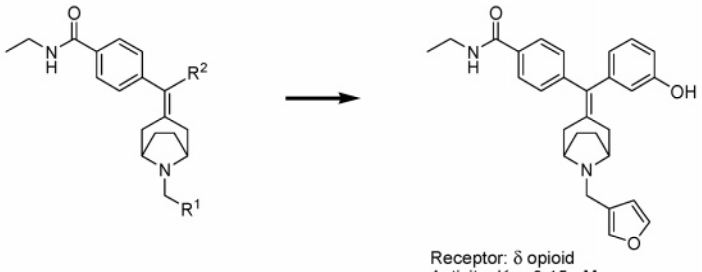
Receptor: δ opioid
Activity: IC_{50} = 2.4 μM

Library: 3.30
Name: Tropanylidene
Size: 243 members
Reference: Coats, S. J.; *et al.* [87]



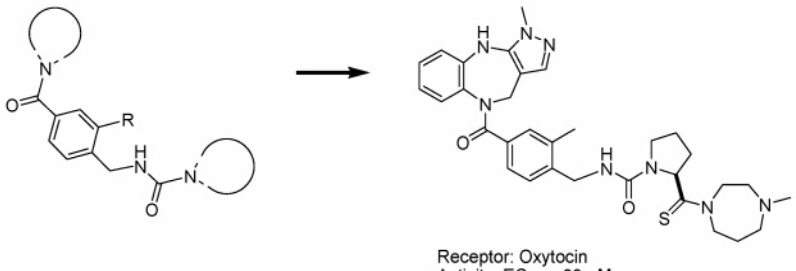
Receptor: δ opioid
Activity: K_i = 1.8 nM, δ; K_i = 1.9 nM, μ

Library: 3.31
Name: Tropanylidene
Size: 192 members
Reference: Coats, S. J.; *et al.* [87]
Note: Follow-up solution-phase library to Library 3.30.



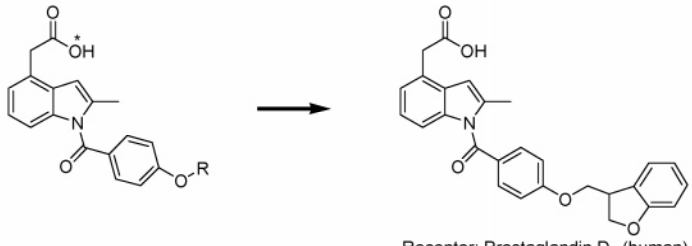
Receptor: δ opioid
Activity: K_i = 0.15 nM

Library: 3.32
Name: Benzamide
Size: Not defined
Reference: Pitt, G. R. W.; *et al.* [311]



Receptor: Oxytocin
Activity: EC_{50} = 33 nM

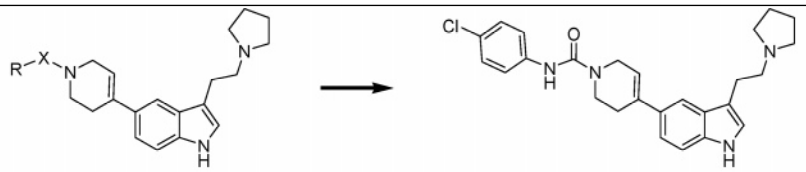
Library: 3.33
Name: Indole-4-acetic acid
Size: 19 members
Reference: Torisu, K.; *et al.* [395]



Receptor: Prostaglandin D_2 (human)
Activity: IC_{50} = 13 nM

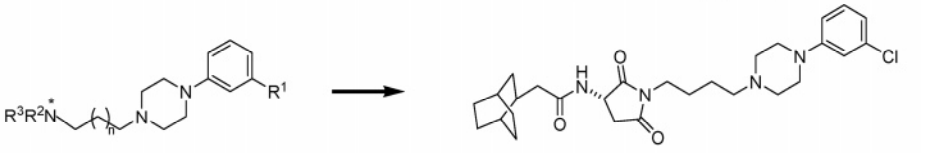
Table 3. (Continued)

Library: 3.34
Name: Indole derivative
Size: Not defined
Reference: Egle, I.; *et al.* [118]

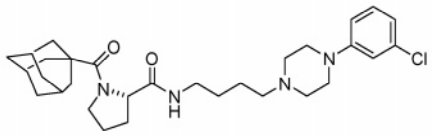


Receptor: Serotonin 5-HT_{1D} (human)
Activity: K_i = 6.1 nM 5-HT_{1D} (agonist);
K_i = 82 nM 5-HT_{1B} (agonist)

Library: 3.35
Name: Arylpiperazine
Size: 72 members
Reference: Zajdel, P.; *et al.* [436]

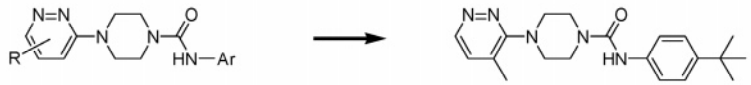


Receptor: Serotonin 5-HT_{2A}
Activity: K_i = 1 nM, 5-HT_{2A}; K_i = 30 nM, 5-HT_{1A}



Receptor: Serotonin 5-HT_{1A}
Activity: K_i = 24 nM, 5-HT_{1A}; K_i = 1950 nM, 5-HT_{2A}

Library: 3.36
Name: Pyridazinylpiperazine
Size: 39 members
Reference: Tafesse, L.; *et al.* [384]



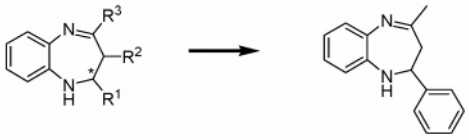
Receptor: Vanilloid-1 (VR1)
Activity: IC_{50} = 47 nM, capsaicin assay; IC_{50} = 220 nM, pH assay

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

Table 4. Chemical Libraries Targeting Non-G-Protein-Coupled Receptors[a]

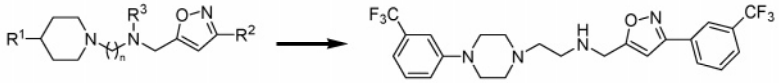
Ion channels

Library: 4.1
Name: Dihydrobenzodiazepine
Size: 4 members
Reference: Kong, K.- H.; *et al.* [217]



Channel: Neuronal sodium
Activity: IC_{50} = 114 μM

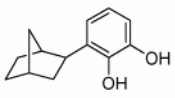
Library: 4.2
Name: Piperazinylalkylisoxazole
Size: 600 members
Reference: Jung, H. K.; *et al.* [195]



Channel: T-type Ca^{2+}
Activity: IC_{50} = 1 μM

Library: 4.3
Name: Not defined
Size: 10,000 members
Reference: Zaks-Makhina, E.; *et al.* [437]
Note: Commercial collection obtained from Chembridge, Inc.

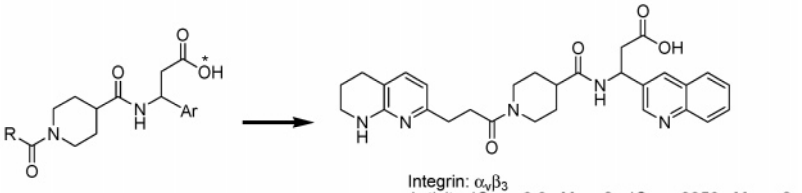
Commercial collection



Channel: K^+ (mammalian)
Activity: EC_{50} = 60 μM

Integrins

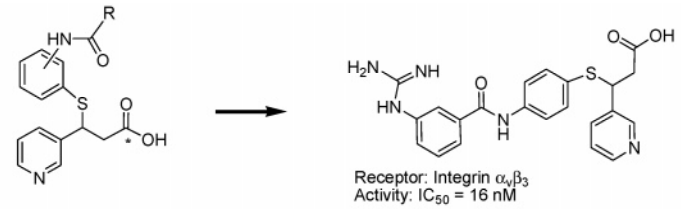
Library: 4.4
Name: Isonipecotamide
Size: Not defined
Reference: De Corte, B. L.; *et al.* [101]



Integrin: $\alpha_v\beta_3$
Activity: IC_{50} = 2.6 nM, $\alpha_v\beta_3$; IC_{50} = 3850 nM, $\alpha_{IIb}\beta_3$

Table 4. (Continued)

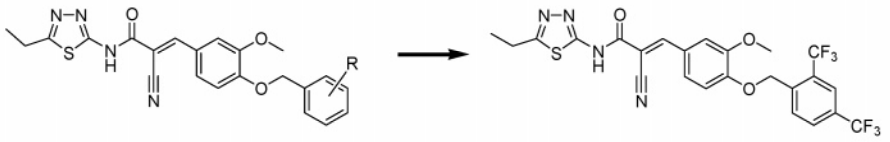
Library: 4.5
Name: Nicotinyl propionate
Size: Not defined
Reference: Vianello, P.; *et al.* [404]



Receptor: Integrin $\alpha_v\beta_3$
Activity: IC_{50} = 16 nM

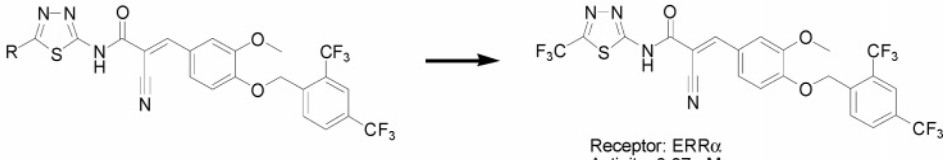
Nuclear receptors

Library: 4.6
Name: Thiadiazoleacrylamide
Size: 100 members
Reference: Busch, B. B.; *et al.* [56]



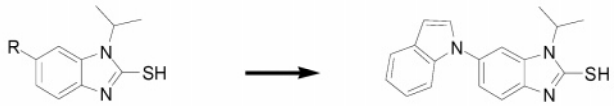
Receptor: Estrogen-related receptor α (ERRα)
Activity: IC_{50} = 0.54 μM

Library: 4.7
Name: Thiadiazole-acrylamide
Size: Not defined
Reference: Busch, B. B.; *et al.* [56]
Note: Follow-up to library 4.6.



Receptor: ERRα
Activity: 0.37 μM

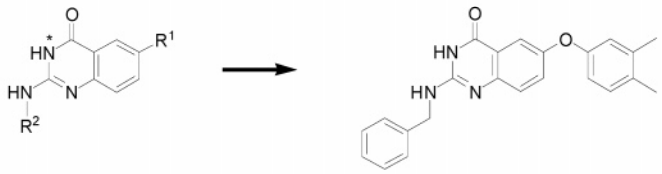
Library: 4.8
Name: Benzimidazol-2-thione
Size: Not defined
Reference: Dong, Y.; *et al.* [114]



Receptor: Nonsteroidal progesterone receptor
Activity: EC_{50} = 3 nM

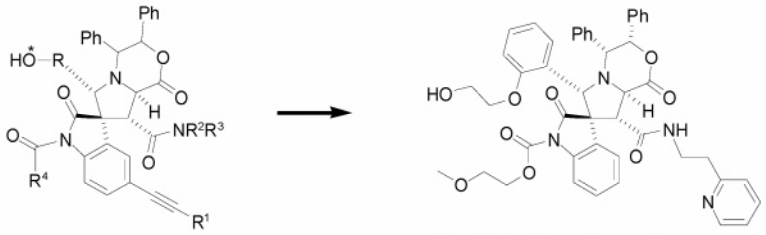
Phenotypic assays

Library: 4.9
Name: Guanidine mimetic
Size: 270 members
Reference: Miller, S. C.; *et al.* [275]
Note: Phenotypic screening



Target: BS-C-1 (monkey) cells; phenotypic assay
Activity: Minimum effective concentration = 300 nM, actin/microtubule disruptor

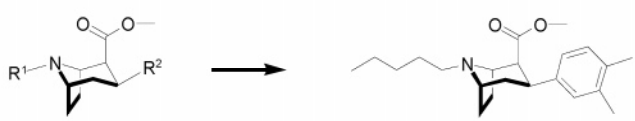
Library: 4.10
Name: Spirooxindoles
Size: 3520 members
Reference: Lo, M. M.-C.; *et al.* [248]
Note: Encoded split-pool library.



Target: Yeast growth arrest
Activity: EC_{50} = 550 nM; enhancer of latrunculin B, an actin polymerization inhibitor

Transporters

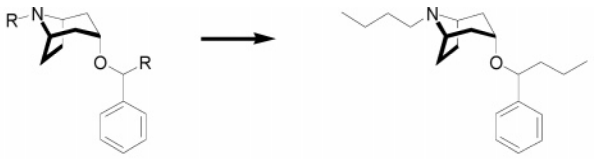
Library: 4.11
Name: Tropane
Size: 150 members
Reference: Bulow, A.; *et al.* [52]
Note: Multi-libraries from conjugate addition of Grignard reagents to N-alkyl ecgonidine.



Transporter: Dopamine
Activity: K_i (binding) = 14 nM; K_i (uptake) = 34 nM

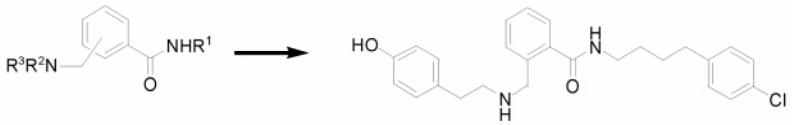
Table 4. (Continued)

Library: 4.12
Name: Benzotropine
Size: 125 members
Reference: Pederson, H.; *et al*. [304]



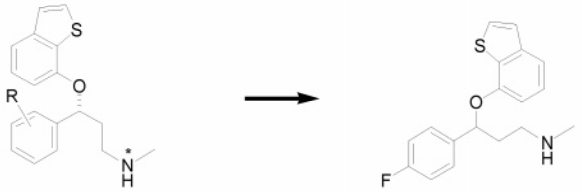
Transporter: Dopamine
Activity: K_i = 1.6 μM

Library: 4.13
Name: 2-Aminomethylbenzamide
Size: Not defined
Reference: Ho, K.-K.; *et al*. [457]
Note: Library synthesis conducted using acid labile and photolabile linkers.



