Review

Comprehensive Survey of Combinatorial Library Synthesis: 2003

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Reviews

Comprehensive Survey of Combinatorial Library Synthesis: 2003

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This is the seventh comprehensive survey in an ongoing annual review series in combinatorial chemistry.[1] The format remains largely the same as in past years with libraries demonstrating biological activity segregated into one of five generic target classes (Tables 1−5) and libraries without accompanying biological data segregated into one of five generic structural classes (Tables 6−10). Polymer-supported reagents and scavengers, polymer-supported linkers, and polymer-supported chiral ligands are listed separately in Tables 11−13. In preceding years, a distinction was made regarding the origin of a particular library, academia versus industry, by indicating either the company name (industry) or senior author's last name (academia) in an affiliation note field in the tables. This distinction is no longer made. All entries are referenced by the first author's last name to facilitate reference cross-checking. Some 468 total entries are captured in the tables.[2−427]

Publications of large libraries (>1000 members), which were prevalent in the late 1990s for broad screening purposes and structure−activity relationship (SAR) development, have given way to small, focused, compound arrays for lead optimization. Of the 120 biologically active libraries in Tables 1−5 with a defined number of members, 79% were under 500 members, 6% contained 500−1000 members, and 15% contained >1000 members. Researchers are increasingly utilizing both solid- and solution-phase techniques to analogue multiple regions of a lead molecule to establish SARs. Representative examples of this activity in the year 2003 include libraries for plasmepsin (library 1.4),[270] Factor Xa (library 1.11),[193] Factor VIIa (libraries 1.14−1.16),[281,282,341] caspase-3 (library 1.21),[170] dihydrofolate reductase (library 2.21),[401] p56^{lck} (libraries 2.4 and 2.5),[81,394] μ-opioid agonists (libraries 3.16 and 3.17),[141,331] ORL-1 (libraries 318 and 319),[58] LFA-1/ICAM-1 (library 4.6),[48] Kv1.5 channel (libraries 4.7 and 4.8),[290] FXR (library 4.15),[267] and antibacterials (libraries 5.10, 5.11, and 5.13).[65,424,180]

Wyss and co-workers at Hoffman-La Roche in Switzerland reported a head-to-head comparison of structure-based versus diversity-based synthon selection methods in the synthesis of dihydrofolate reductase (DHFR) inhibitor libraries.[401] A higher percentage of and more potent DHFR inhibitors were found by the former selection method. This is one of a small number of detailed accounts involving selection method comparisons, despite a great deal of published literature on the subject.[428−431]

The discovery of antagonists of protein−protein interactions remains a challenging and high-risk endeavor in medicinal chemistry. Braisted[43] at Sunesis Pharmaceuticals identified a potent IL-2/IL2Rα antagonist (IC_{50} = 60 nM) starting from a micromolar active lead. This was accomplished using a fragment assembly strategy combined with X-ray crystallography. One interesting finding was the adaptive rearrangement of the protein, yielding a binding site to accommodate small molecule fragments despite an otherwise flat featureless surface. This may have ramifications for the discovery of small-molecule antagonists against other protein−protein targets.

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Forward chemical genetics is an emerging field of study using small-molecule ligands to pan for cellular and organismal phenotype changes and retrospectively understand/identify the ligands' target(s).[432] This approach was used to identify compounds that induce neuronal differentiation in embryonic stem cells.[93] Chang developed a pretagged library to facilitate this process.[180] Hergenrother discovered selective apoptosis inducers in cancer cells.[265] Several other papers appeared on this topic,[433−440] including high-end technology for printing chemical libraries on microarrays for fluid-phase nanoliter reactions.[128] This field is closely tied to diversity-oriented synthesis generating large collections of structurally complex molecules for screening.[441]

The discovery of tyrosine kinase inhibitors,[3,81,199,394] including the application of dynamic combinatorial chemistry,[69] the identification of an endothelin A receptor antagonist back-up clinical candidate,[262] Nicolaou's FXR agonist optimization campaign,[267] and selected solution-/solid-phase methodology and heterocyclic syntheses, are presented herein.

Kinase Inhibitors. CDK5, along with its regulatory subunit p35, is a serine/threonine kinase complex that phosphorylates a variety of substrates in vivo. One of these substrates is τ-protein in Alzheimer's diseased brains. CDK5/p35, also known as τ-protein kinase II (TPKII), is constitutively activated in brain tissue of Alzheimer's patients and is known to co-localize with neurofibrillary tangles that accumulate in neuronal cell soma. These findings provide a therapeutic rationale for CDK5 inhibitors in the treatment or prevention of Alzheimer's disease. Screening of the compound file at Pharmacia, now Pfizer, turned up 4-acylamino-1,3-thiazole **1** as a CDK5 inhibitor (K_i = 0.5−2 μM) possessing reasonable specificity (∼10-fold) against the cell cycle regulatory kinase complex CDK2/cyclin A (Figure 1).[199] Nascent SAR indicated simple urea analogues **2** were inactive. An elegant catch-and-release protocol was devised to prepare two-dimensional arrays of **2** analogues. Thioureas **3** were converted to acyl azides **4** in an efficient 3-step synthesis. Heating of the acid azides **4** to 80 °C (toluene) furnished isocyanates **7** in situ, which were trapped upon addition of oxime resin to afford intermediate resin-bound carbamates **6**. Carbamates **6** were extensively washed, conveniently removing impurities generated during the thermolysis reaction. Carbamates **6** were then heated to 80 °C in toluene or 1,2-dichloroethane, regenerating solutions of isocyanates **7**, which were reacted with hydrazides or O-substituted oximes, yielding library compounds **8**. Triethylamine was found to greatly facilitate the regeneration (elimination) of isocyanate into solution and subsequent reaction with nucleophiles. Yields of several sets of libraries (library 2.2) averaged 70%, with purity of most members exceeding 80%. Although biological evaluation of library 2.2 did not reveal any strikingly more potent agents, phenoxyamine analogue **10** retained CDK5 affinity with greatly improved >100-fold selectivity versus the cell cycle kinase, CDK2/A.

A working hypothesis at Aventis, now Sanofi, was that inhibition of Janus Kinase 3 (JAK 3) may result in effective therapy for arthritis, diabetes, or other autoimmune disease states in which the immune system is up-regulated. This

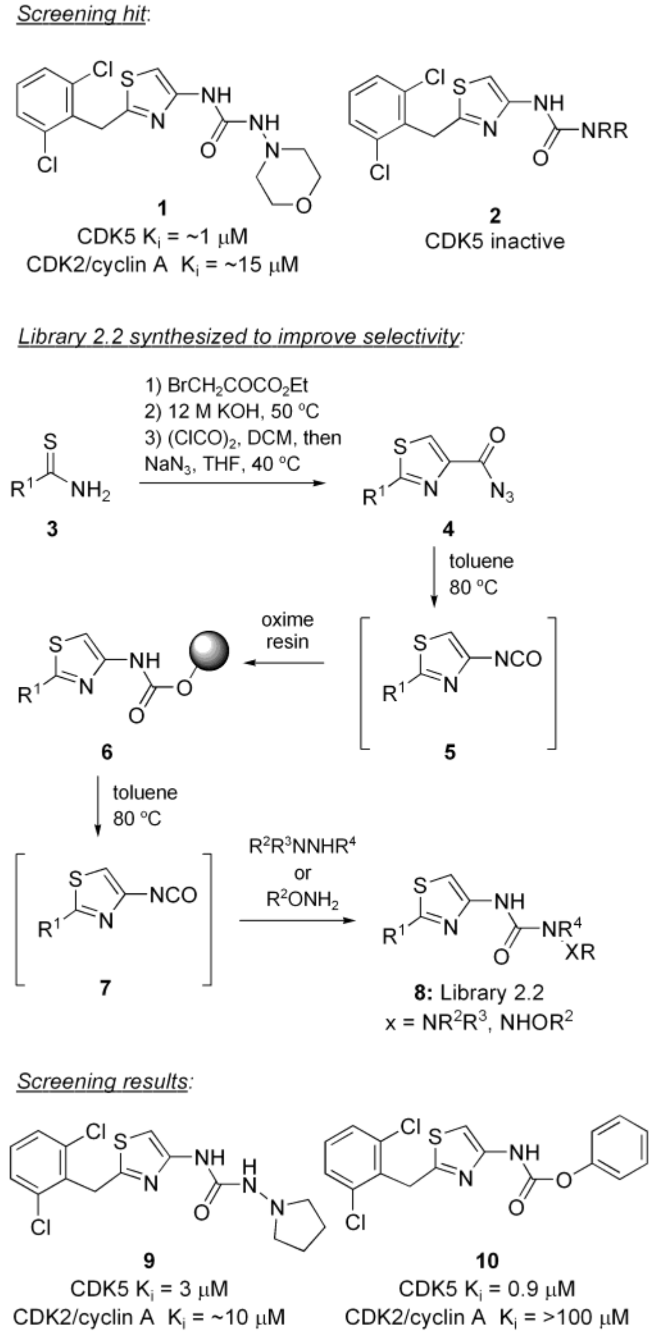


Figure 1. Catch-and-release synthesis of acylaminothiazole-based CDK5 inhibitors.[199]