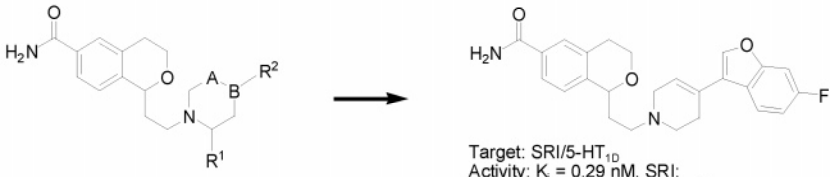
Transporter: Glycine type-2
Activity: IC_{50} = 77 nM

Library: 4.14
Name: Benzothiophene
Size: *ca*. 12 members
Reference: Boot, J. R.; *et al*. [41]



Target: Serotonin (5-HT) and norepinephrine (NE) reuptake
Activity: K_i = 0.5 nM, 5-HT; K_i = 0.6 nM, NE

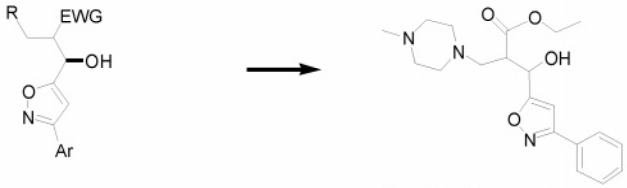
Library: 4.15
Name: 3,4-Dihydrobenzopyran
Size: Not defined
Reference: Timms, G. H.; *et al*. [394]



Target: SRI/5-HT_{1D}
Activity: K_i = 0.29 nM, SRI;
K_i = 28 nM, 5-HT_{1D} (antagonist)

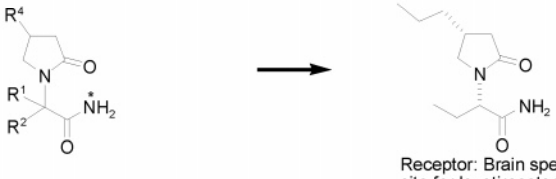
Alphabetical listing

Library: 4.16
Name: Isoxazole
Size: *ca*. 50 members
Reference: Batra, S.; *et al*. [25]



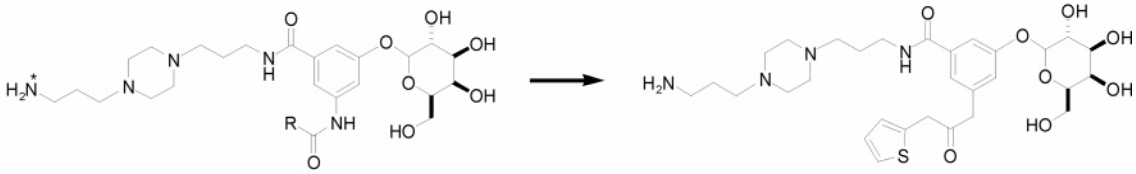
Target: Antithrombosis
Activity: IC_{50} = 20 μM, ADP (5 μM)-induced aggregation in rats; 60% *in vivo* protection

Library: 4.17
Name: Pyrrolidinone
Size: 91 members
Reference: Kenda, B. M.; *et al*. [204]



Receptor: Brain specific binding site for levetiracetam
Activity: pIC_{50} = 7

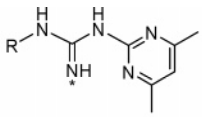
Library: 4.18
Name: Galactosides
Size: *ca*. 20 members
Reference: Mitchell, D. D.; *et al*. [276]

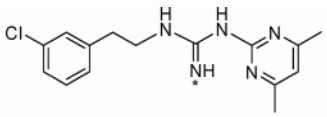


Target: Cholera toxin
Activity: IC_{50} = 0.2 mM (antagonist)

Table 4. (Continued)

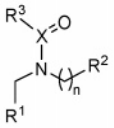
Library: 4.19
Name: Biaryl guanidine
Size: Not defined
Reference: Jefferson, E. A.; *et al.* [186]
Note: Library also prepared by solution-phase.

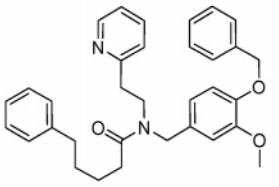




Target: HCV-internal ribosome entry site (HCV-IRES)
Activity: IC_{50} = 12 μM

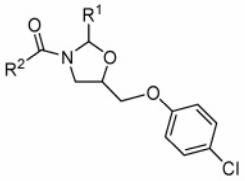
Library: 4.20
Name: Amide analog
Size: 300 members
Reference: Lu, Y.; *et al.* [254]

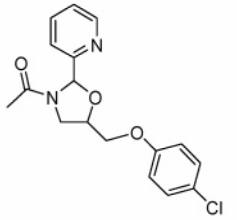




Target: ELKI luciferase assay
Activity: IC_{50} = 9 μM; GI_{50} = 16 μM, HCT-116 cell proliferation assay

Library: 4.21
Name: 1,3-Oxazolidine
Size: Not defined
Reference: Hahn, H. - G.; *et al.* [155]

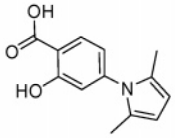




Target: β-Hexosaminidase release from mast cells
Activity: 47% inhibition at 3 μM

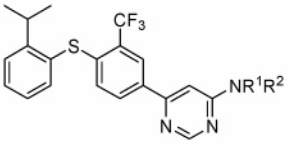
Library: 4.22
Name: Not defined
Size: 33,040 members
Reference: Jiang, S.; *et al.* [192]
Note:"Universal" library of "drug-like" compounds from ChemBridge Corp.

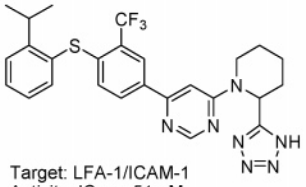
Commercial library



Target: HIV fusion
Activity: EC_{50} = 1 μM, HIV-1_{IIIB} replication

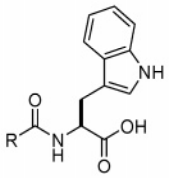
Library: 4.23
Name: Arylpyrimidine
Size: 24 members
Reference: Wang, G. T.; *et al.* [410]

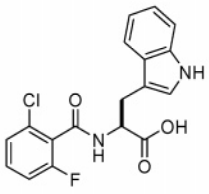




Target: LFA-1/ICAM-1
Activity: IC_{50} = 51 nM

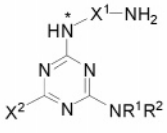
Library: 4.24
Name: Tryptophan derivatives
Size: *ca.* 58 members
Reference: Burdick, D. J.; *et al.* [54]

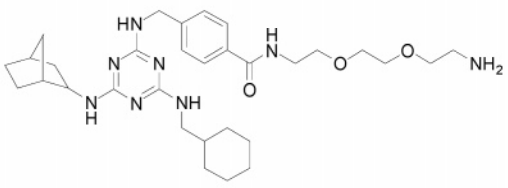




Target: ICAM-1/LAF-1
Activity: IC_{50} = 0.25 μM

Library: 4.25
Name: Triazine
Size: 2688 members
Reference: Uttamchandani, M.; *et al.* [398]

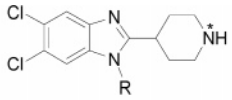


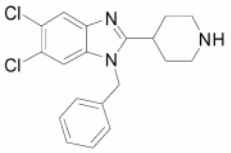


Target: IgG (human)
Activity: K_d = 2 μM

Table 4. (Continued)

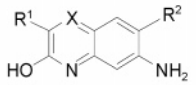
Library: 4.26
Name: Benzimidazole
Size: *ca.* 23 members
Reference: He, Y.; *et al.* [162]

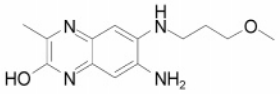




Target: *E. coli* 16S ribosomal RNA A-site
Activity: IC_{50} = 60 μM

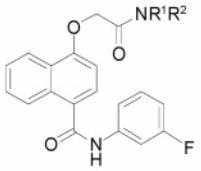
Library: 4.27
Name: 2-Quinoxalinol analog
Size: *ca.* 75 members
Reference: Zhang, L.; *et al*. [440]

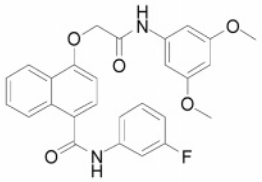




Target: TNF-α release (mouse macrophage)
Activity: IC_{50} = 0.4 μM

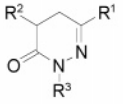
Library: 4.28
Name: 1,4-Substituted naphthalene
Size: 32 members
Reference: Ji, T.; *et al.* [190]

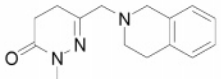




Target: Transcription factor
PBXI/DNA binary complex
Activity: IC_{50} = 65 μM

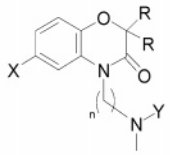
Library: 4.29
Name: Pyridazinone
Size: 25 members
Reference: Gouault, N.; *et al.* [147]

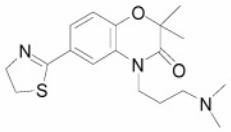




Target: Isolated rat aorta
Activity: E_{max} = 70.5% vasorelaxation

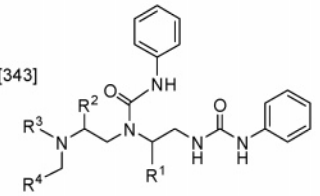
Library: 4.30
Name: Benzoxazine
Size: 19 members
Reference: Caliendo, G.; *et al.* [61]

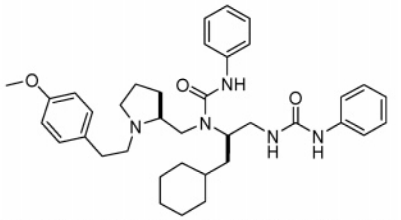




Target: Isolated rat aorta
Activity: 97.6% of relaxatin at 10^{-4} M
(EC_{50} = 41 μM,
vasorelaxant activity)

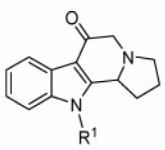
Library: 4.31
Name: Polyphenylurea
Size: 89,856 members
Reference: Schimmer, A. D.; *et al.* [343]
Note: Positional scanning library.

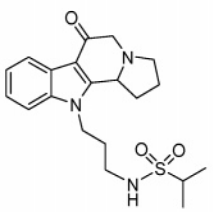




Target: XIAP-mediated derepression of caspase-3
Activity: IC_{50} = *ca.* 10 μM (Jurkat luekemia cells)

Library: 4.32
Name: Hexahydroindoloquinolizinone
Size: Not defined
Reference: Jennings, L. D.; *et al.* [189]

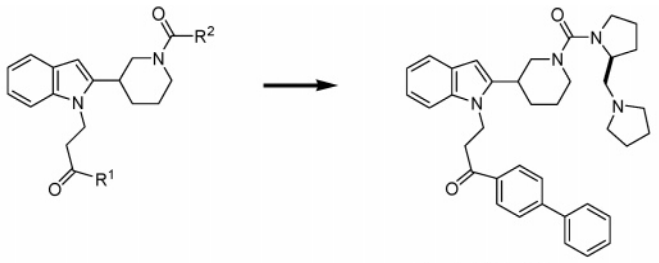




Target: ZipA-FtsZ protein-protein
interaction (antiinfective target)
Activity: 46% inhibition at 1 mM

Table 4. (Continued)

Library: 4.33
Name: Indole
Size: *ca.* 22 members
Reference: Jennings, L. D.; *et al.* [188]
Note: One of several small library sets.

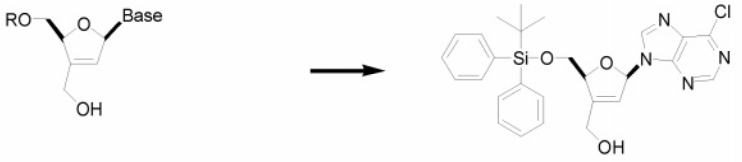


[a] Asterisk (*), point of attachment to resin.

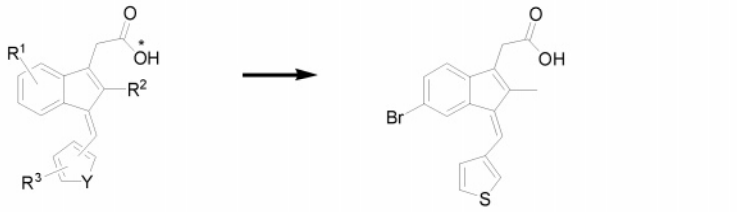
Table 5. Chemical Libraries Yielding Cyclotoxic and Antiinfective Agents[a]

Oncolytics

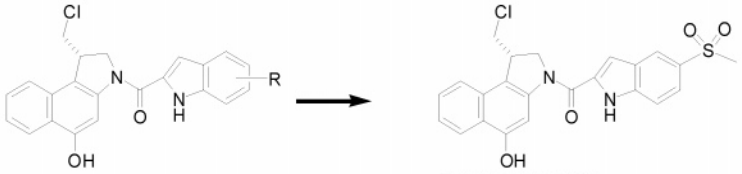
Library: 5.1
Name: Carbocyclic nucleoside
Size: *ca.* 21 members
Reference: Velcicky, J.; *et al.* [453]



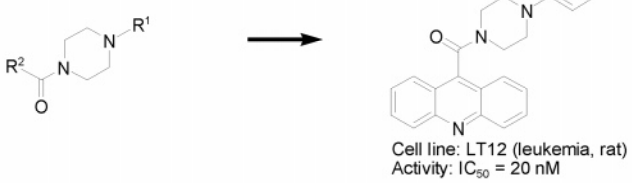
Library: 5.2
Name: Sulindac analogues
Size: 239 members
Reference: Mueller, O.; *et al.* [283]



Library: 5.3
Name: Duocamycin analog
Size: 45 members
Reference: Ham, Y.-W.; *et al.* [156]
Note: Selection assay that enables the direct identification of the most effective DNA alkylating agents from a mixture library.



Library: 5.4
Name: Acylpiperazine
Size: 320 members
Reference: Gerlach, M.; *et al.* [140]



Library: 5.5
Name: Crambescidin analog
Size: *ca.* 10 members
Reference: Aron, Z. D.; *et al.* [12]

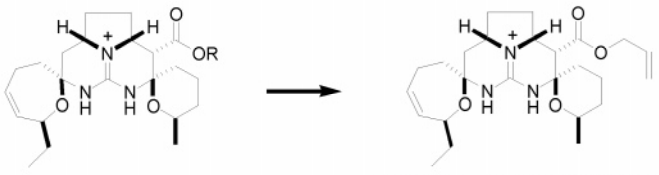
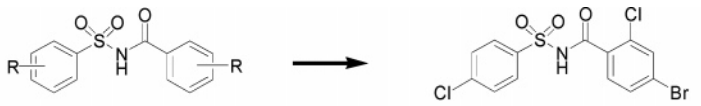


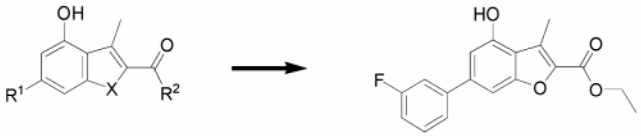
Table 5. (Continued)

Library: 5.6
Name: Acylsulfonamides
Size: Not defined
Reference: Lobb, K. L.; *et al.* [249]



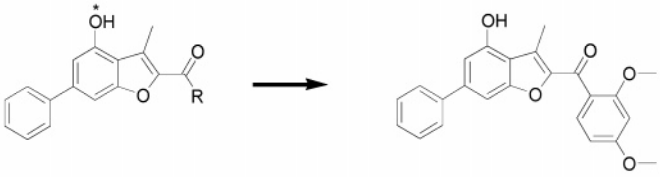
Target: Vascular endothelial growth factor-stimulated proliferation of human umbilical vein endothelial cells (VEGF-HUVEC)
Activity: IC_{50} = 0.2 μM

Library: 5.7
Name: Benzofuran/indole
Size: *ca.* 40 members
Reference: Hayakawa, I.; *et al.* [161]



Cell line: VA13
Activity: EC_{50} = 17 ng/mL

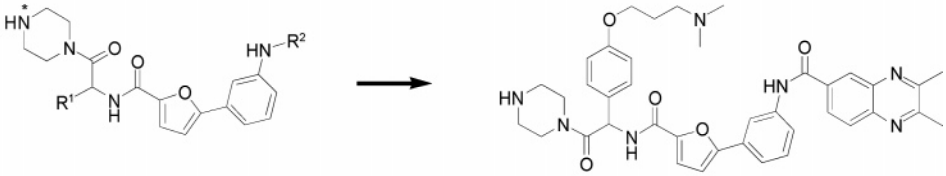
Library: 5.8
Name: Benzofuran
Size: Not defined
Reference: Hayakawa, I.; *et al.* [160]
Note: Series of libraries prepared by solid and solution phase synthesis.



Cell line: VA13 (tumor)
Activity: EC_{50} = 40 ng/mL

Antiinfectives

Library: 5.9
Name: Biaryl
Size: Not defined
Reference: Jefferson, E. A.; *et al.* [187]

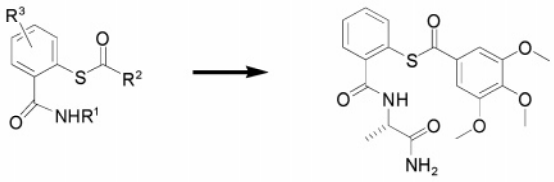


Microbe: *E. coli* (in vitro bacterial translation)
Activity: IC_{50} = 1.0 μM

Library: 5.10
Name: Azacyclic urea
Size: *ca.* 15 members
Reference: Huang, P. P.; *et al.* [173]

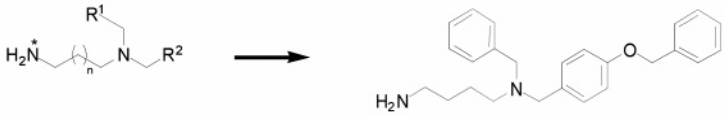
Virus: HIV (whole cell assay)
Activity: EC_{50} = 0.2 μM

Library: 5.11
Name: Thioester
Size: Not defined
Reference: Srivastava, P.; *et al.* [374]



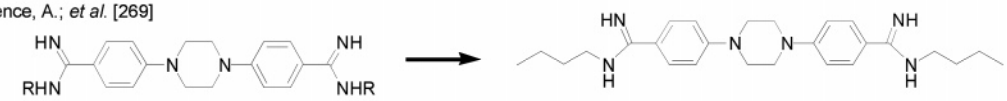
Virus: HIV cell to cell transmission
Activity: EC_{50} = 200 nM

Library: 5.12
Name: Diamine
Size: 78 members
Reference: Labadie, G. R.; *et al.* [224]



Microbe: *Leishmania donovani*
Activity: EC_{50} = 0.37 μM

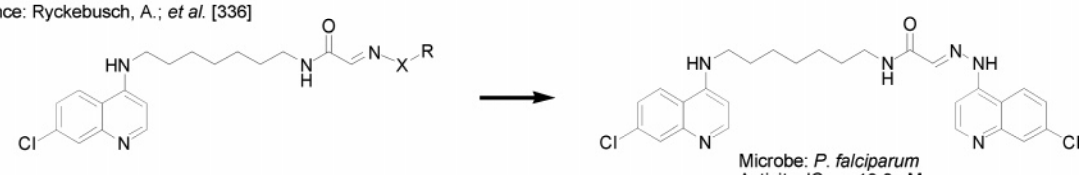
Library: 5.13
Name: Bisbenzamidines
Size: 6 members
Reference: Mayence, A.; *et al.* [269]



Microbe: *P. falciparum*
Activity: IC_{50} = 3 nM

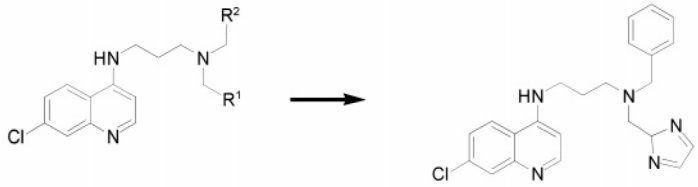
Table 5. (Continued)

Library: 5.14
Name: Quinolylhydrazone
Size: *ca.* 28 members
Reference: Ryckebusch, A.; *et al.* [336]



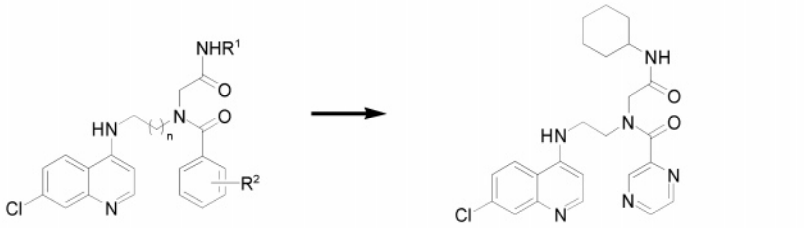
Microbe: *P. falciparum*
Activity: IC_{50} = 19.3 nM
(inhibition of parasite growth)

Library: 5.15
Name: Chloroaminoquinoline
Size: 48 members
Reference: Madrid, P. B.; *et al.* [260]



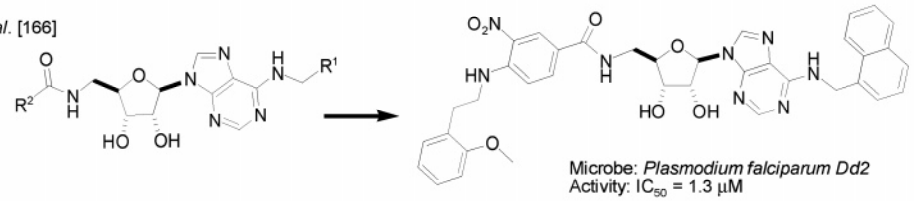
Microbe: *P. falciparu 3D7*
Activity: 0-10% growth after 74 h
at 30 nM drug concentration

Library: 5.16
Name: 4-Aminoquinoline
Size: 10 members
Reference: Musonda, C. C.; *et al.* [285]



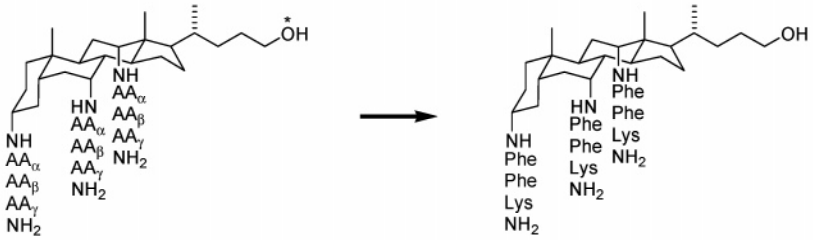
Microbe: *P. falciparum*
Activity: IC_{50} = 0.24 μM, strain D10; IC_{50} = 0.52, strain K1; IC_{50} = 0.88 μM, strain W2

Library: 5.17
Name: Adenosine
Size: 298 members
Reference: Herforth, C.; *et al.* [166]



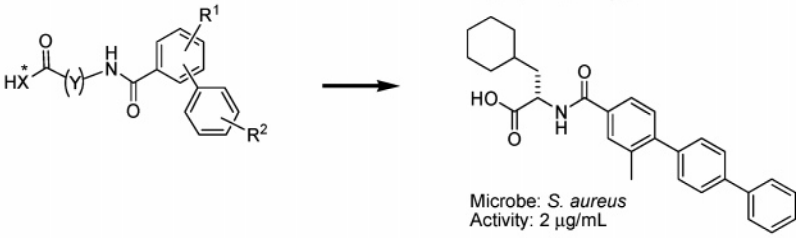
Microbe: *Plasmodium falciparum Dd2*
Activity: IC_{50} = 1.3 μM

Library: 5.18
Name: Cationic steriod
Size: 216 members
Reference: Ding, B.; *et al.* [108]



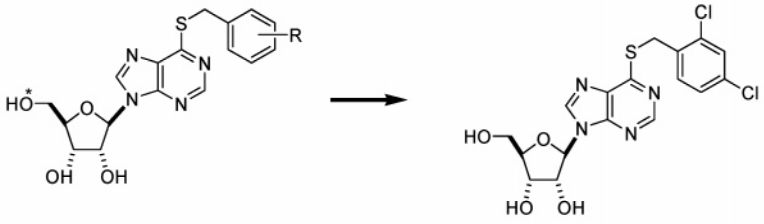
Microbes: *S. aureus*
Activity: MIC = 8 μg/mL

Library: 5.19
Name: Biaryl
Size: 1000 members
Reference: Look, G. C.; *et al.* [251]



Microbe: *S. aureus*
Activity: 2 μg/mL

Library: 5.20
Name: Benzylthioinosine
Size: 20 members
Reference: Yadav, V.; *et al.* [426]

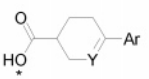


Microbe: *Toxoplasma gondii*
Activity: K_m = 0.7 μM

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

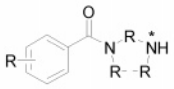
Table 6. Scaffold Derivatization[a]

Part A: Solid-phase

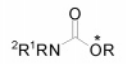


- Ohnmacht [292]
- 20 ex; 42-100%
- Suzuki coupling of resin-bound aryl and heteroaryl carboxylic acids

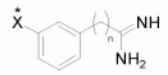
- Gros [151]
- 12 ex; 50-87%
- Suzuki coupling with resin-bound 2-pyridylboron



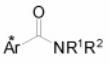
- Wang [411]
- 8 ex; high yield
- monoacylation of unprotected symmetrical diamines with resin-bound benzoic acids



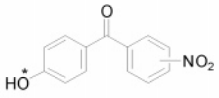
- Mormeneo [282]
- 13 ex; 69-99%
- reaction of amines with chloroformate resin



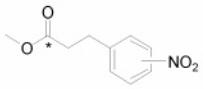
- Cesar [68]
- 6 ex; 71-82%
- reduction of aldoximes with $SnCl_2$ in DMF; X = HO, COOH, CH_2NH_2



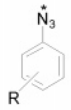
- Yamazaki [427]
- *ca.* 10 ex; 60-90%
- Pd catalyst, amine, $Mo(CO)_6$ and resin-bound aryl halide



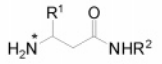
- Lee [230]
- 1 ex; 42%
- acylation of phenols bound to H-ROMP resin



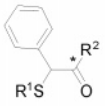
- Lee [230]
- 1 ex; 87%
- nitration of hydrocinnamate bound to H-ROMP resin



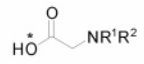
- Avemaria [17]
- 19 ex; 94-96%
- from resin-bound triazines, $TMSN_3$, and TFA



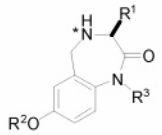
- Cantel [65]
- 8 ex; 56-92%
- Arndt-Eistert homologation of resin-bound amino acids



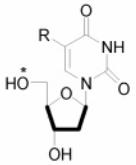
- Fruchart [129]
- 7 ex; 11-63%
- acid-mediated release and trapping of α-keto carbocations with thiols



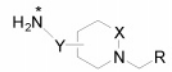
- Hu [171]
- 12 ex; good yield
- from PEG bound bromoacetate and amines



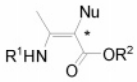
- Im [179]
- 62 members
- benzodiazepine scaffold attached to resin and derivatized



- Aucagne [16]
- 13 ex; good yield
- various Pd-catalyzed coupling reactions using resin-bound iodo deoxyuridine

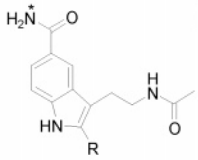


- Ayesa [18]
- *ca.* 80 members
- reductive amination of resin-bound aminopiperidines and pyrrolidines



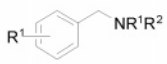
- Chen [73]
- 12 ex; 63-83%
- nucleophilic displacement of resin-bound alkenyl iodonium salt

- Shimojo [362]
- 4 ex; 31-47%
- enzyme-mediated enantioselective hydrolysis of PEG-supported carbonates



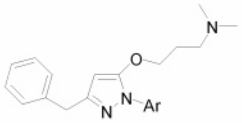
- Berthault [33]
- 4 ex; 62-96%
- Pd-catalyzed cross-coupling of resin-bound 2-iodoindole

Part B: Solution-phase

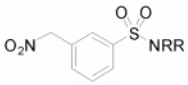


- Zhang [443]
- 15 ex; 68-98%
- *N*-benzylation of secondary amines using oligomeric benzylsulfonate esters prepared via ROM polymerization

- Wang [412]
- 18 ex; 50-98%
- microwave-assisted Suzuki using polymer-supported Pd catalyst



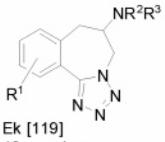
- Rossiter [332]
- 26 ex; 0-47%
- Cu (II)-mediated N-arylation of pyrazoles



- Caddick [60]
- 7 ex; 61-94%
- reaction of amines with triphenylphosphine-activated sulfonate esters

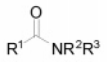
- Anderson [8]
- 11 ex; 80-100%
- hydrolysis of esters without aqueous work-up

- Rasmussen [321]
- *ca.* 27 ex; 43-99%
- N-, C-, and O-arylation using resin-bound triaryl bismuthanes



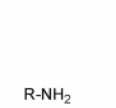
- Ek [119]
- 18 members
- reductive amination of corresponding ketone prepared by DiazAll reaction

- Crosignani [97]
- 27 ex; 74-99%
- esterification of polymer-supported *O*-alkylisoureas

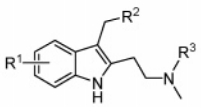


- Crosignani [96]
- 14 ex; 15-100%
- amide synthesis using polymer-supported Mukaiyama reagent

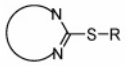
- Crosignani [96]
- 15 ex; 45-100%
- ester synthesis using polymer-supported Mukaiyama reagent



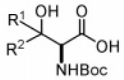
- Saulnier [341]
- 20 ex; 70-97%
- microwave-assisted synthesis of primary amines from halides and sulfonates in 7 M NH_3 in MeOH



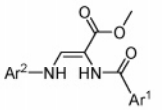
- Lizarzaburu [247]
- 33 ex; good yield
- nucleophilic ring opening reactions of 2,2-dialkyl-1,2,3,4-tetrahydro-γ-carbolinium salts with thiols



- Jonsson [193]
- *ca.* 44 ex; good yield
- S-alkylation of acidic thiourea containing heterocycles via automated flow through synthesis

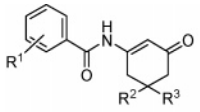


- Dettwiler [454]
- *ca.* 8 ex; >50%
- addition of Grignard reagents to N-Boc serine methyl ester

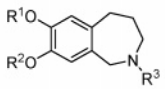


- Cebasek [66]
- 24 ex; 70-91%
- from anilines and methyl (Z)-2-arylamino-3-(dimethylamino)prop-2-enoates

Table 6. (Continued)