hypothesis was supported in part by data showing the down-regulation of JAK 3 in certain severely immune-compromised patient subpopulations. A search of JAK 3 inhibitors originated with high-throughput screening, leading to the identification of **11** (Figure 2).[3] Lead **11** was docked into a homology model of JAK 3 kinase. The model was derived from the crystal structure of cyclic adenosine monophosphate (cAMP)-dependent protein kinase (cAPK) complex. Docking was carried out by fitting the acceptor−donor pair of **11** onto the acceptor−donor pair of ATP. This led to the pyrrole ring's projecting outward toward the solvent while the 5-position of the oxindole ring projected into an unfulfilled region of the active site. Thus, library 2.3 (**13**) was conceived as a means to explore the SAR in this region of **11**. Custom prepared oxindole cores **12** displaying hydrogen bond

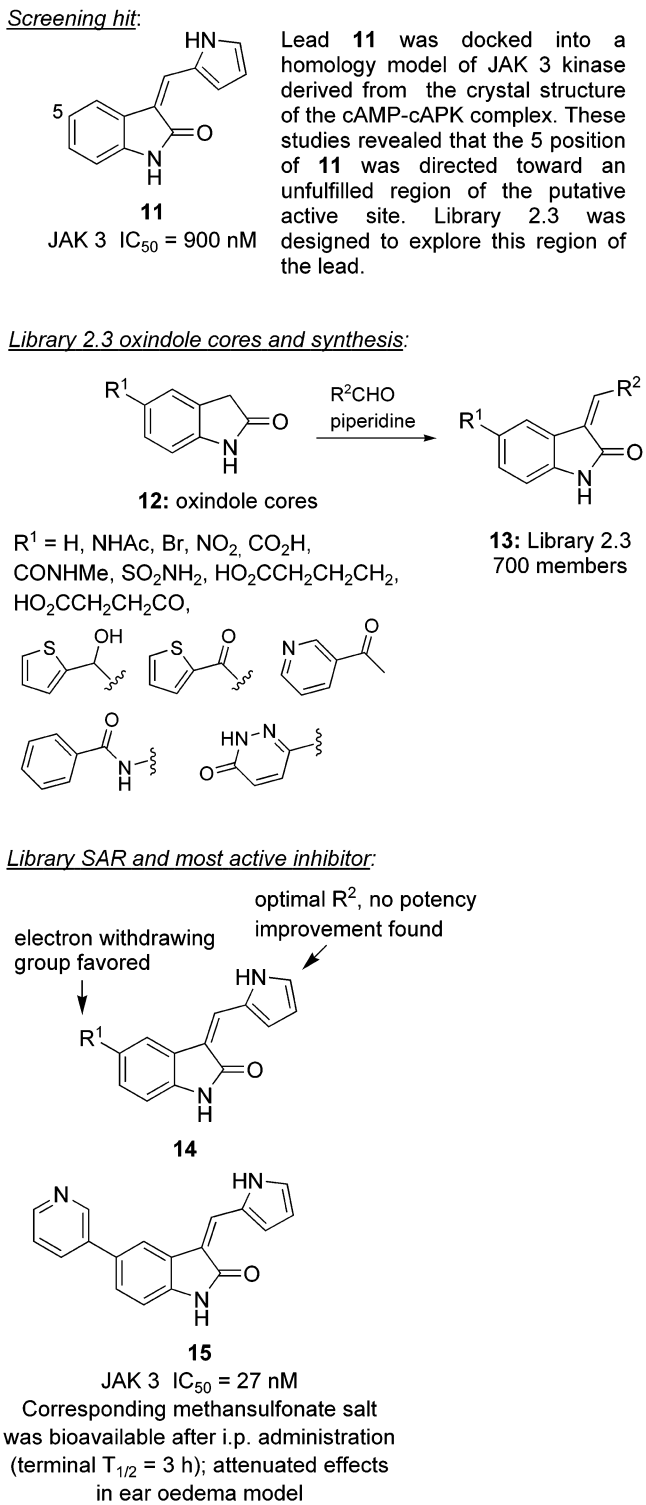


Figure 2. Janus kinase 3 (JAK 3) inhibitors.[3]

donor−acceptor, hydrophobic, hydrophilic, and negatively charged 5-substitutents were condensed with commercially available aldehydes (R^2CHO), yielding a two-dimensional array. A nascent SAR was immediately apparent upon screening against JAK 3. First, no improvement in binding affinity was observed for the broad range of R^2 inputs. The original pyrrole in **11** appeared to be the optimal R^2 appendage. However, increases in affinity were clearly associated with electron-withdrawing aryl-type substituents, as exemplified by inhibitor **15** (IC_{50} = 27 nM). Docking **15** into the homology model did, indeed, reveal deep positioning of the 5-(3-pyridyl) ring into the previously unfulfilled region of the active site. No data were given regarding kinase and other enzyme/receptor specificity. Bioavailability was observed for the corresponding methanesulfonate salt of **15** (soluble at 3.6 mg/mL) upon i.p. administration. A 200-μg dose of the salt applied topically attenuated the increase in ear weight in a murine ear oedema model.

In a third series of publications regarding kinase inhibitor discovery,[81,394] Bristol-Myers Squibb applied parallel synthesis to define SAR around **16**, a novel inhibitor of $p56^{lck}$ (Lck; Figure 3). This particular kinase is a member of the Src family of kinases. It is expressed primarily on T-cells and NK cells, playing an essential role in T-cell development, activation, and T-cell antigen receptor signaling. As was the case for the other kinase targets highlighted above, compound **16**, $IC_{50} = 3.2$ μM, was obtained from random screening of an in-house compound file. Extensive examination of substituents attached to the thiazole core led to amide **17**, IC_{50} = 35 nM and benzothiazole analogue **18**, IC_{50} = 290 nM. Parallel synthesis of amide library 2.5a (**20**) and a companion urea library, 2.5b (**25**), utilized a common set of benzothiazole amide cores, **19**. Evaluation of the libraries afforded new analogues with improved affinity. Most striking was the difference in Lck inhibition of isopropyl amide **21** (IC_{50} = 1800 nM) versus cyclopropyl amide **22** (IC_{50} = 15 nM). Simply joining the methyl groups together in **21** into a three-membered ring yielded a 100-fold increase in activity. The cyclopropyl ring could be substituted, as per **23** and **24**, without attenuation of enzyme inhibition. The cyclopropyl urea analogue **26** from the companion urea library 2.5b was not as effective a substituent as found in the amide series. Although sterically demanding R^2 substitutents were tolerated, one of the preferred agents was **27**, BMS-243177. This compound displayed an Lck IC_{50} = 4 nM and good selectivity against a panel of kinases and other enzymes and receptors. A binding model was developed using the coordinates of activated Lck kinase domain complexed to a non-hydrolyzable ATP mimic. Compound **27** is thought to bind in an extended conformation to the kinase's ATP-binding site, making several productive hydrophobic contacts and hydrogen bond interactions. BMS-243117 demonstrated activity in a T-cell proliferation assay, $IC_{50} = 1$ μM.