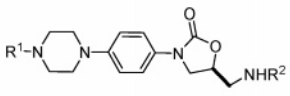


• Anderson [7]
• 12 members
• benzoylation of 3-amino-2-cyclohexenones

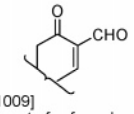


• Tafesse [383]
• ca. 33 ex; 41-96%
• *N*-derivatization of benzazepines; R^1 = H or Me

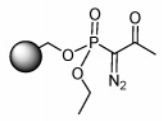
• Christensen [82]
• 7 ex; 43-96%
• deprotection of 2-nitrobenzenesulfonyl group with perfluorinated thiol



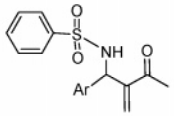
• Kim [211]
• 150 members
• derivatization of orthogonal protected diamine oxazolidinone



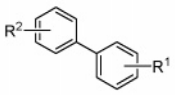
• Liu [1009]
• treatment of α-formyl-α,β-unsaturated cycloanones with resin-bound 4-(phenylseleno) morpholine, then oxidation and elimination



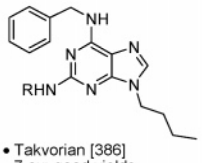
• Barrett [21]
• 9 ex; 63-91%
• from resin-bound ethyl 1-diazo-2-oxo-phosphonate and aldehydes



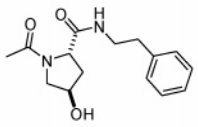
• Zhao [449]
• 8 ex; <5-99%
• resin bound phosphine-catalyzed aza-Baylis-Hillman Reaction



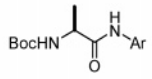
• Zhang [446]
• 12 ex; 74-95%
• Suzuki cross-coupling with aryl perfluorooctyl sulfonates and boronic acids



• Takvorian [386]
• 7 ex; good yields
• microwave-assisted S_N2Ar reaction of 2-fluoropurine derivatives with amines



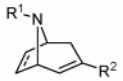
• Shaginan [353]
• 1 ex
• from an orthogonal safety-catch photolabile protected hydroxyproline



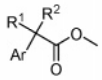
• Quéléver [318]
• 8 ex; good yield
• acylation of weakly nucleophilic heterocyclic amines by amino acids

• Levi [237]
• 14 ex; good yield
• alkylation of isoquinuclidine

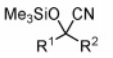
• Bai [19]
• 84-96%
• cross-coupling of phenylboronic acid and Ar-Br using polymer-supported Pd-catalyst



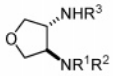
• Lyapkalo [463]
• 5 ex; good yields
• from enol triflate and Pd-catalyzed cross-coupling



• Sheng [358]
• 9 ex; 79-86%
• treatment of aryl-alkyl ketones with $HC(OMe)_3$ and polymer-supported (diacetoxyiodo)-styrene



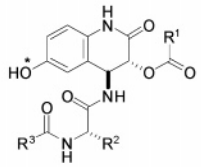
• Karimi [203]
• 56-98%
• TmSCN, ketone and resin-bound Sc(III) catalyst



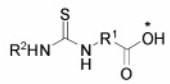
• Lai [272]
• 9 ex; good yield
• multi-step sequence from amino alcohols

Table 7. Acyclic Synthesis[a]

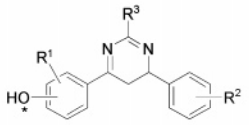
Part A: Solid-phase



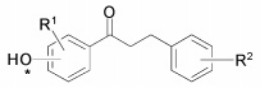
• Couve-Bonnaire [94]
• 27 members
• from resin-bound from corresponding *N,O*-diprotected tetrahydroquinoline



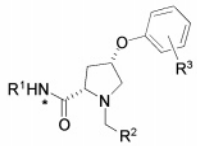
• Boas [40]
• 9 ex; 50-100%
• prepared from resin-bound amino acids, CS_2, peptide coupling reagent and amine



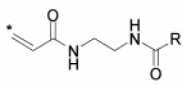
• Bowman [46]
• 12 ex; good purity
• from support-bound chalcones and amidines; microwave-assisted SPOT-synthesis on planar cellulose



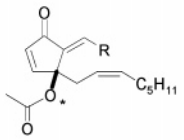
• Bowman [46]
• 38 ex; good purity
• microwave-assisted reaction of ArCHO and resin-bound arylmethylketones SPOT-synthesis on planar cellulose



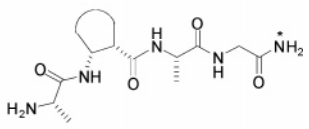
• Vergnon [402]
• 10200 members
• from resin-bound *O*-THP, *N*-Fmoc protected hydroxyproline



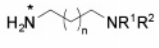
• Ciolli [84]
• 8 ex; 63-73%
• derived from TRAM linker



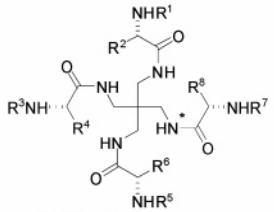
• Tanaka [387]
• 8 ex; good yield
• multi-step squence from resin-bound 4-hydroxy-4-(Z-3-iodoallyl)cyclopent-2-enone



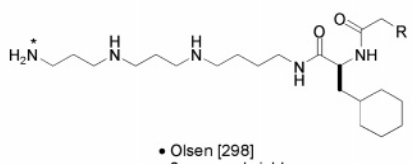
• Fulop [132]
• 3 ex; good purity
• acylation of resin-bound amines with β-lactams



• Olsen [297]
• *ca.* 8 ex; good yield
• resin-bound (trityl)amino alcohols converted to iodides then displacement with amines



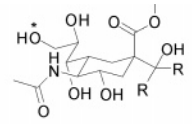
• Virta [407]
• 11 ex; good yield
• from resin-bound orthogonally-protected tetramine



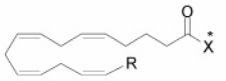
• Olsen [298]
• 3 ex; good yield
• from resin-bound ethylenediamine via Fukuyama-Mitsunobu alkylation sequence

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

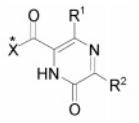
Table 7. (Continued)



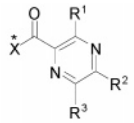
- Baytas [28]
- 5 ex; 42-81%
- SmI_2-mediated C-glycoside synthesis with resin-bound Neu5Ac and RRCO



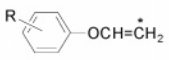
- Qi [315]
- 12 ex; 5-65%
- repetitive Cu-mediated coupling reaction between resin-bound terminal alkynes and propargyl halides or allylic halides, cleavage, then reduction to alkene



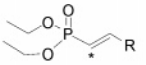
- Matsushita [268]
- 12 ex; 13-93%
- N-H insertion reaction of resin-bound α-diazo-β-ketoesters and Boc-amino acids, X = OR, NRR



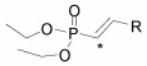
- Matsushita [268]
- 8 ex; 8-60%
- N-H insertion reaction of resin-bound α-diazo-β-ketoesters and Boc-amino acids, X = OR, NRR



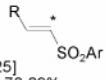
- Sheng [357]
- 8 ex; 92-95%
- phenols coupled to β-bromoethyl selenide resin, oxidation, elimination



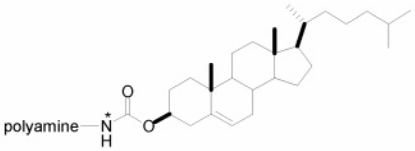
- Sheng [359]
- 7 ex; 85-91%
- alkylation of resin-bound α-diethoxyphosphorylmethyl selenide with LDA followed by alkylation and oxidative deselenation



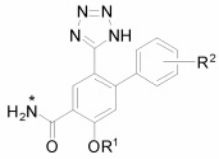
- Xu [425]
- 6 ex; 62-84%
- alkylation of resin-bound α-selenomethylphosphonate then H_2O_2-mediated elimination



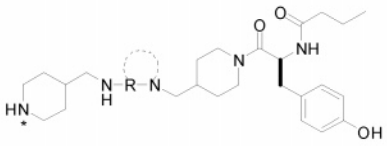
- Xu [425]
- 14 ex; 73-89%
- alkylation of resin-bound α-selenomethyl-arylsulfonate then H_2O_2-mediated elimination



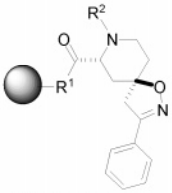
- Oliver [295]
- 4 ex; 87-93%
- from resin-bound polyamine and cholesterol



- Kivrakidou [214]
- 20 members
- simultaneous biphenyl formation and phenol deallylation under Suzuki cross-coupling conditions and tetrazole ring formation on solid support.

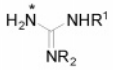


- Olsen [296]
- 2 ex; 39-44%
- multi-step sequence from resin-bound piperidine 4-carboxylic acid

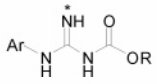


- Hwang [176]
- 1890 members
- library encoded by halogenated mass-tags

- Enders [123]
- 5 ex; good purity
- photolytic cleavage of triazene T2 linker

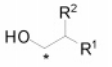


- Sandanayake [339]
- 68 members
- TMI-isocyanate synPhase lanterns reacted with R^1NH_2, dehydrated to carbodiimides, further reacted with R^2NH_2 then cleavage

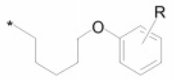


- Robinson [328]
- 15 ex; 0-91%
- Mitsunobu alkylation or resin-bound guanidines

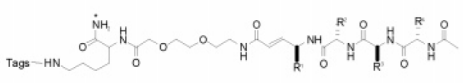
- Tai [385]
- 12 ex; 58-87%
- Pummerer rearrangement of resin-bound sulfides then hydrolysis



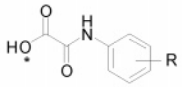
- Tai [385]
- 13 ex; 52-82%
- Pummerer rearrangement of resin-bound sulfides, hydrolysis then borohydride reduction



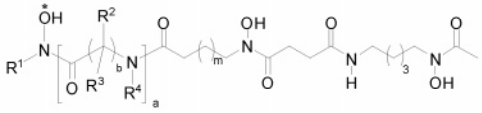
- Ruhland [335]
- 3 ex; 48-62%
- traceless homolytic cleavage of resin-bound tellurium alkylethers



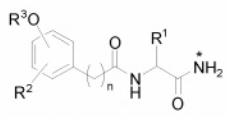
- Debaene [104]
- 4000 members
- peptide nucleic acid (PNA) encoded library of putative cysteine protease inhibitors



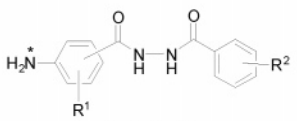
- Georgiadis [139]
- 60 members
- resin-bound oxylyl chloride and anilines



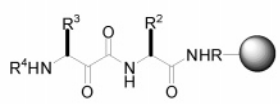
- Poreddy [313]
- 22 members
- multi-step sequence from resin-bound nosyl-protected hydroxylamine



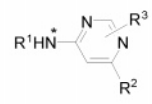
- Patek [303]
- 15,360 members
- directed sort and combine synthesis with 2D and 3D spatially addressed arrays



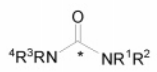
- Park [301]
- 144 members
- R_f encoded library from resin-bound amino benzoic acid



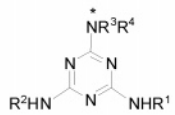
- Papanikos [300]
- 6 ex; good purity
- acid-labile α-keto carbonyl group introduced as its 1,3-dithiolane derivative



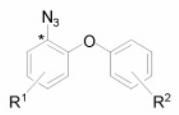
- Ma [257]
- 10 ex; 40-99%
- Suzuki-coupling or amination of resin-bound chloropyrimidines



- Lee [235]
- 25 ex; 58-100%
- resin-bound carbamates cleaved with Al-amide complexes



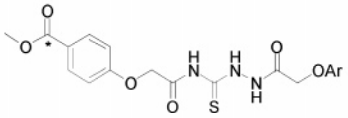
- Khersonsky [208]
- *ca.* 34 ex; good purity
- safety-catch method using thiophenol resin and dichloroamino triazine



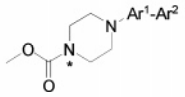
- Knepper [215]
- 32 ex; 34-83%
- Ullmann-type reaction on resin-bound *o*-halo triazines

Table 7. (Continued)

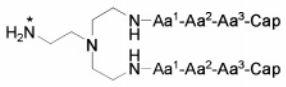
- Wang [414]
- 12,288 members
- encoding method for "one-bead oe-compound" library using a biphasic approach for ladder-synthesis of coding tags.



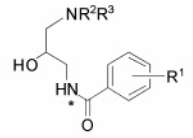
- Wang [415]
- 11 ex; good purity
- from PEG-bound 4-hydroxy-benzoic acid



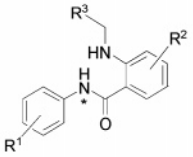
- Ruhland [334]
- 20 ex; 7-48%
- consecutive C-N, C-B, and C-C Pd-catalyzed cross-coupling reactions



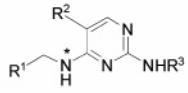
- Shukla [364]
- 300 members



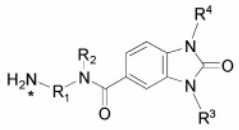
- Coats [88]
- *ca.* 6 ex; 10-39%
- alkylation of alloc-protected Rink resin with epichlorohydrin, acylation, epoxide ring opening with amines



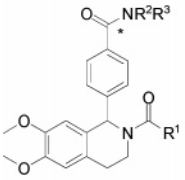
- El-Araby [120]
- 10,800 members
- acylation of resin-bound anilines with nitrobenzoyl chloride, NO_2 reduction then reductive amination



- Arvanitis [14]
- 162 members
- attachments of 4-Cl-2 methylthiopyrimidines, *S*-oxidation, amine substitution

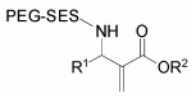


- Bianchi [35]
- 48 members
- acylation of resin-bound diamines with benzimidazolone carboxylic acid

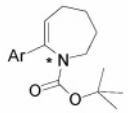


- Bunin [53]
- 3 ex; 31-42%
- deprotection of resin-bound Boc-protected tetrahydroisoquinoline then *N*-acylation

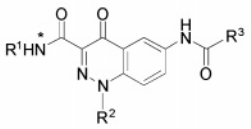
- Revell [323]
- 9 ex; 71-82%
- Suzuki reaction using resin-bound arylsulfonates



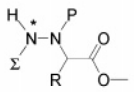
- Ribière [324]
- 14 ex;
- aza-Baylis-Hillman reaction yielding resin-bound β-amino-esters



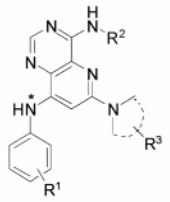
- Campbell [63]
- 12 ex; 0-72%
- Suzuki cross-coupling of resin-bound lactam enol phosphates



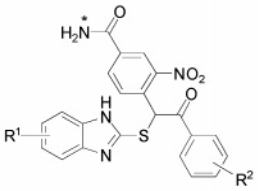
- Sereni [351]
- 8 ex; 42-88%
- *N*-alkylation, NO_2 reduction then acylation of resin-bound 6-nitro-4-oxo-1,4-dihydro-cinnoline-3-carboxylic acid



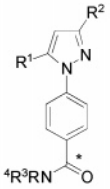
- Bouillon [45]
- 10 ex; 40-65%
- Mitsunobu coupling of resin-bound *N*-alkyloxycarbonylamino phthalimides then deprotection reprotection strategy; Σ, P = Boc, Cbz, $COCF_3$



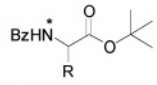
- El-Araby [121]
- 16,000 members
- three controlled S_NAr reactions from resin-bound anilines and 2,4,8-trichloropyrimidinopyrimidine



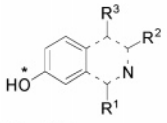
- Roy [353]
- 9 ex; 66-90%
- multi-step sequence from resin-bound 4-fluoro-3-nitro-benzoic acid via a novel intramolecular S_NAr rearrangement



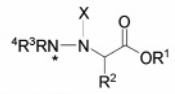
- Vickerstaffe [405]
- 192 members
- capture of 1,5-biarylpyrazole carboxylic acids onto TFP resin and release upon reaction with amines



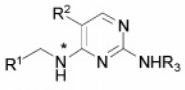
- Park [302]
- 10 ex; 50-92%
- phase-transfer catalytic alkylation of resin-bound glycine imine



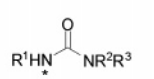
- Taylor [390]
- 10 ex; 50-69%
- skeletal-diversity produced by manipulation of enamine moiety of resin-bound dihydro-isoquinoline



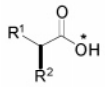
- Bouillion [45]
- 10 ex; 35-80%
- reaction of resin-bound trimellitic anhydride with Boc- or Cbz- protected hydrazine, then phthalimide formation, alkylation and cleavage; X = Boc, Cbz



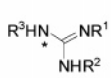
- Arvanitis [14]
- 162 members
- hetero arylation of resin-bound amines with 4-Cl-2-methylthiopyrimidines, sulfur oxidation and amine displacement



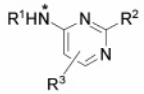
- Martinez-Teipel [264]
- 192 members
- Marshall resin-supported carbamates and amines using microwave



- Kotake [218]
- 3 ex; ca. 50%
- asymmetric alkylation using a resin-bound Evans-type chiral auxiliary



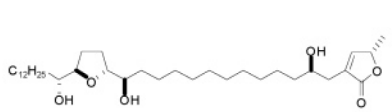
- Boguszewski [42]
- 14 ex; 42-92%
- amine resin capture of carbodiimides and release



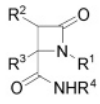
- Ma [257]
- 10 ex; 40-99%
- Suzuki-coupling or amination of resin-bound chloropyrimidines

Table 7. (Continued)

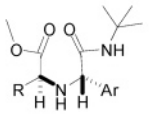
Part B: Solution-phase (Continued)



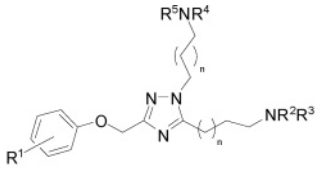
- Zhang [444]
- 16 members
- fluorous mixture synthesis of (+)-murisolin and fifteen diastereoisomers



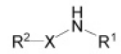
- Pirrung [310]
- 12 ex; 16-75%
- 3-CC Ugi of β-keto acids in water



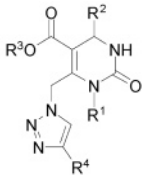
- Godet [142]
- 16 ex; 75-90%
- 3-CC mediated by catalytic $TiCl_4$ in MeOH



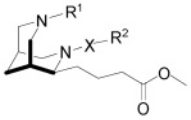
- Martin [262]
- 192 members
- Mitsunobu alkylation of *N,N*-dialkylamino alcohols with triazoles



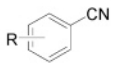
- de Kort [102]
- 8 ex; 26-54%
- novel ionic support with acid-cleavable linker; X = CO, SO_2



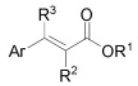
- Khanetskyy [207]
- 17 ex; 15-46%
- bromination/azidation/click sequence from dihydropyrimidines



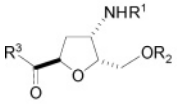
- Ivachtchenko [184]
- 48 members
- acylation and sulfonylation of bispidines



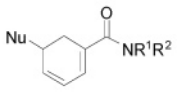
- Srivastava [375]
- 11 ex; 84-99%
- Pd-catalyzed cyanation of aryl halides



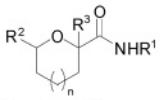
- Fukuyama [131]
- 16 ex; 47-99%
- Mizoroki-Heck arylation of α,β-unsaturated carboxylic acids and esters using F-626 as a solvent



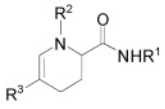
- Edwards [117]
- 99 members
- from orthogonal protected furanose scaffold



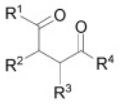
- Graden [149]
- 20 ex; 15-76%
- nucleophiles added to tricarbonyl(cyclohexa-1,3-dienylcarboxylic acid 4-nitro-phenyl ester)iron hexafluorophosphate, aminolysis and decomplexation



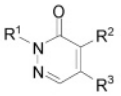
- Masdeu [265]
- 6 ex; 56-71%
- α-carbamoylation of cyclic enol ethers



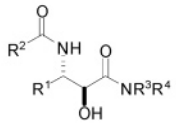
- Masdeu [265]
- 6 ex; 64-97%
- α-carbamoylation of dihydropyridines



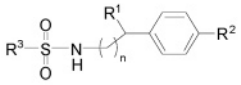
- Barrett [22]
- 17 ex; 68-99%
- condensation of RCHO and α,β-unsaturated ketone catalyzed by ROMP gel-supported thiazolium iodide



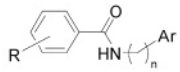
- Sotelo [373]
- 9 ex; 60-87%
- derived from 4,5-dihalo-2-hydroxymethylpyridazinone; R^2 = H, CHO



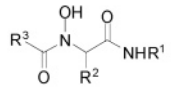
- Voronkov [408]
- 20 members
- Lewis-acid mediated reaction of glycidic amides and nitriles



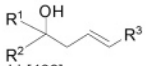
- Villard [406]
- 27 members
- use of a fluorous-tagged acid-labile amine protecting group



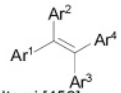
- Villard [406]
- 18 members
- use of a fluorous-tagged acid-labile amine protecting group



- Basso [24]
- 17 ex; 27-95%
- Ugi 4-CC with *O*-benzylhydroxylamine then H_2/Pd



- Li [462]
- *ca.* 9 ex; good yield
- 3-compenent synthesis via allyl(isopropoxy)-dimethylsilane

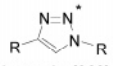


- Itami [458]
- 23 ex; 14-85%
- sequential assembly using (2-pyrimidyl)-vinylsulfide (also see: Kamei [459])

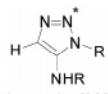
[a] Asterisk (*), point of attachment to resin.

Table 8. Monocyclic Synthesis[a]

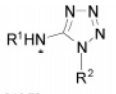
Part A: Solid-phase



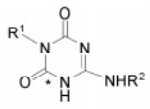
- Raghavendra [320]
- 8 ex; 28-57%
- Bamford-Stevens reaction between resin-bound tosyl hydrazine, $TiCl_4$ and amines



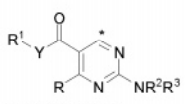
- Raghavendra [320]
- 3 ex; 11-17%
- Bamford-Stevens reaction between resin-bound tosyl hydrazine, $TiCl_4$ and amines



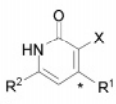
- Yu [435]
- 16 ex; 61-75%
- resin-bound thioureas displayed by NaN_3 in the presence of $HgCl_2$ then nucleophilic cyclization



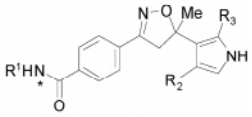
- Yu [434]
- 13 ex; 79-88%
- reaction of resin-bound *S*-methylisothiourea with isocyanate, amines then intracyclative cleavage



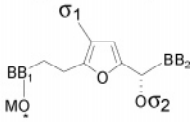
- Porcheddu [312]
- 42 ex; high yield
- microwave-assisted cyclocondensation of resin-bound β-ketoesters/amides



- Li [240]
- 15 ex; 12-49%
- multi-step sequence from sodium benzenesulfinate resin

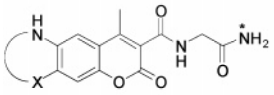


- Hwang [177]
- 24 ex; 0-100%
- pyrrole annulation from resin-bound vinyl sulfones

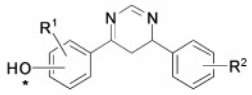


- Burke [55]
- 1260 members
- diversity-oriented split-pool synthesis

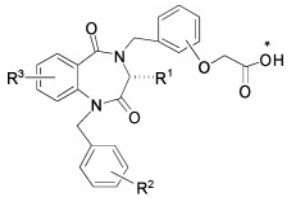
Table 8. (Continued)



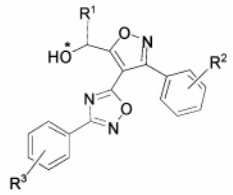
- Song [371]
- *ca.* 16 ex; good yield
- from resin-bound 7-fluoro-4-methyl-6-nitrocoumarin



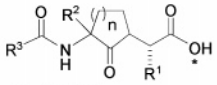
- Bowman [46]
- 12 ex; good purity
- from support-bound chalcones and amidines; microwave-assisted SPOT-synthesis on planar cellulose



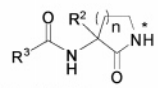
- Cheng [77]
- 15 ex; good overall yield
- 8-step sequence from PEG-bound 3- and 4-formyl phenoxyacetic acids



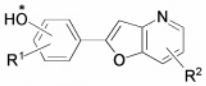
- Quan [317]
- 18 ex; 8-27%
- multi-step sequence employing nitrile oxide 1,3-dipolar cycloaddition reaction



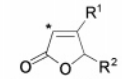
- Scott [347]
- 11 ex; 32-62%
- alkylation of resin-bound amino acid aldimine-derived Schiff base with α,ω-dihalide, cyclization, hydrolysis, acylation, and cleavage



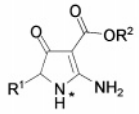
- Scott [347]
- 3 ex; 34-43%
- alkylation of resin-bound amino acid aldimine-derived Schiff base with α,ω-dihalide, cyclization, hydrolysis, acylation, and cleavage



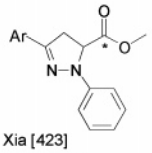
- Cironi [86]
- 4 ex; 25-79%
- Sonogashira cross-coupling of resin-bound phenolic iodides and 2-ethynylpyridin-3-yl acetate then base treatment and cleavage



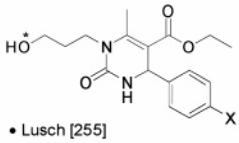
- Sheng [356]
- traceless sulfone linker strategy from epoxides



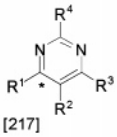
- Detsi [107]
- 4 ex; good yield
- *C*-acylation of resin-bound amino acid benzotriazoles then acid cleavage



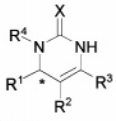
- Xia [423]
- 8 ex; 0-94%
- 1,3-dipolar cycloaddition of PEG-supported acrylic acid with aldehyde phenyl-hydrazones under microwave irradiation



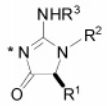
- Lusch [255]
- 2 ex; good purity
- Lewis-acid catalyzed split-pool Biginelli synthesis demonstrated from resin-bound N-(3-hydroxy)propylurea



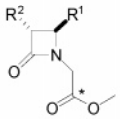
- Kong [217]
- 11ex; 20-53%
- *S*-alkylation of resin-bound sulfinate, sulfone anion alkylation with an epoxide, γ-hydroxyl sulfone to γ-ketosulfone oxidation, and traceless product release by a one-pot elimination-cyclization



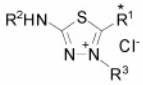
- Kong [217]
- 8 ex; 7-42%
- *S*-alkylation of resin-bound sulfinate, sulfone anion alkylation with an epoxide, γ-hydroxyl sulfone to γ-ketosulfone oxidation and traceless product release by a one-pot elimination-cyclization; X = O, S



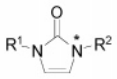
- Li [238]
- 10 ex; 23-39%
- guanidinylation of resin-bound amino acid then intracyclative cleavage



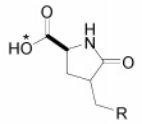
- Delpiccolo [105]
- 9 ex; 43-57%
- polymer-supported Staudinger reaction using a controlled excess of the nonactivated acid chloride and tertiary amine



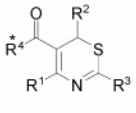
- Kappel [202]
- 17 ex; 38-94%
- condensation of thio-semicarbazides with resin-bound aldehyde then TMSCl-promoted cyclization



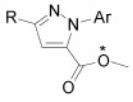
- Rosse [331]
- 11 ex; 11-86%
- amines attached to bromo acetal linker, reaction with RNCO, then intracyclative cleavage



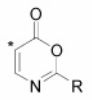
- Lamberto [225]
- 2 ex; 41-60%
- thiol-mediated free radical cyclization of resin-bound alkenyl isocyanides



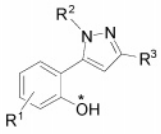
- Strohmeier [373]
- 20 ex; 7-61%
- Knoevenagel condensation of resin-bound β-keto esters then acid-catalyzed ring closure with thioureas



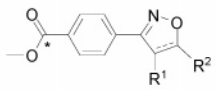
- Lin [242]
- 9 ex; 83-93%
- 1,3-dipolar cycloaddition of PEG bound acrylate and nitrilimines then DDQ oxidation



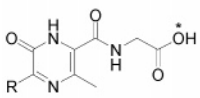
- Liu [246]
- 9 ex; 65-87%
- thermolysis of resin-bound acylaminomethylene cyclic malonic acid esters



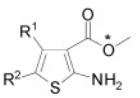
- Borrell [43]
- 82 members
- condensation of hydrazines with resin-bound β-diketones; regio-isomers formed



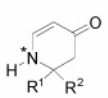
- Shang [354]
- 10 ex; 87-60%
- 1,3-dipolar cycloaddition of PEG-bound nitrile oxide and alkyne/alkene



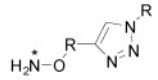
- Christensen [83]
- 22 ex; 0-95%
- oxidation of threonine adjacent to N-terminal amino acids



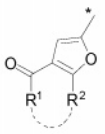
- Zhang [439]
- 10 ex; 0-91%
- Gewald synthesis via soluble resin-bound cyano-acetate



- Sax [342]
- 12 ex; 26-68%
- hetero-Diels-Alder reaction with Danishefsky's diene and resin-bound imines

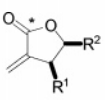


- Su [380]
- 5 ex; 95-98%
- Mitsunobu coupling of resin-bound *N*-hydroxy-phthalamide with alkynyl alcohols then Cu-catalyzed cycloaddition with azides