Dynamic combinatorial chemistry (DCC) is a molecular recognition strategy whereby building blocks react with one another reversibly under thermodynamic control in the presence of a molecular target, enzyme, or receptor, and specific members of the library are amplified on the basis of their preferred target interactions. The use of DCC was elegantly demonstrated in a proof of concept study using neuroamidinase[151] and a report by Bunyapaiboonsri.[46] In its application to the discovery of cyclin-dependent kinase 2 (CDK2),[69] oxindole and aryl hydrazine building blocks were reacted together in the presence of enzyme crystals (Figure 4). The exposed crystals in turn were subjected to X-ray crystallography, and the electron density maps so obtained furnished the ligand structure and detailed binding mode. In solution studies in the absence of protein, 5 oxindoles, **28a**−**e**, and 6 hydrazines, **29a**−**f**, were combined in 20% aqueous

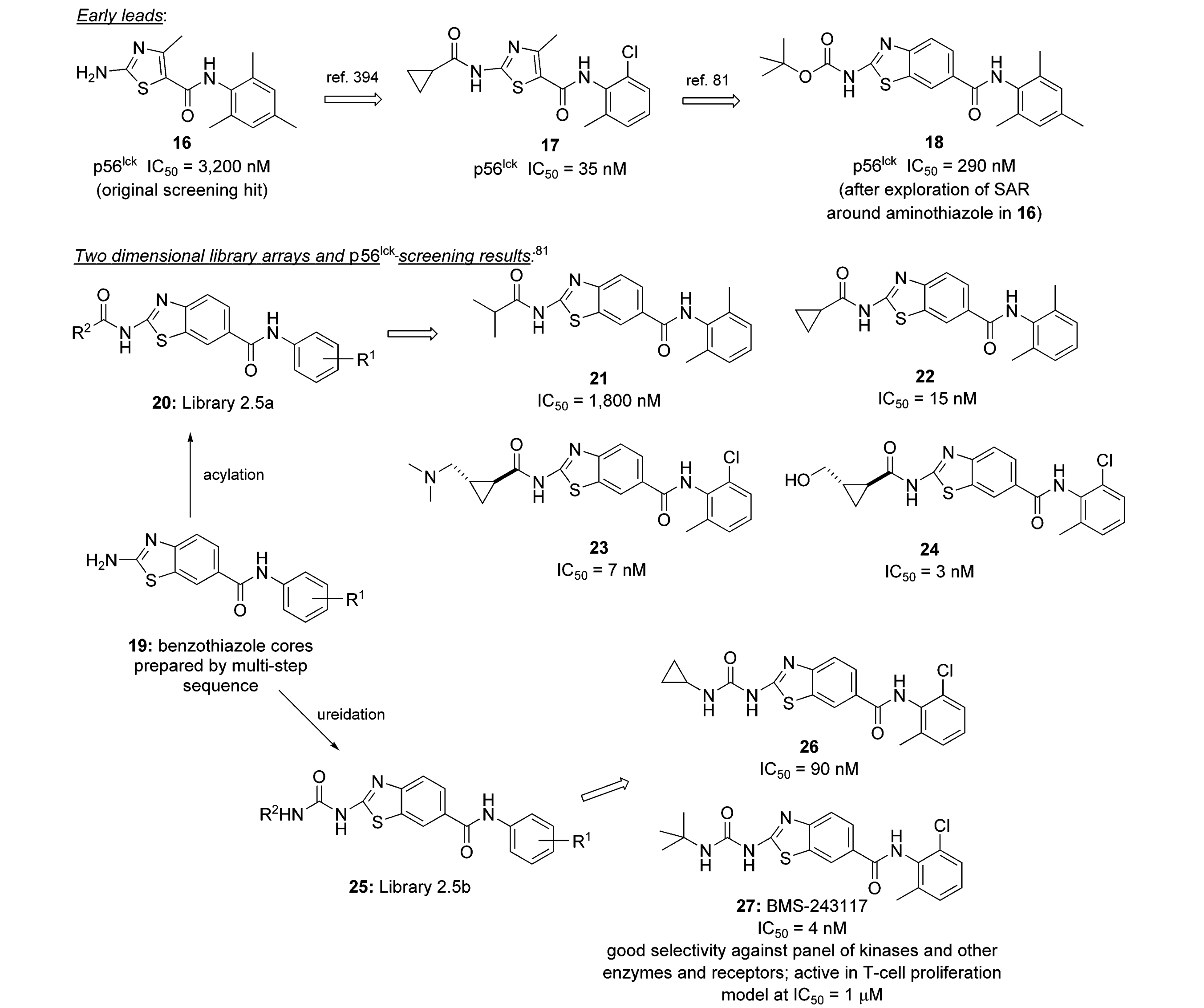


Figure 3. p56^{lck} inhibitors.[394,81]

solution of DMSO at 25 °C for 48 h. All possible combinations, 30 products in total, were found present by LC/MS. The reaction was then carried out in the presence of protein crystals. Several pilot studies were carried out with single pairs of building blocks, ultimately running the DCC at its maximal degeneracy of 30 (library 2.6). Electron density maps solved for ligand **31** in the active site. Hydrazone **31**, derived from **28b** and **29e**, was resynthesized and found to be a potent inhibitor of CDK2: $IC_{50} = 30$ nM.

Dihydrofolate Reductase (DHFR) Inhibitors. DHFR is a validated clinical target. Trimethoprin (TMP, **33**; Figure 5) is a chemotherapeutic agent used for the treatment of Gram-negative pathogens associated with community-acquired and urinary tract infections. Interest in developing DHFR inhibitors against Gram-positive pathogens, such as *Staphylococcus aureus* and TMP-resistant pathogens, prompted the synthesis of TMP analogues at Hoffmann-La Roche.[402] Compound **32**, RO-64-5781, was identified as an exceptionally potent DHFR inhibitor but suffered from high plasma protein binding and low solubility, making it difficult to formulate for clinical use. Efforts were directed toward introducing a basic nitrogen into the structural class to decrease lipophilicity and increase water solubility. Because crystal structures of DHFR-inhibitor complexes showed that the 2,4-diaminopyrimidine fragment neatly fit in the active site of the enzyme and that previous modification to this region of TMP led to inactive compounds, it was decided to retain this fragment in analogue synthesis. Intrigued by a patent report from the old laboratories at the Wellcome Foundation citing **34** as an antibacterial pyrimidine, the Roche group resynthesized **34**; however, it was found biologically inactive. Not deterred, a limited set of analogues around **34** was prepared, giving rise to **35**, which was active against a TMP-resistant DHFR enzyme obtained from *Streptococcus pneumoniae* with an $IC_{50} = 210$ nM. This stands in contrast to TMP **33** itself, which possesses an $IC_{50} = 34\,000$ nM against the resistant enzyme. In addition, inhibitor **35** had a minimum inhibitory concentration (MIC) of 4 μg/mL against the same live pathogen. Lead **35**, thus, fulfilled the initial requirement for an improved version of **33**; namely, it contained a water-solubilizing basic nitrogen. Chemistry was then optimized for high-throughput parallel synthesis. Simply reacting 5-(bromomethyl)-2,4-pyrimidinediamine dihydrobromide with amines proved problematic due