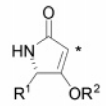


- Tang [388]
- 6 ex; 71-80%
- derived from resin-bound seleneyl bromide and α-allyl substituted 1,3-dicarbonyls

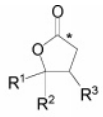
Table 8. (Continued)



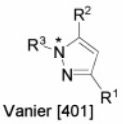
• Breitenstein [49]
• 12 ex; 31-54%
• Nozaki-Hiyama allylation of resin-bound allylic bromides with R^2CHO then intracyclative cleavage



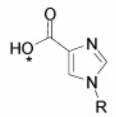
• Schobert [345]
• *ca.* 6 ex; 40-93%
• consecutive addition and Wittig alkenation of α-ammonium esters with resin-bound (triphenylphosphoranylidene)ketene



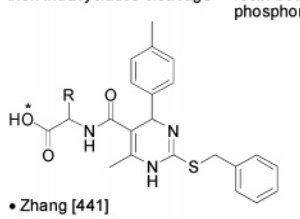
• Kerrigan [205]
• *ca.* 12 ex; good yield, 70-96% ee
• α,β-unsaturated esters bearing an ephedrine chiral auxiliary are reacted with aldehydes and ketones in the presence of SmI_2



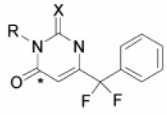
• Vanier [401]
• 13 ex; 13-29%
• DDQ activation of resin-bound oxazines then reaction with hydrazines



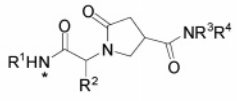
• Henkel [165]
• 11 ex; 20-90%
• microwave-assisted condensation of amines with resin-bound 3-*N*,*N*-(dimethylamino) isocyanoacrylate



• Zhang [441]
• 6 ex; 55-76%
• Knoevenagel condensation of resin-bound β-acetoacetamido acid with *p*-tolualdehyde then 2-benzyl-2-thiopseudourea

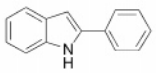


• Fustero [133]
• 10 ex; 55-89%
• condensation of resin-bound ester enolate with α,α-difluoronitrile, then isothiocyanate and intracyclative cleavage; X = O, S

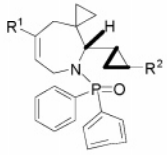


• Vergnon [403]
• 12,000 members
• resin-bound primary amines alkylated with β-monomethyl itaconate, hydrolysis, amide formation, cleavage

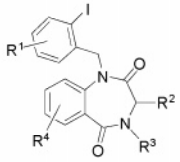
Part B: Solution-phase



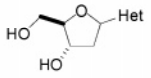
• Slough [367]
• 1 ex; 56%
• phenyacetylene and *o*-iodo aniline domino coupling-cyclization reaction using a copper activated resin



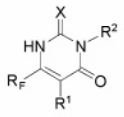
• Wipf [421]
• 7 ex; 63-84%
• multicomponent condensation of *N*-diphenylphosphinoylimines, alkynes, zirconocene hydrochloride and diiodomethane



• Cuny [98]
• 9 ex; good yield
• intramolecular *N*-arylation as fused ring forming step

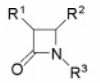


• Adamo [2]
• 3 ex; good yield
• *C*-nucleosides from α-chloroketone 2-deoxyribose

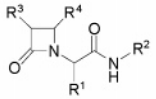


• Fustero [133]
• 20 ex; 64-90%
• condensation of fluorinated β-enamino esters wth R^2NCX; X = O, S

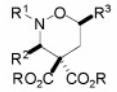
• Lu [252]
• 10 ex; good yield
• carbonylative ring expansion of aziridines with Rh-complexed dendrimers



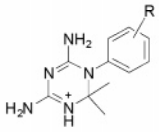
• Donati [112]
• 9 ex; 60-88%
• Staudinger reaction using polymer-supported Mukaiyama reagent



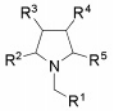
• Pirrung [309]
• 32 members
• Ugi 3-CC in water



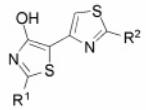
• Young [433]
• 21 ex; 66-94%
• 3-CC of nitrones with RCHO and 1,1-cyclopropanediesters



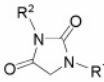
• Lee [231]
• 20 members
• microwave-assisted 3-CC of anilines, cyano-guanidine, acetone



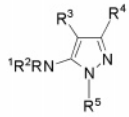
• Meyer [273]
• 7 ex; 36-77%
• alkylation of α-(alkylideneamino)nitriles with enones then $NaBH_3CN$ reduction



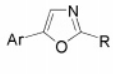
• Arcadi [11]
• 13 ex; 68-97%
• multi-step sequence using polymer-supported reagents



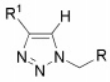
• Lee [234]
• 15 ex; 70-94%
• microwave-assisted liquid-phase synthesis from chloroacetylated PEG-OH



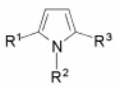
• Dodd [109]
• 21 ex; 13-95%
• 3-CC of β-ketoamide, aryl or alkyl hydrazines and Lawesson's reagent



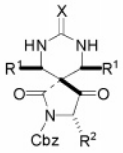
• Chen [71]
• 9 ex; 78-93%
• treatment of aromatic α-methyl ketones and nitriles with poly[styrene (iodosodiacetate)]



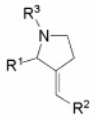
• Appukkuttan [10]
• 8 ex; 86-93%
• microwave assisted Cu-catalyzed 3-CC of RCH_2Br, NaN_3 and alkyne



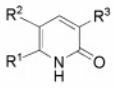
• Hansford [158]
• 30 ex; 49-98%
• condensation of amines with γ-oxoketones under Paal-Knorr conditions



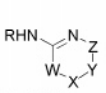
• Byk [58]
• 29 ex; 12-85%
• anomalous regioselective 4 member multicomponent Biginelli reaction; X = O, S



• Huang [174]
• 10 ex; 40-75%
• Olsson's 3-CC of cyclopropylketones, aldehydes, and primary amines then reduction of corresponding 1,2-disubstituted-3-alkylidenly-pyrrolium salts



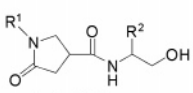
• Gorobets [146]
• >18 ex; 27-96%
• microwave-assisted 3-CC of CH-acidic carbonyl compounds, *N*,*N*-dimethylformamide and methylene active nitriles



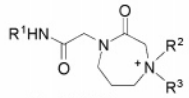
• Heinelt [163]
• 11 ex; 31-94%
• reaction of isothiocyanates with amino alcohols, diamines, or aminothiols then ring closure using TsCl/NaOH

• Chen [72]
• 11 ex; 55-80%
• poly[styrene(iodosodiacetate)]-promoted ring expansion reaction of 1-alkynylcycloalkanols

• Coppo [92]
• 200 members
• cyclization of acylhydrazines and isothiocyanates facilitated by polymer-supported reagents

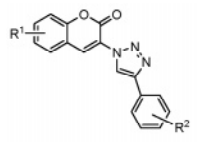


• Irving [182]
• 96 members
• from primary amines and dimethylitaconate

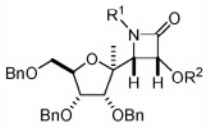


• Masip [266]
• 22 members
• multi-step sequence from chloroacetamides

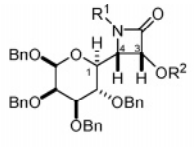
Table 8. (Continued)



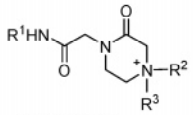
- Sivakumar [366]
- 24 members
- 1,3-dipolar cycloaddition reaction of corresponding azides and alkynes



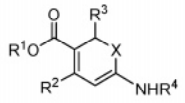
- Dondoni [113]
- 3 ex; 68-92%
- Staudinger reaction of *C*-formyl sugar, amine, acid chloride; Bn = $PhCH_2$



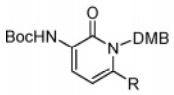
- Dondoni [113]
- 7 ex; 65-94%
- Staudinger reaction of *C*-formyl sugar, amine, acid chloride; Bn = $PhCH_2$



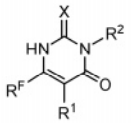
- Masip [266]
- 44 members
- multi-step sequence from chloroacetamides



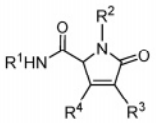
- Strohmeier [379]
- 29 ex; 10-97%
- multi-step sequence using polymer supported reagents and catch and release strategy; X = S, Se



- Chen [74]
- 8 ex; 51-84%
- RCM reaction of α-amino acrylamide then DDQ oxidation



- Fustero [133]
- 20 ex; 64-90%
- condensation of fluorinated β-aminoesters with iso(thio)cyanate; X = O, S

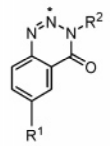


- Beck [32]
- 24 ex; 7-94%
- 4-CC of R-NC, phosphono acetates, RNH_2 and glyoxals then Wittig ring closure

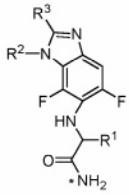
[a] Asterisk (*), point of attachment to resin.

Table 9. Bicyclic and Spirocyclic Synthesis[a]

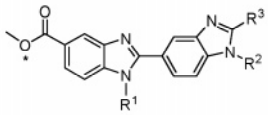
Part A: Solid-phase



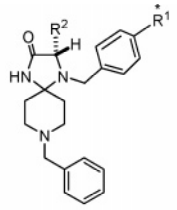
- Gil [141]
- ca. 42 ex; 13-81%
- TFA-mediated cleavage-cyclization of resin-bound benzotriazinones



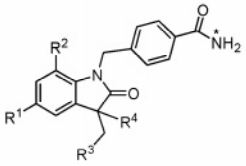
- Ji [191]
- 6 ex; 26-47%
- 1:1 mixture of heterocycles produced from resin-bound aminoacid ester and 6-nitro-2,3,4,5-tetra-fluorobenzene



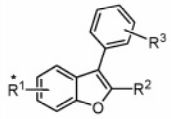
- Lin [241]
- 13 ex; 72-94%
- from PEG-bound 4-fluoro-3-nitrobenzoic acid



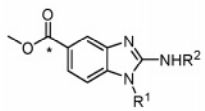
- Feliu [125]
- 120 members
- condensation of *N*-benzyl-4-piperidone



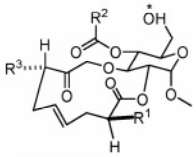
- Akamatsu [3]
- 27 ex; 55-100%
- microwave-assisted radical cyclization of resin-bound *N*-(2-bromophenyl) acrylamides



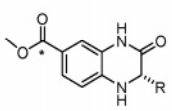
- Hu [172]
- 210 member
- Pd-catalyzed annulations of ArI and resin-bound *o*-alkynylphenols



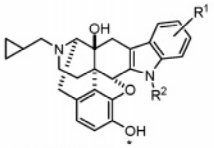
- Su [381]
- 13 ex; good yield
- resin-bound *o*-amino anilines, iso(thio)cyanate, $HgCl_2$ in microwave



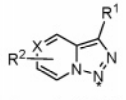
- Kim [212]
- 122 member
- diversity-oriented synthesis via RCM



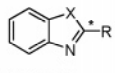
- Tung [397]
- 8 ex; good yield
- from PEG-supported 4-fluoro-3-nitrobenzoic acid



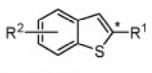
- Ohno [293]
- 16 ex; good yield
- Fisher indole synthesis with resin-bound naltrexone



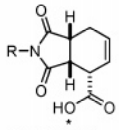
- Raghavendra [320]
- 5 ex; 33-62%
- Bamford-Stevens reaction between resin-bound tosyl hydrazine, $TiCl_4$ and amines



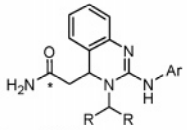
- Matsushita [267]
- *ca.* 25 ex; 17-95%
- Lewis acid-mediated cleavage of resin-bound esters with 2-aminothiophenols and 1,2-phenylenediamines; X = NH, NMe, S



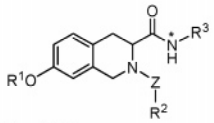
- Roberts [327]
- 12 ex; 30-73%
- conversion of resin-bound esters to enol ethers with Ti (IV) benzilidines bearing a masked sulfur nucleophile then TFA cleavage



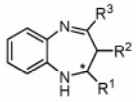
- Kiriazis [213]
- 8 ex; 30-46%
- Diels-Alder reaction of resin-bound diene and maleimides



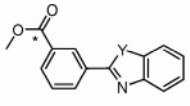
- Song [370]
- 19 ex; 59-83%
- from resin-bound *N*-Fmoc-β-amino-2-nitrobenzene-propanoic acid



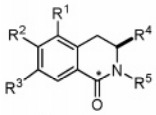
- Kane [201]
- *ca.* 6 ex; 29-57%
- from carboxyl-bound tyrosine and Pictet-Spengler reaction



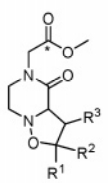
- Kong [217]
- 4 ex; 10-38%
- *S*-alkylation of resin-bound sulfinate, sulfone anion epoxide alkylation, γ-hydroxysulfone oxidation followed by a traceless product release using a one-pot elimination-cyclization process



- Chen [69]
- 6 ex; 22-62%
- reaction of PEG-supported terephthalic acid fluoride with *o*-substituted anilines then cyclization and cleavage with methoxide

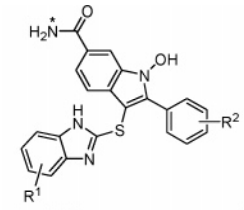


- Chern [78]
- 13 ex; 52-82%
- Bischler-Napieralski cyclization and concomitant cleavage

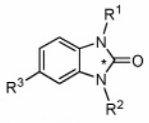


- Wierschem [419]
- 6 ex; 0-40%
- [3+2] cycloaddition reaction of resin-bound nitrone

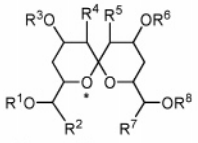
Table 9. (Continued)



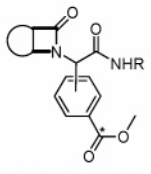
- Roy [333]
- 8 ex; 65-88%
- multi-step sequence from resin-bound 4-fluoro-3-nitrobenzoic acid



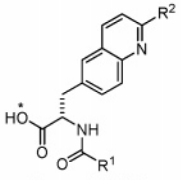
- Wang [409]
- 12 ex; 48-88%
- arylation of resin-bound carbamate-linked amines with *o*-fluoronitroaryls, reduction, then intracyclative cleavage



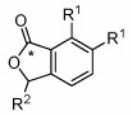
- Barun [23]
- 5 ex; 6-16%
- multi-step sequence including two sequential asymmetric aldol reactions



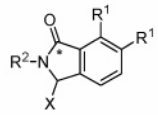
- Gedey [215]
- 6 ex; 22-59%
- Ugi 4-center-3-CC using resin-bound acid aldehyde then esterification



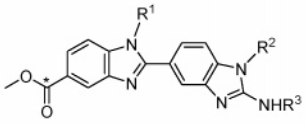
- Demaude [106]
- 16 members
- 3-CC with resin-bound 4-aminophenylalanine, RCHO and phenylvinyl sulfide



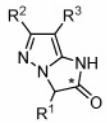
- Knepper [216]
- *ca*. 12 ex; good yield
- addition of organometallics to resin-bound 2-formylbenzoic acid then intracyclative cleavage



- Knepper [216]
- 9 ex; 17-97%
- addition of primary amines to resin-bound 2-formylbenzoic acid wth intracyclative cleavage
X = OH, NHR^2

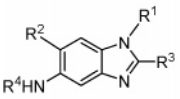


- Yeh [251]
- 13 ex; 71-93%
- multi-step sequence from PEG-bound 4-fluoro-3-nitrobenzoic acid

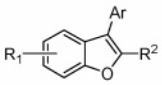


- Blass [38]
- 14 ex; 21-70%
- acylation of resin-bound hydrazinoacids with malononitriles then intracyclative cleavage

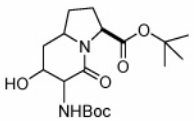
Part B: Solution-phase



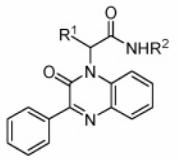
- Li [239]
- 24 members
- multi-step sequence starting from 1,5-di-fluoro-2,4-dinitrobenzene



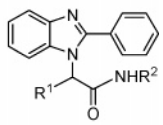
- Hu [172]
- 12 ex; 52-87%
- Pd-catalyzed annulations of aryl iodides and o-alkynylphenols



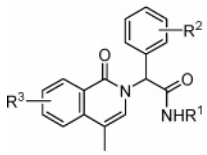
- Bravin [48]
- 8 ex; good yield
- aldol condensation of pyroglutamate-derived aldehyde and N-Boc-Gly-OEt



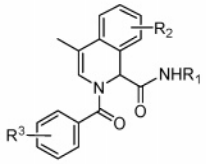
- Zhang [445]
- 8 ex; 52-81%
- microwave-assisted fluorous Ugi/de-Boc/cyclization from mono-fluorous Boc-protected diamine



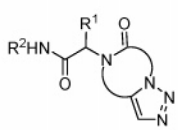
- Zhang [445]
- 8 ex; 11-62%
- microwave-assisted fluorous Ugi/de-Boc/cyclization from mono-fluorous Boc-protected diamines



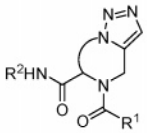
- Xiang [424]
- 10 ex; good yields
- Ugi 4-CC using *o*-iodo benzoic acids then Heck reaction



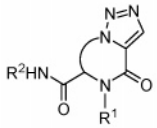
- Xiang [424]
- 10 ex; good yields
- Ugi 4-CC using *o*-iodo benzaldehydes then Heck reaction



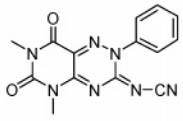
- Akritopoulou-Zanze [6]
- 4 ex; 56-77%
- Ugi 4-CC then alkyne/azide cyclization



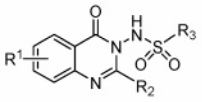
- Akritopoulou-Zanze [6]
- 2 ex; 32-48%
- Ugi 4-CC then alkyne/azide cyclization



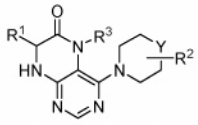
- Akritopoulou-Zanze [6]
- 1 ex; 43%
- Ugi 4-CC then alkyne/azide cyclization



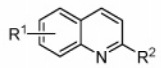
- Lee [232]
- 7 ex; 15-77%
- coupling reaction of aryldiazonium salt with 1-cyano-3-(2,6-dioxo-1,2,3,6-tetra hydropyrimidin-4-ylamino)-2-methylisothiourea followed by intramolecular cyclization



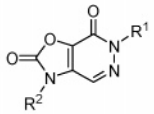
- Zhou [451]
- 90 members
- from benzoxazinones and substituted sulfonyl hydrazides



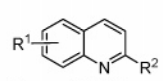
- Nagashima [286]
- 64 ex; good purity
- from 4,6-dichloro-5-nitropyrimidine and fluorous amino acids



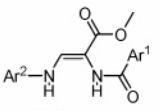
- Macleod [259]
- 8 ex; 41-67%
- from resin-bound esters and titanium benzylidene reagents



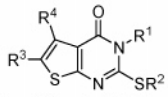
- Frolov [128]
- 4 ex; good yield
- derived from 5-nitro-4-hydroxy-3(2*H*)-pyridazinones



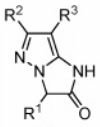
- Demaude [106]
- 25 members
- 3-cc of anilines, RCHO and phenylvinyl sulfide; oxidation and aromatization



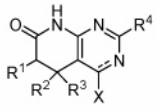
- Cebasek [66]
- 24 ex; 70-91%
- from anilines and methyl (Z)-2-acylamino-3-(dimethylamino)-prop-2-enoates



- Ivachtchenko [183]
- 3000 members
- condensation of aminothiophenecarboxylates or reactive derivatives with isothiocyanates or amines

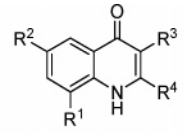


- Blass [37]
- 16 ex; 16-84%
- acylation of hydrazino acids with malononitriles then intramolecular cyclodehydration

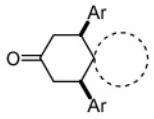


- Mont [464]
- 32 ex; 40-95%
- multi-step sequence from α,β-unsaturated esters and methyl cyanoacetate;
X = Cl, O

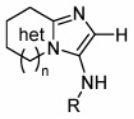
Table 9. (Continued)



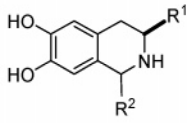
- Kuznetov [223]
- 18 ex; 10-34%
- condensation of anilines and α-substituted β-keto esters



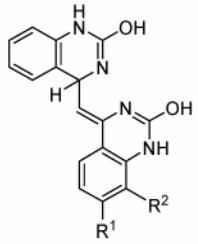
- Barbas, III [460]
- 32 ex; 60-99%
- multicomponent reactions through combinations of Aldol, Wittig, Knoevenagel, Michael, Diels-Alder, and Huisgen cycloaddition reactions



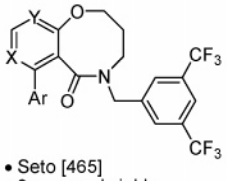
- Lyon [256]
- 12 ex; 13-72%
- glyoxylic acid an MP-glyoxylate as formaldehyde equivalents in the 3-CC of 2-aminoazines, aldehydes and isonitriles



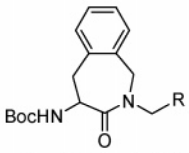
- Campiglia [64]
- 11 ex; good yield
- microwave-assisted Pictet-Spengler reaction



- Ganai [137]
- 7 ex; good yield
- $SbCl_3$-Al_2O_3-catalyzed condensation of benzylidene acetophenones and urea



- Seto [465]
- 9 ex; good yields
- from 2-chloro-4-iodopyridine carboxylic acid and a 3-hydroxpropylamine

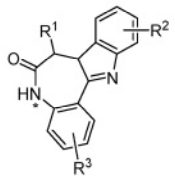


- Van den Eynde [400]
- 16 members
- multi-step sequence from *N*-Boc-*O*-amino methyl-phenylalamine

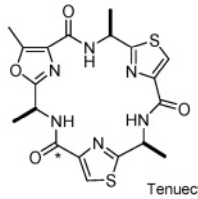
[a] Asterisk (*), point of attachment to resin.

Table 10. Polycyclic and Macrocyclic Synthesis[a]

Part A: Solid-phase

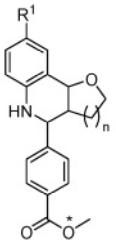


- Saha [338]
- 48 members
- from resin-bound amino acids, *o*-fluoronitrobenzene and *o*-nitrobenzaldehydes

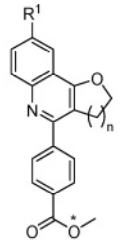


Tenuecyclamide A and related analogs

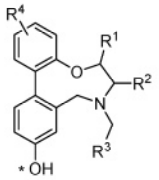
- You [432]
- *ca.* 4 ex; 38-71%
- sequential coupling of heterocyclic amino acids on resin, cleavage and macro-cyclization



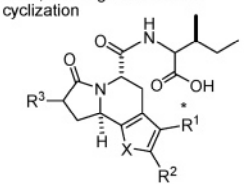
- Wang [413]
- 10 ex; 69-90%
- 3-component aza-Diels-Alder reaction of PEG-supported benzaldehyde, anilines and dihydrofuran/pyran



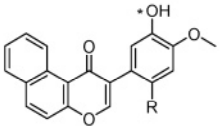
- Wang [413]
- 10 ex; 53-78%
- 3-component aza-Diels-Alder reaction of PEG-supported benzaldehyde, anilines and dihydrofuran/pyran then DDQ



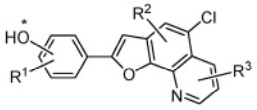
- Krishnan [221]
- 202 members
- multi-step sequence using amino alcohol, aldehyde and bromophenol inputs



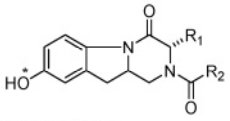
- Nielsen [288]
- *ca.* 20 ex; high purity
- intramolecular Pictet-Spengler reaction using N-Boc-1,3-oxazinanes as masked aldehyde equivalents



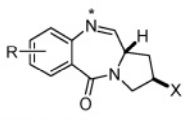
- Cironi [85]
- 2 ex; good yield
- multi-step sequence from resin-bound bis-arylacetylene



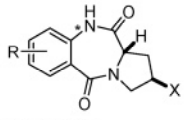
- Cironi [86]
- 3 ex; 53-86%
- Sonogashira cross-coupling of resin-bound phenolic iodides and 5-chloro-7-ethynylquinolin-8-yl acetate then base treatment and cleavage



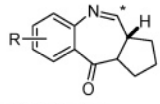
- Khadem [206]
- 1 ex
- multi-step sequence utilizing RCM reaction



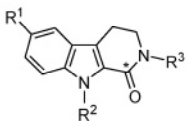
- Kamal [197]
- 6 ex; 64-72%
- reaction of resin-bound isatoic anhydride with proline then TFA-mediated cleavage



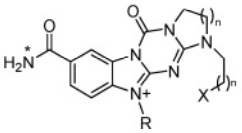
- Kamal [197]
- 6 ex; 64-72%
- reaction of resin-bound isatoic anhydride with proline then TFA-mediated cleavage



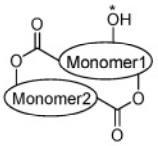
- Kamal [199]
- 8 ex; 57-65%
- DIBAL reduction of resin-bound thioesters then intramolecular aza-Wittig



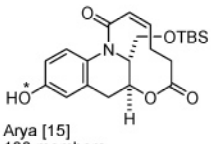
- Chem [79]
- 12 ex; 50-72%
- Bischler-Napieralski reaction for intracyclative cleavage



- Hoesl [169]
- 8 ex; good purity
- one pot aza-Wittig/hetero-cyclization/substitution from resin-bound benzimidazoles

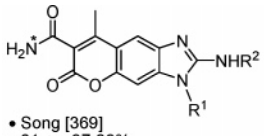


- Schmidt [344]
- 24 members
- study exploring factors controlling macro-cyclization

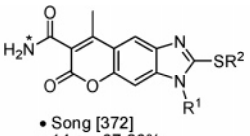


- Arya [15]
- 100 members
- resin-bound hydroxyindoline acylated with *N*-nosylamino acids then tricycle formed by intramolecular Mitsunobu

Table 10. (Continued)

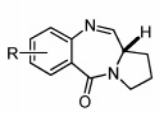


• Song [369]
• 21 ex; 37-83%
• aromatic substitution of resin-bound 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-benzopyran-3-carboxylic acid with primary amines, NO_2 reduction then cyclization with aryl isothiocyanates and DCC

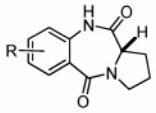


• Song [372]
• 14 ex; 67-86%
• multi-step sequence from resin-bound 7-fluoro-4-methyl-nitro-2-oxobenzopyran carboxylic acid

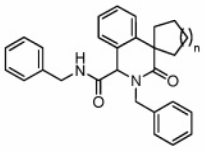
Part B: Solution-phase



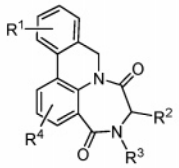
• Kamal [198]
• 7 ex; good yield
• multi-step sequence from *o*-azido benzoic acid using polymer-supported reagents



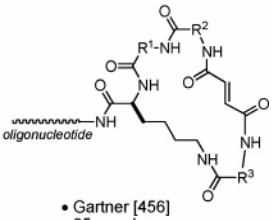
• Kamal [198]
• 7 ex; good yield
• multi-step sequence from *o*-azido benzoic acid using polymer-supported reagents



• Gracias [148]
• 3 ex; good yield
• Ugi 4-CC then Heck cyclization reaction



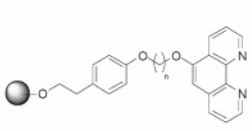
• Cuny [98]
• 7 ex; good yield
• domino intramolecular Buchwald-Hartwig amidation, C-H activation, and aryl-aryl bond formation from Ugi 4-CC precursors



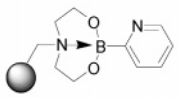
• Gartner [456]
• 65 members
• DNA-templated organic synthesis

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

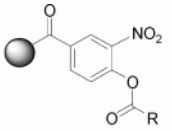
Table 11. Polymer-Supported Reagents and Scavengers



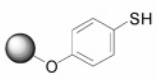
• Slough [367]
• copper chelator used in domino Cu-catalyzed coupling-cyclization yielding indoles



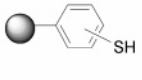
• Gros [151]
• source of 2-pyridylboron for Suzuki coupling



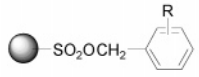
• Mormeneo [282]
• *in situ* generated resin-bound chloroformates for carbamylation of amines



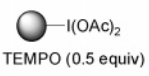
• Tai [385]
• sulfide safety-catch linker for Pummerer rearrangement reaction



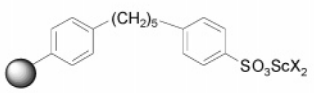
• Becht [31]
• scavenger prepared in two-steps from polystyrene resin



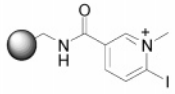
• Zhang [443]
• benzylation of secondary amines



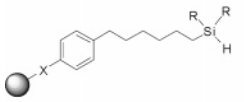
• Tashino [389]
• oxidation of ROH and RCHO to RCOOH



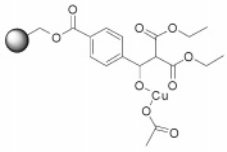
• Iimura [178]
• C-C bond formation in water



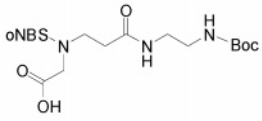
• Donati [112]
• polymer-supported Mukaiyama reagent