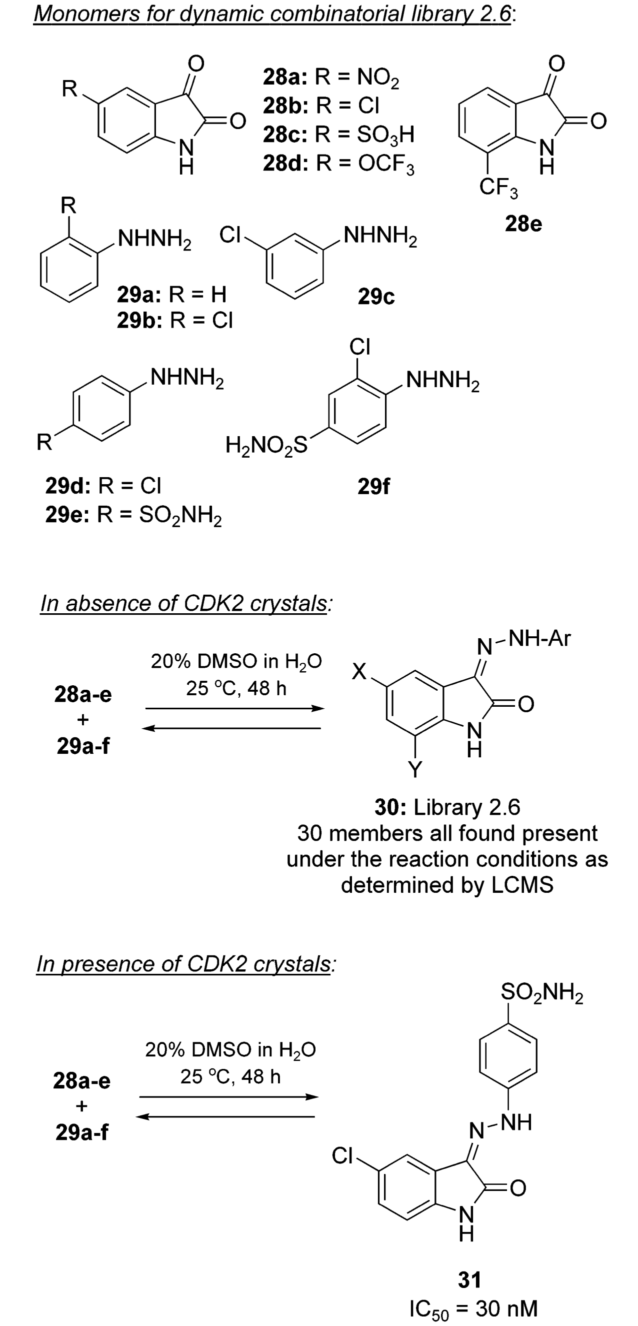
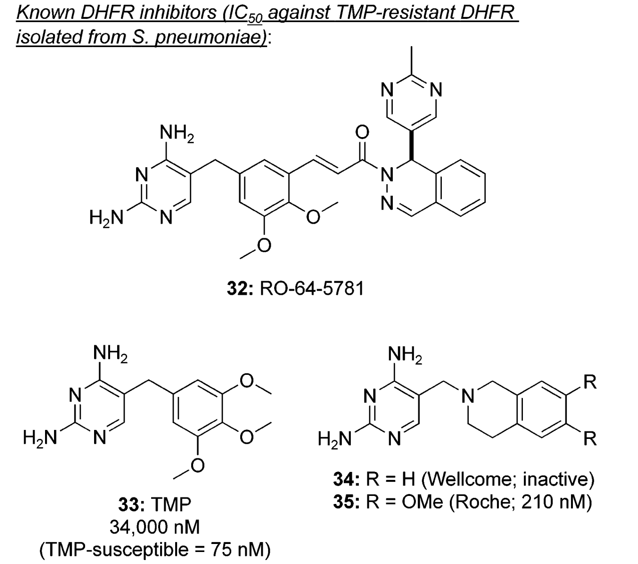
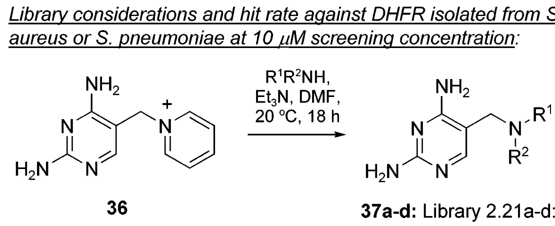


Figure 4. CDK2 inhibitors from dynamic combinatorial X-ray crystallography.[69]





Library	Synthon selection	Size	% Hits
2.21a	Structure-based (top score)	252	21
2.21b	Structure-based (low score/no docking solution)	269	1
2.21c	Diversity-based	510	3
2.21d	Analogs of hits identified from 2.21a	370	24

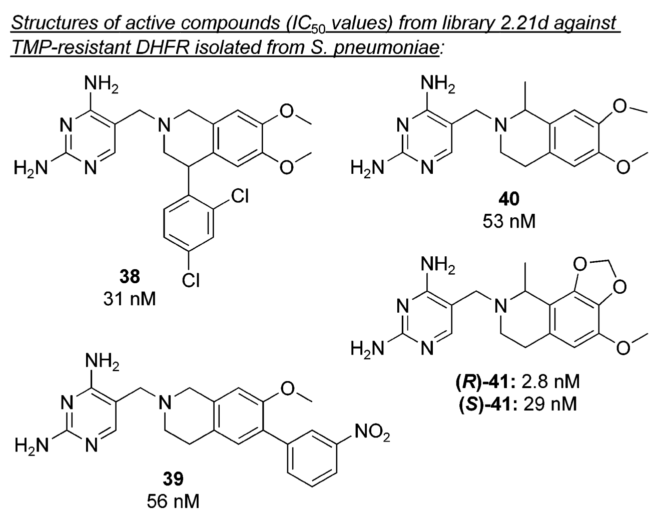


Figure 5. Structure-based versus diversity-based library design for DHFR inhibitors.[402]

to the insolubility of the bromide and formation of complex mixtures. This was alleviated by using the corresponding pyridinium salt, **36**. Over 9000 secondary amines were culled from Roche's proprietary compound file for potential library construction. To limit the number of compounds for testing yet providing meaningful SAR, the amines were analyzed by two different selection methods: structure-based selection and diversity-based selection. The former selection method relied on docking 9448 enumerated virtual library products into the crystal structure of DHFR from TMP-sensitive *S. aureus* complexed with **32**. FlexX was employed as the docking program with the 2,4-diaminopyrimidine fragment as a fixed constraint. On the basis of computed score, the 252 out of 300 top scorers were synthesized as one library (library 2.21a). A second library of 269 members was prepared, derived from 150 of the lowest scorers plus 150 randomly selected candidates for which no docking solution was found (library 2.21b). For diversity-based compound selection, the same virtual library of 9448 members was clustered according to chemical similarity. This was accomplished by superimposing pairs of library molecules at the newly formed C−N bond and then generating single conformations and maximizing volume and H-bond donor−

acceptor overlap. With the list of pairwise similarity scores in hand, compounds were clustered in a binary tree. Approximately 500 compounds adequately represented the chemical space from which the 501-member library 2.21c was prepared. All compounds in libraries 2.21a−c were assayed against bacterial and human DHFR enzymes and selected whole pathogens. Last, library 2.21d, a follow-up to hits identified from library 2.21a, was prepared. No details were given regarding amine selection for this library. Compounds were resynthesized, provided they inhibited DHFR isolated from both *S. aureus* and *S. pneumoniae* at 10 μM (>50% inhibition) and demonstrated antibacterial activity at 25 μM in the presence of 10% human serum and thymidine antagonism.

The results for this head-to-head comparison of selection methods were the following. The FlexX docking solutions filtered out largely inactive compounds, because there was a 21-fold higher hit rate in library 2.21a versus library 2.21b. Library 2.21a (structure-based) afforded a 7-fold higher hit rate versus library 2.21c (diversity-based). The hits in library 2.21a were significantly more potent than in library 2.21c. None of the 17 structures (3% hit rate) from library 2.21c were found among the 54 structures (17% hit rate) from library 2.21a (P. Wyss; personal communication). The activity of **35** was significantly improved in this exploratory study, as represented by **38**−**40**, (*R*)-**41** and (*S*)-**41**. These latter four compounds were found in library 2.21d (P. Wyss, personal communication).

Endothelin Receptor Antagonists. Compound **42** (Figure 6) is an endothelin (ET) receptor antagonist showing hemodynamic effects in phase II clinical studies for congestive heart failure. It binds selectively to ET_A, one of two G-protein coupled endothelin receptors, ET_A and ET_B. Both receptor subtypes are found on smooth muscle cells and mediate the vasoconstrictor and -pressor actions of endogenous endothelin. Researchers at Bristol-Myers Squibb developed **42**, and a backup agent was sought that would possess even greater potency and selectivity against the human ET_A receptor with improved pharmacokinetics (Figure 6).[262] The 2′-position was targeted for modification. Using both discrete synthesis and solution-phase parallel synthesis techniques, the CHO moiety in **44** was converted to CH_2X, where X = OR, NRCOR (amide), CONRR (retroamide), and N-cyclic ureas. In particular, some 160 amide-type derivatives were generated. Compounds emerged with subnanomolar ET_A binding with high selectivity against ET_B; however, they generally suffered from poor oral bioavailability that was traced to poor absorption. To overcome this issue, an additional 160 library compounds (library 3.4) were prepared with all members possessing a N-alkylated amide nitrogen to reduce the hydrogen bond donor count in the molecules by one. Exceptionally potent and selective compounds were obtained, in particular, **46** (EC_{50} = 1 pM) and **47** (EC_{50} = 20 pM). Previous PK studies in rat showed that **48** underwent O−N isoxazole bond cleavage (**48** → **49**). Thus, a final series of analogues containing an isoxazole regioisomer yielded **50** as a viable second-generation ET_A antagonist. Compound **50**, 10 pM against ET_A and 810 000 pM against ET_B, was 100% oral bioavailable (rat) and demonstrated a superior