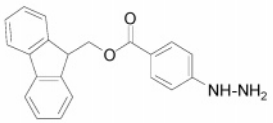
• Doi [110]
• trialkylsilyl linked polymer supports prepared by reacting benzyl chloride resin and a di-Grignard reagent with CuBr-Me_2S followed by dialkyl-chlorosilanes



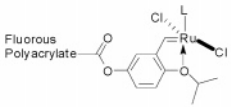
• Chiang [80]
• copper complex for C-N and C-O cross-coupling



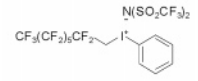
• Ciolli [84]
• acylation of resin-bound amines generates TRAM linker (traceless release of acrylamides



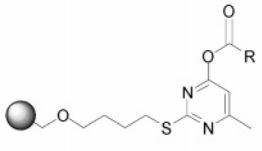
• Shannon [355]
• chromophoric reagent for the quantitative measuring of resin-bound aldehydes



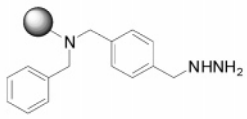
• Yao [430]
• fluorous Ru-catalyst for RCM



• Montanari [279]
• *N*-fluorous capping reagent for amino acids to facilitate peptide purification

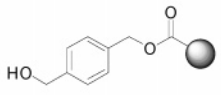


• Petricci [307]
• acyl transfer reagent

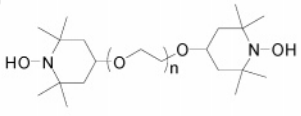


• Zhu [452]
• aldehyde and ketone scavenger

• Bosanac [44]
• precipiton reagent for Staudinger reaction and reduction of secondary ozonides



• Wu [422]
• capping reagent for oligosaccharide synthesis



• Ferreira [126]
• catalyst for oxidation of alcohols

Table 11. (Continued)

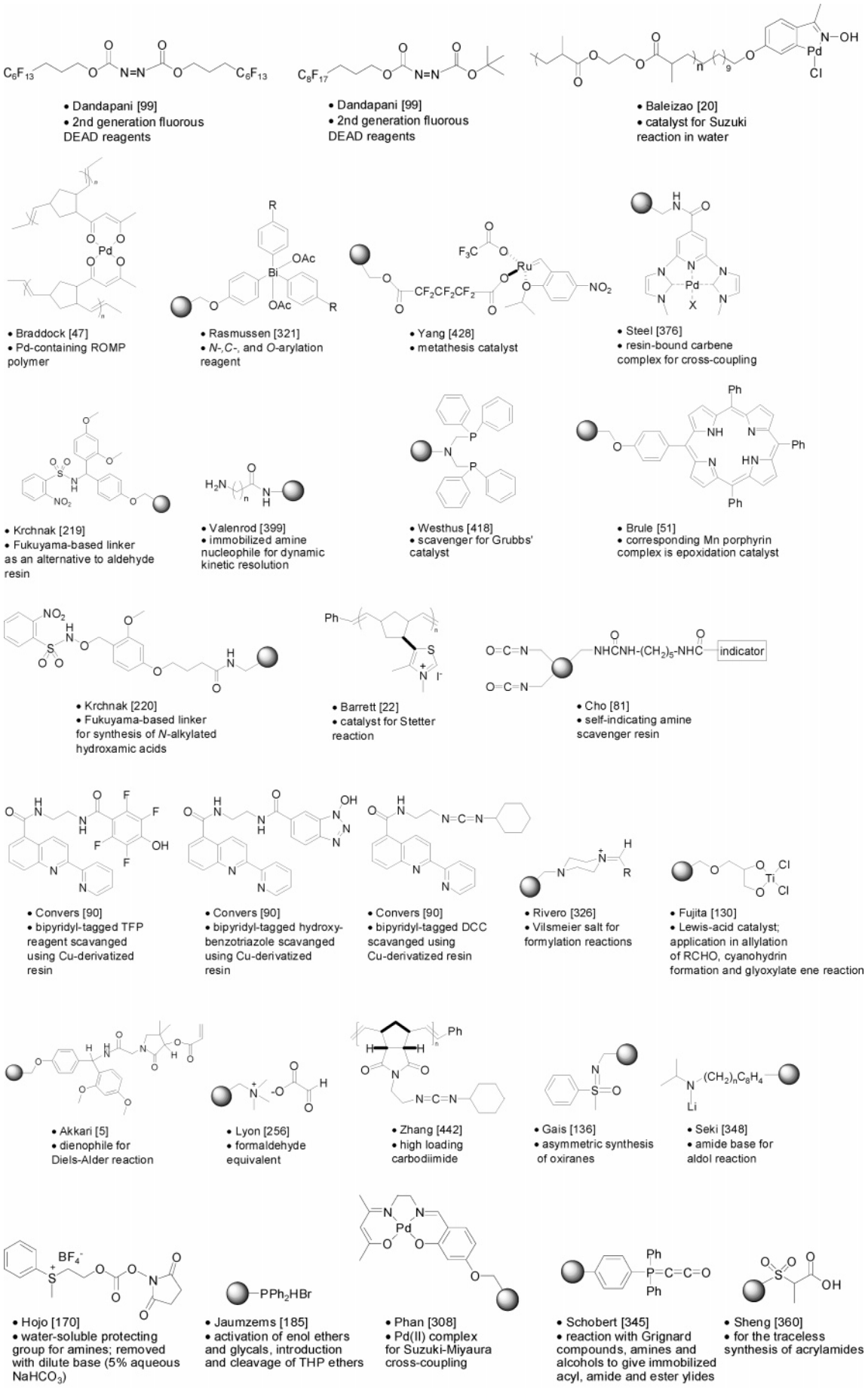
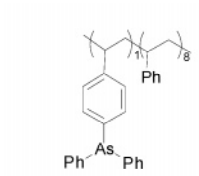
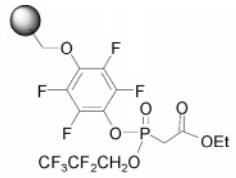


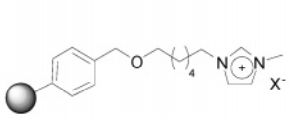
Table 11. (Continued)



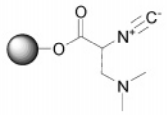
• Lau [226]
• Suzuki cross-coupling reagent



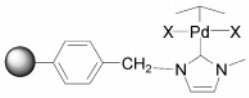
• Martina [263]
• synthesis of Z-α,β-unsaturated esters



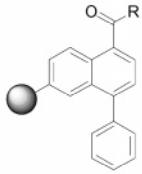
• Kim [209]
• for nucleophilic displacement reactions



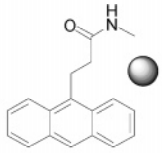
• Henkel [165]
• reaction with primary amines gives imidazoles



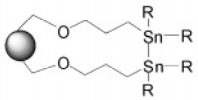
• Byun [59]
• for Suzuki cross-coupling



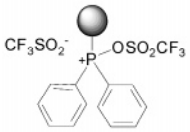
• Arseniyadis [13]
• *N*-acyl dihydroquinoline/*N*-acyl quinolinium-switch based safety-catch linker for acyl transfer reaction



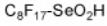
• Lei [236]
• dienophile scavenger



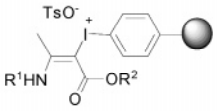
• Hernan [167]
• reagent for iodine atom transfer cyclizations



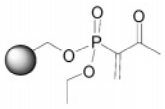
• Elson [122]
• dehydrating reagent for ester and amide formation



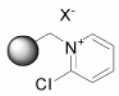
• Crich [95]
• allylic oxidation of alkenes to enones



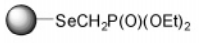
• Chen [73]
• alkenyl transfer reagent



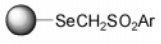
• Barrett [21]
• aldehyde to alkyne conversion



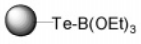
• Convers [91]
• Mukaiyama reagent on solid support for dehydration of thioureas to carbodiimides



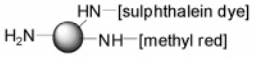
• Xu [425]
• vinylphosphonate synthesis; RCH_2X then H_2O_2-mediated elimination



• Xu [425]
• vinylsulfone synthesis; RCH_2X then H_2O_2-mediated elimination

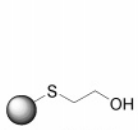


• Ruhland [335]
• traceless homolytic cleavage releasing alkyl functionality

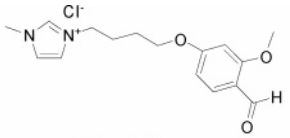


• Cho [135]
• pH indicating resin

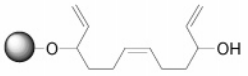
Table 12. Polymer-Supported Linkers



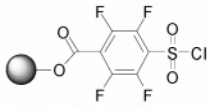
• De Napoli [103]
• Mitsunobu coupling of nucleoside bases to solid-phase



• de Kort [102]
• ionic support with acid cleavable linker (ionic analog of AMEBA resin)

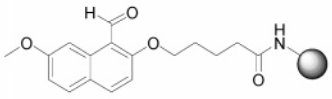


• Timmer [393]
• liberates cyclopent-2-yl alcohols via RCM; application in oligosaccharide synthesis

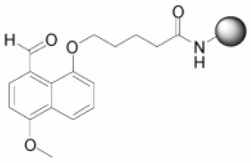


• Cammidge [62]
• solid-phase equivalent to the triflate group

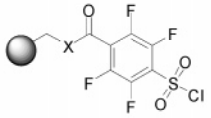
• Oikawa [294]
• formylacetal linker on soluble support



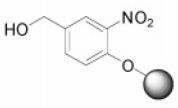
• Boas [39]
• backbone amide linker cleaved with mild acid



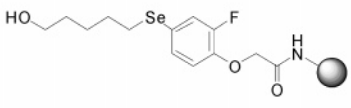
• Boas [39]
• backbone amide linker cleaved with mild acid



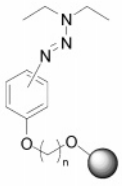
• Revell [323]
• reaction with phenols yields arylsulfonates for traceless synthesis and Pd-catalyzed cross-couplings



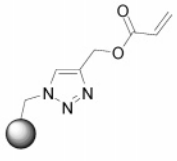
• Ohno [293]
• linker stable to strong acid or base; upon nitro reduction and acylation it is cleaved with mild acid



• Mogemark [277]
• synthesis of *n*-pentenyl glycosides

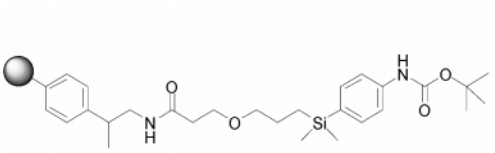


• Lazny [228]
• new triazine linkers for the direct generation of polmer-supported diazonium ions

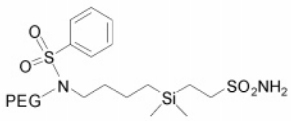


• Lober [250]
• REM resin prepared using "click" chemistry

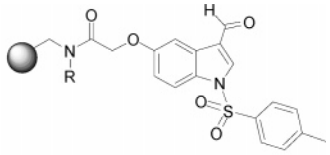
Table 12. (Continued)



• Mun [284]
• silicon based traceless linker for synthesis of amine-containing heterocycles

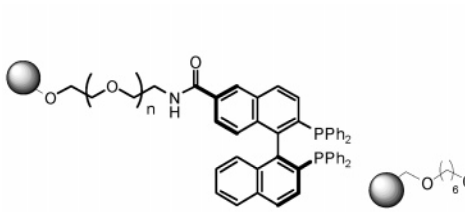


• Ribière [324]
• synthesis of *N*-supported β-aminoesters via the aza-Baylis-Hillman reaction

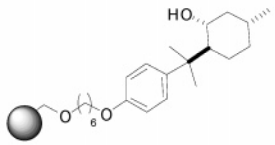


• Scicinski [346]
• safety-catch linker

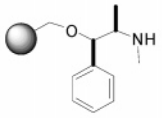
Table 13. Polymer-Supported Chiral Ligands



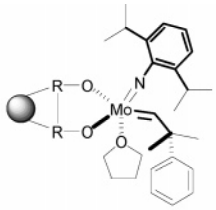
• Otomaru [299]
• for Rh-catalyzed asymmetric 1,4-addition of phenylboronic acid in water



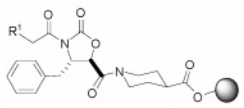
• Shintani [363]
• acylation with α,β-unsaturated acid then diastereoselective [2+2] photocyclization



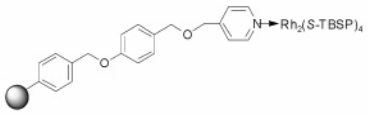
• Hutchinson [175]
• acylation then asymmetric alkylation



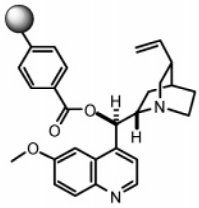
• Dolman [111]
• enantioselective olefin metathesis



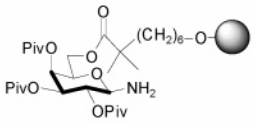
• Kotake [218]
• Evans-type auxiliary for asymmetric alkylation reactions



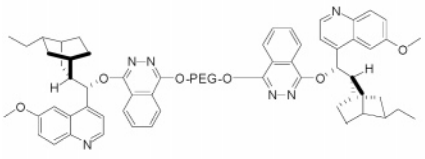
• Davies [100]
• immobilized dirhodium tetraprolinate catalyst for cyclopropanation



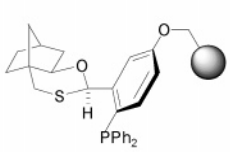
• Thierry [392]
• enantioselective electrophilic fluorination of silyl enol ethers



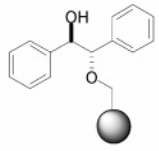
• Zech [438]
• chiral auxiliary in stereoselective synthesis of piperdines and amino acids; Piv = pivaloyl



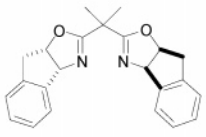
• Yang [429]
• asymmetric amino hydroxylation of alkenes



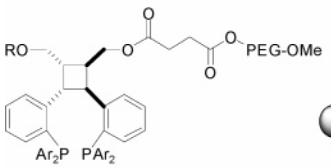
• Nakano [287]
• ligand for Pd-catalyzed asymmetric allylation



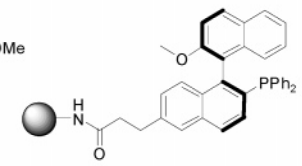
• Gaertner [134]
• stereoselective α-alkylation reactions



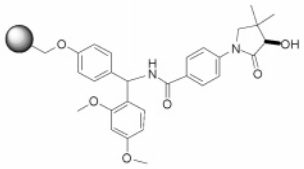
• Kurosu [222]
• asymmetric hetero-Diels-Alder reaction using resin-bound dienophiles



• Zhao [447]
• Pd-catalyzed enantioselective allyllic substitution reaction



• Hocke [168]
• asymmetric π-allylic reduction



• Akkari [4]
• chiral auxiliary for asymmetric Diels-Alder reaction

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