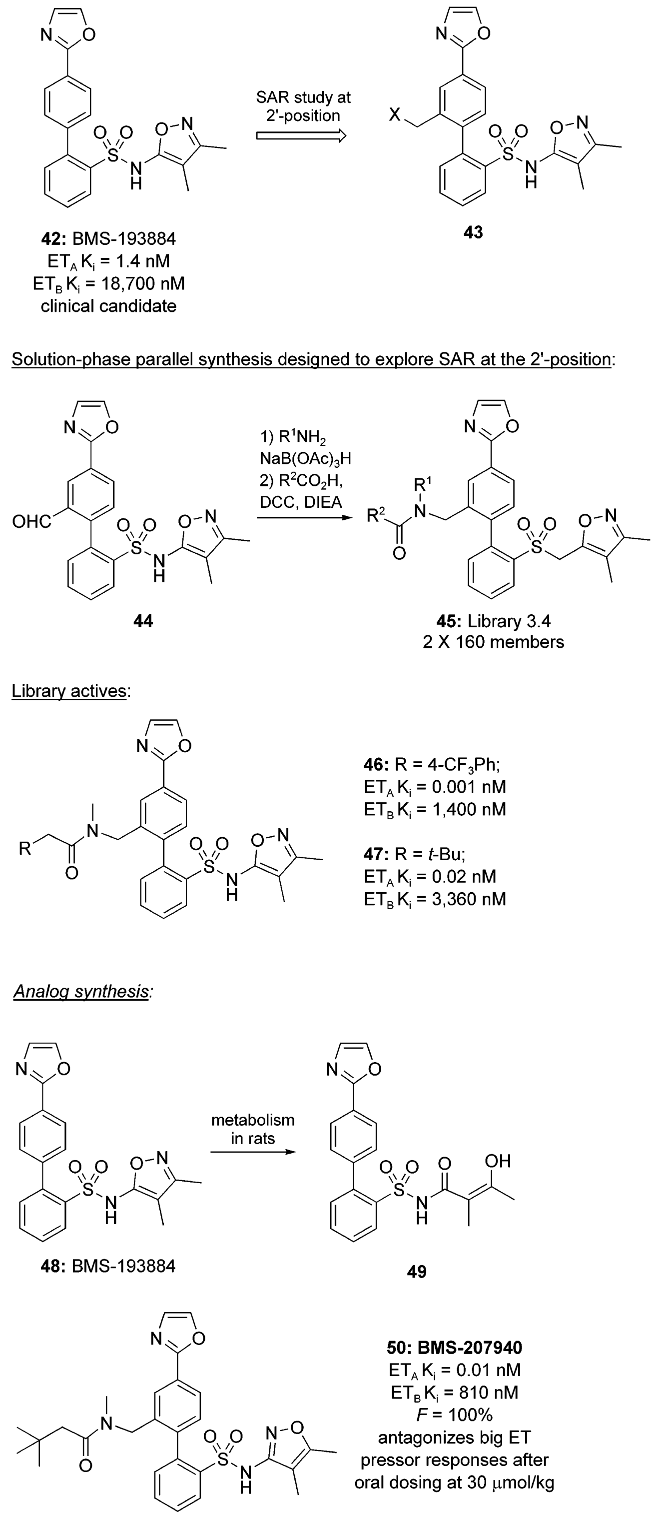


Figure 6. Second generation endothelin A and B receptor antagonists.[262]

clearance and volume of distribution profile. In rats, **50** blocked big ET pressor responses with 30-fold greater potency than the clinical agent after orally dosing at 3 μmol/kg.

FXR Activation. Nicolaou previously reported the synthesis of a 10 000-membered library of benzopyrans encoded with Rf tags. This year, the results of screening the library for farnesoid X receptor (FXR) activation utilizing a cell-based reporter assay were given (Figure 7).[267] FXR is a

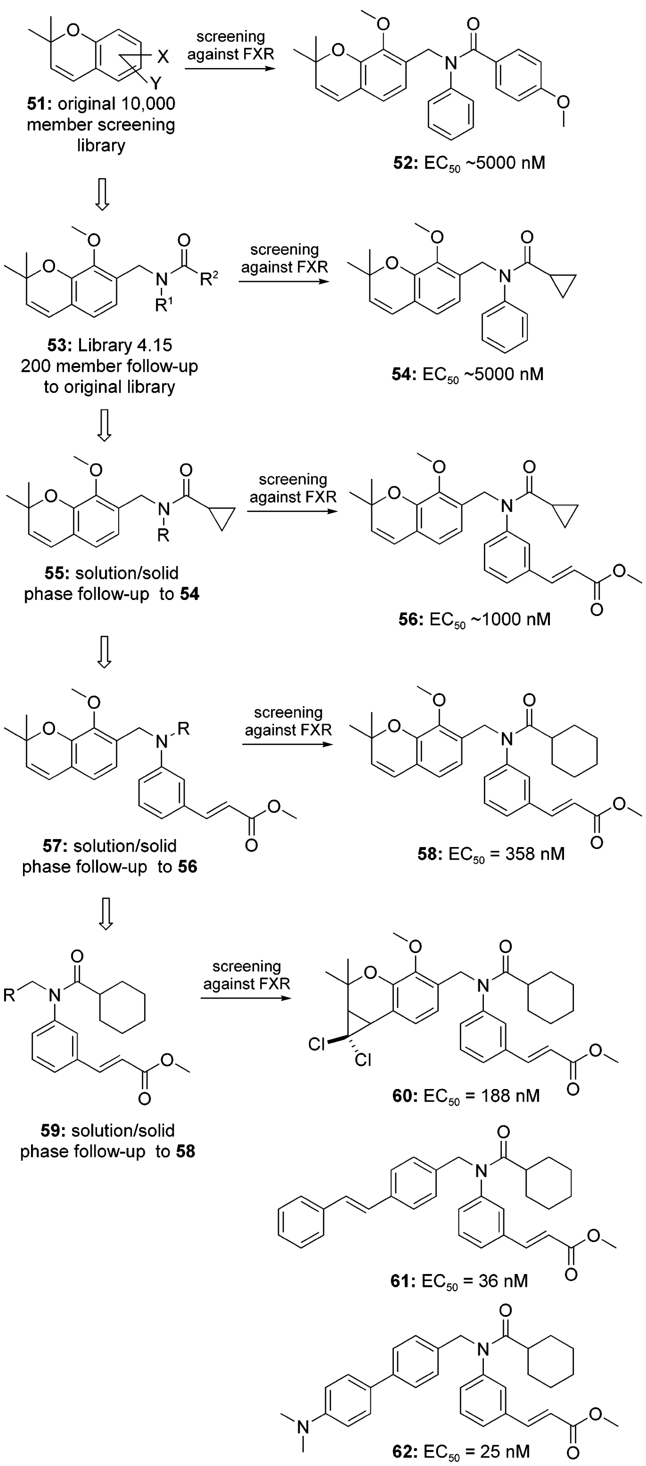


Figure 7. Nicolaou's nonsteroidal FXR agonists.[267]

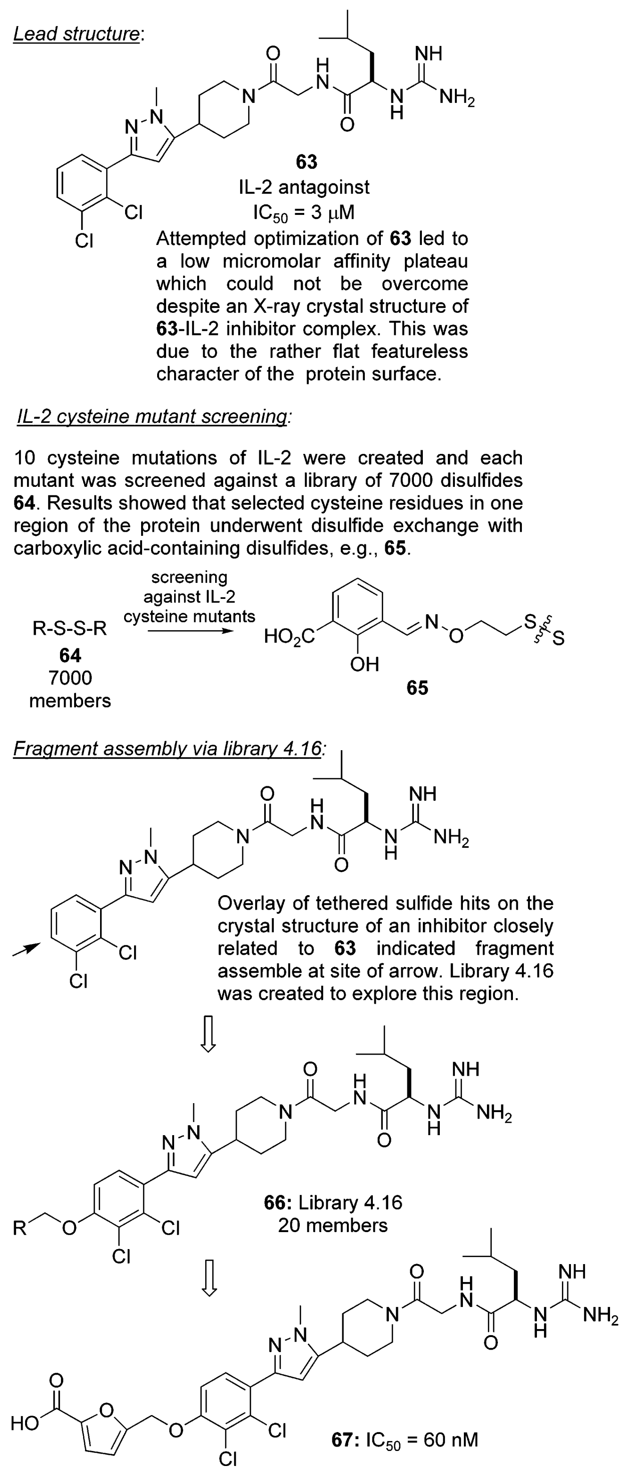


Figure 8. IL-2 inhibitors by fragment assembly.[43]

transcriptional sensor for bile acids. It is intimately linked to lipid homeostasis by controlling transcription of gene products involved in cholesterol absorption, metabolism, and transport. Selective small molecule agonists and antagonists would greatly assist in defining the physiological role of FXR. Structure **52** ($EC_{50} = 5\ \mu M$) is representative of the ~12 screening hits obtained from the original library. A benzopyran core tethered to a tertiary amide via a single methylene unit appeared to be the common pharmacophoric theme. To explore the theme further, a 200-membered follow-up library 4.15, **53**, was designed and synthesized. Library 4.15 affirmed the nascent SAR, yielding a number of actives, with **54** being selected for detailed SAR exploration. Discrete analogue preparation, solid- and/or solution-phase, parallel synthesis systematically examined three regions of **54**, *N*-aryl substituents (region 1), *N*-acyl substituents (region 2) and the aryl (benopyran, region 3). This SAR strategy **53** → **55** → **57** → **59** led to progressively more potent compounds **54** ($EC_{50} = 5000$ nM) → **56** ($EC_{50} = 1000$ nM) → **58** ($EC_{50} = 358$ nM) → **60** ($EC_{50} = 188$ nM)−**62** ($EC_{50} = 25$ nM) as each region was optimized sequentially. A significant breakthrough in FXR agonist potency came from incorporation of the acrylic ester moiety into the *N*-phenyl ring (**54** → **56**). Further increases in potency were

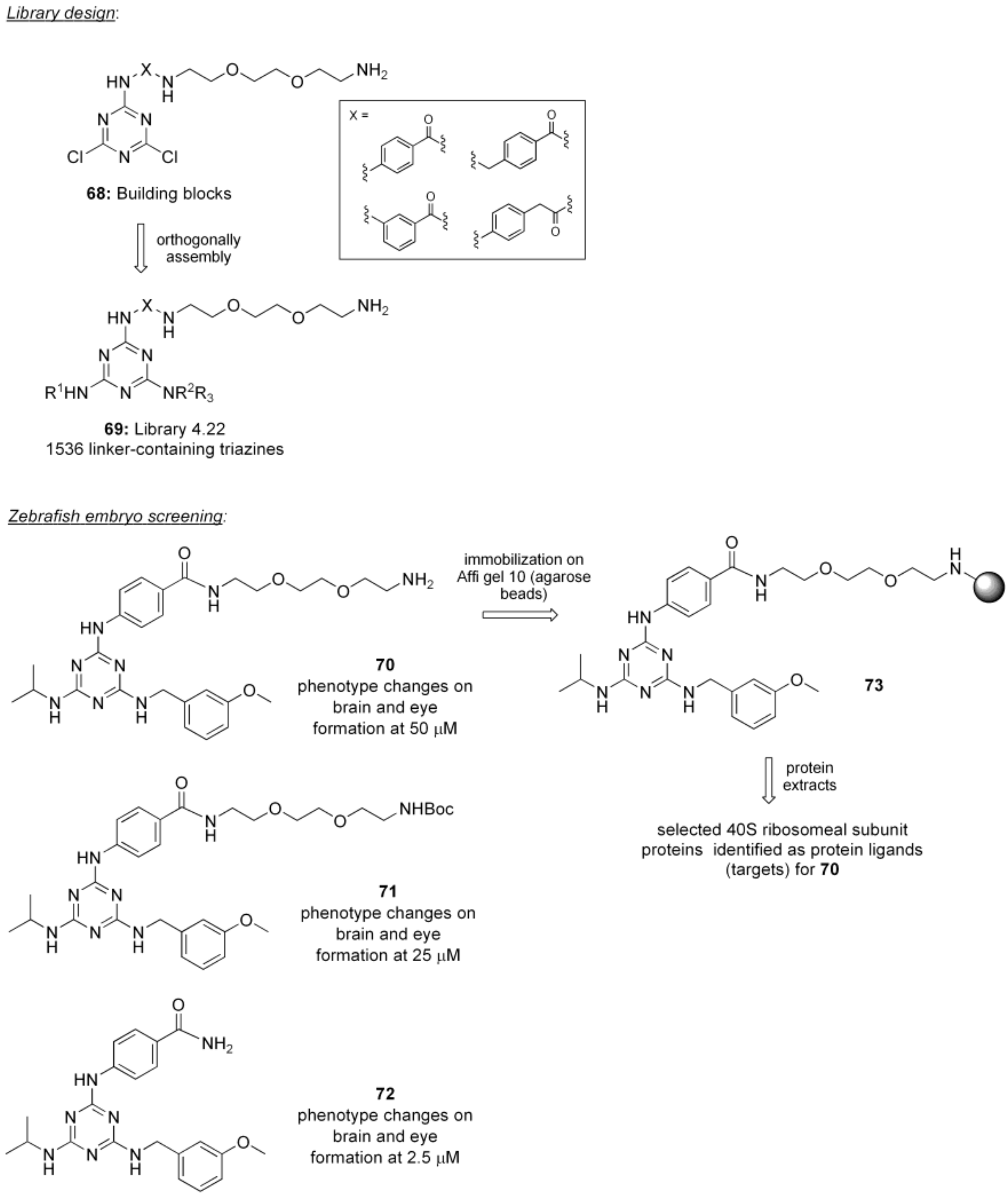


Figure 9. Tagged triazine library for forward chemical genetic studies.[185]

achieved when the benzopyran was replaced by a biaryl or a stibenyl unit. Indeed, **60**−**62** (EC_{50} = 25−188 nM) are the most potent FXR agonists reported to date and may find utility as pharmacological tools to elucidate the complex physiological role of the transcriptional bile acid sensor; however, be further considered as drug leads, several potential liabilities would have to be addressed. First, the methyl ester would likely rapidly hydrolyze in blood to the carboxylic acid, an inactive FXR analogue. Second, the optimized leads contain an α,β-unsaturated ester. This functionality is notorious for indiscriminate alkylation of bioactive nucleophiles in vivo, leading to toxicity. Cyclopropanation and reduction of the double bond led to analogues with higher EC_{50} values. The overall high logP of the class may translate to a poor pharmacokinetic performance. Nonetheless, the identification of **60**−**62** represents an important first step in finding agents that may treat disease associated with the accumulation of toxic bile acids.

IL-2 Receptor Antagonists. Finding high affinity small molecules that antagonize protein−protein interactions remains one of the most challenging and high-risk tasks in medicinal chemistry. Given their large contact area and flat featureless surfaces, small molecules generally bind weakly (micromolar level) to such systems, because there is little to confer binding energy. Recently, the research group at Sunesis Pharmaceuticals discovered small molecule **67** as a 60 nM antagonist of IL-2/IL2Rα (Figure 8).[43] This significant breakthrough came after several years of intense study of this protein. Initial attempts to optimize lead **63**, IC_{50} = 3

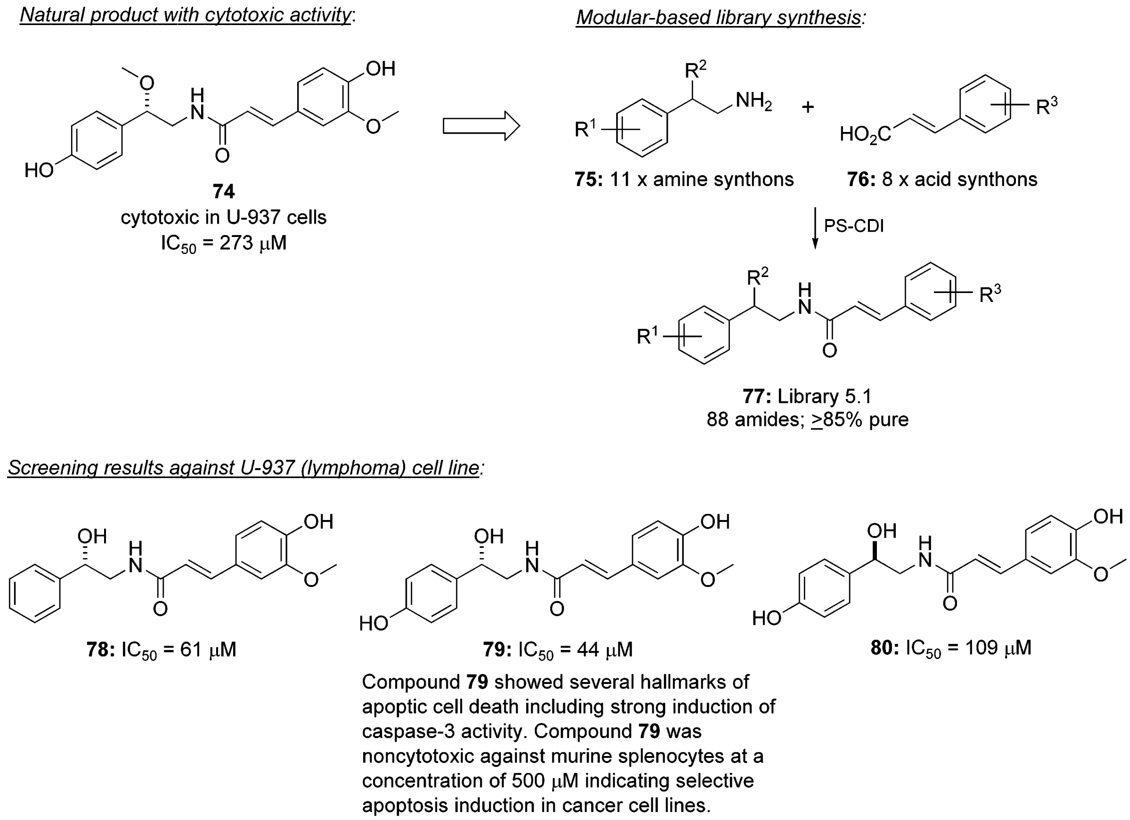


Figure 10. Small molecule apoptosis inducers.[265]

μM, through discrete and parallel synthesis of a large number of analogues proved unsuccessful. A micromolar plateau in activity was obtained, reaffirming the intractable nature of IL-2, as reported by other research groups. To overcome this activity barrier, the group turned to the X-ray crystal structure of RO26-4550 bound to the surface of IL2. Ro26-4550 was a 3 μM small-molecule IL-2/IL2Rα antagonist previously reported by Tilley and co-workers at Roche.[442] Analysis of this complex revealed that IL-2 underwent a significant adaptive change in its surface, creating a binding pocket, or "hot spot" accommodating Ro26-4550. This binding pocket was otherwise nonexistent on the surface of IL-2. Attempting to take advantage of this finding, 10 individual cysteine mutants were generated to scout out the perimeter of the hot spot. Each mutant was exposed to a library of 7000 disulfides, **64**. It was hoped that disulfide exchange might occur with some measure of functional group preference and thus provide "fragments" which might be tethered in some fashion to **64** to improve its affinity. Very few mutants showed fragment bias, but one region accessed by two different cysteine mutants selected small aromatic carboxylic acids. An overlay of the fragments with the crystal structure of a closely related analogue of **63** suggested tethering at the para position of the 2,3-dichlorophenyl ring in **63**. Library 4.16 was then synthesized. Evaluation of the 20-member library led to several IL-2/IL2Rα antagonists possessing submicromolar binding. The most potent of these was **67**, $IC_{50} = 60$ nM.

Forward Chemical Genetics. Forward chemical genetics, using small molecules to induce phenotype changes and retrospectively identifying the molecular basis for the change, is a potentially powerful technique to search for novel drug candidates and their targets.[433−440] In some instances, when a small molecule effects a phenotype change, it is desirable to attach the small molecule to an affinity matrix.[93] The matrix is then used to "fish out" a putative target protein(s) that may assist in elucidating the underlying molecular mechanism(s) responsible for the effect. One of the challenges has been the need for post-SAR study invariably required to introduce a linker (affinity matrix attachment) somewhere in the small molecule effecter without impacting its biological activity. This is not always successful. As a result, Chang and co-workers at New York University,[185] have taken the strategy of designing tagged libraries directly, that is, libraries of compounds already possessing a linker (Figure 9). Hits from tagged libraries should require little post-SAR study and may, therefore, be directly attached to an affinity matrix for target identification. To demonstrate the value of the tagged library approach in forward chemical genetics, a library of 1536 tagged triazines was synthesized (**69**; library 4.22). This was accomplished by using building blocks **68** derived from cyanuric chloride and requisite aryl poly(ethylene glycol)-type amides. The library compounds were screened for brain/eye morphological changes in a zebrafish embryo. Compound **70** significantly altered phenotype changes in brain and eye morphology at 50 μM. Boc analogue **71** and des-linker analogue **72** were subsequently prepared and found more active than **70**, with **72** inducing change at a minimum inhibitory concentration of 2.5 μM. These data indicate that the linker was not responsible for the observed biological activity and that **70** may be a good candidate for attaching to an affinity matrix. Coupling of **70**

to Affi gel 10 afforded immobilized **73**. Freshly prepared protein extracts were then loaded onto the affinity matrix by gently rotating protein extract and beads at 4 °C for 12 h. The beads were extensively washed, and the bound proteins were resolved by 14% SDS−PAGE and detected by silver staining. Two bands at 23 and 18 kDa were observed, and specificity was confirmed. The bands corresponded to four 40S ribosomal subunit proteins, suggesting that **70** may interfere with the function of a corresponding protein complex which includes the four proteins.

Etoposide, doxorubicin, and camptothecin are potent inducers of apoptosis in certain types of cancers. These powerful chemotherapeutic agents have side effects associated with their action on otherwise healthy cells. Agents that may selectively induce programmed cell death in cancer cells versus noncancerous cells would represent a major therapeutic advance. With this ambitious goal of identifying just such molecules, Hergenrother synthesized the 88-member cinnamide library 5.1 (Figure 10).[265] The design was modeled after N-acylated aromatic amines displaying pro- or anti-apoptotic action, including natural product **74**. Upon synthesis and testing, **74** was weakly cytotoxic (IC_{50} = 273 μM) in U-937 cells (lymphoma cell line). The two-dimensional library 5.1 (**77**) was generated from 11 amine synthons **75** and 8 cinnamates **76** in solution using resin-bound carbonyl diimidazole (PS−CDI). The average purity of the products was 85%. Library compounds were screened at 100 μM against two cell lines, U-937 and HL-60 (leukemia). IC_{50} values were assessed for three of the most potent compounds, **78**−**80**, after resynthesis and purification. Compound **79** (IC_{50} = 44 μM, U-937) was ~6-fold more potent than natural product **74**. Cell death was believed to be an apoptotic versus a necrotic event based on, among other biochemical indicators, strong induction of caspase-3 activity. Most significantly, incubation of dividing splenocytes with 500 μM of **79** showed virtually no toxicity. Splenocytes are routinely used to assess the toxicity of small molecules. These data, together with similar low toxicity against noncancerous T-cells, suggest **79** is a selective apoptosis inducer of cancerous cells. The molecular basis of this selectivity remains the subject of future research.

Linkers and Reagents. Waldmann published two full papers on the development of a traceless phenylhydrazide linker[345] and its application in the design and synthesis of a library (**92**; library 2.7) of tyrosine kinase inhibitors (Figure 11).[346] Adipic acid-modified TentaGel, Polystyrol, and ArgoPore resins provided carboxylic acid functionalized polymeric supports, **81**, to which aryl hydrazines were then conveniently coupled employing standard DIC/HOBt reagents, yielding **83**. Two cleavage cocktails were devised for the traceless oxidative cleavage of **83**, releasing the aryl ring **84**. In one cocktail, resin is suspended in neat *n*-propylamine containing 0.5 equiv of $Cu(OAc)_2$ and is shaken for 2 h at 25 °C with oxygen bubbled through the mixture. Alternatively, methanol and 10 equiv of pyridine may replace *n*-propylamine as solvent (cocktail 2). THF may be added to ensure sufficient swelling of the resins. The cleaved products are then treated with polyamine scavenger tris(2-aminoethyl)amine resin to remove traces of residual copper

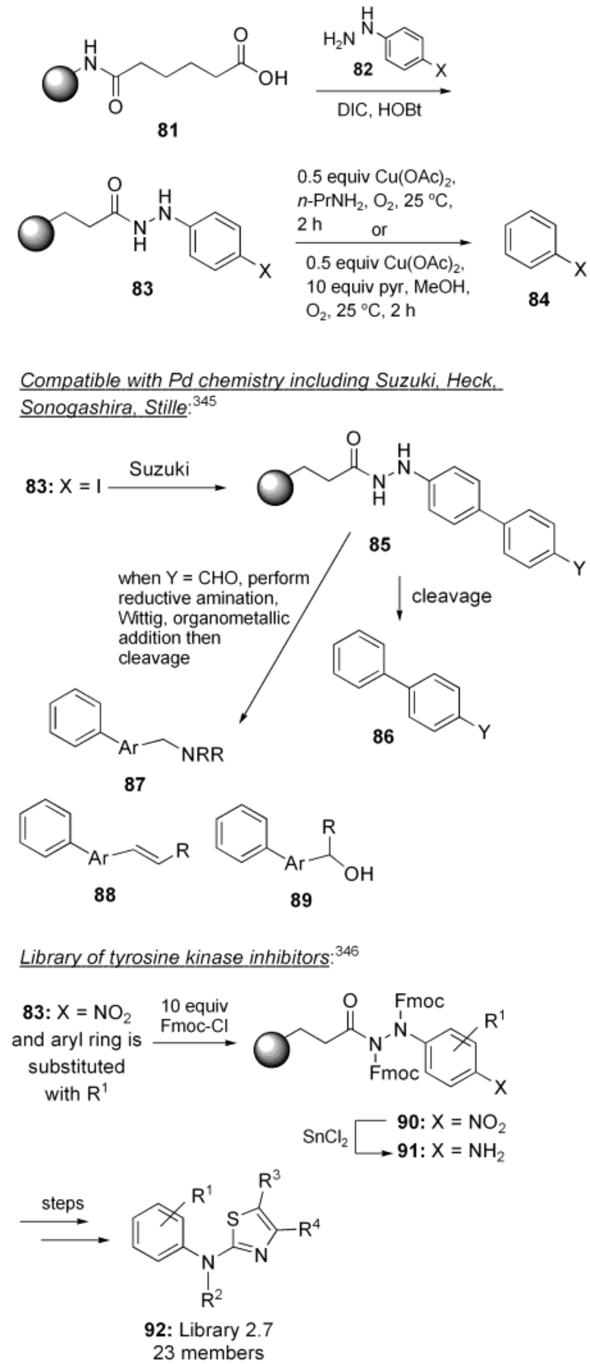


Figure 11. Traceless phenylhydrazine linker.[345,346]

(99.99% removal as determined by atom absorption spectroscopy). The hydrazide linker is compatible with Pd-mediated coupling chemistry (Suzuki, Heck, Sonogashira, Stille), organometallic reagents, and the Wittig reaction. For the synthesis of the tyrosine kinase library **2.7**, the hydrazide NH moieties were protected as their bis-Fmoc derivative on resin using excess Fmoc chloride. This allowed selective manipulation of a latent anilino group to a thiazole ring (**83** → **90** → **91** → **92**).

The attachment of amines to solid support is a relatively straightforward process routinely carried out using a carbamate linkage. It involves displacement of nitrophenol from carbonate-type resin **93** simply by stirring a suspension of the resin in a suitable solvent (DMF) containing an aliphatic primary or secondary amine (Figure 12). This chemistry fails,

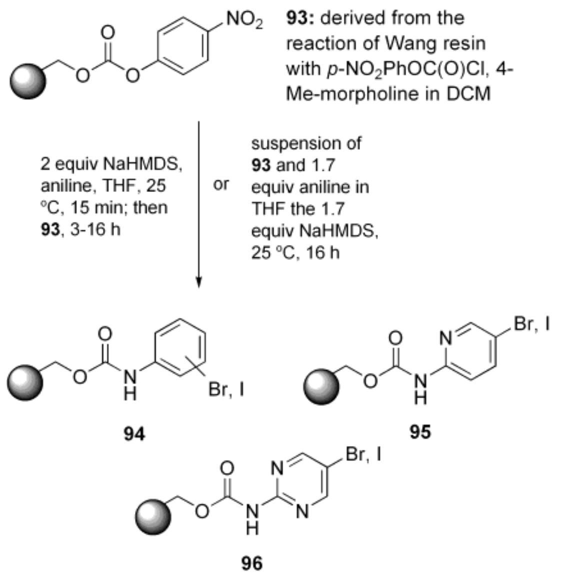


Figure 12. Attachment of unreactive amines to solid support.[426]

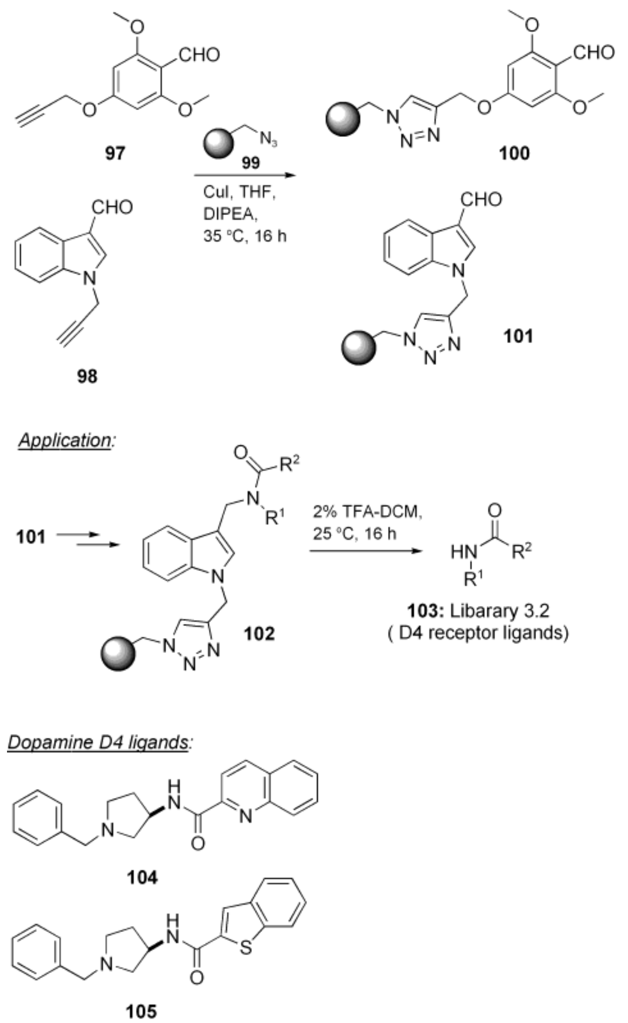


Figure 13. Click linkers.[229]

however, with deactivated amines, such as anilines. Zhu[426] studied the coupling of unreactive amines to resin **93** in detail, and reaction conditions were ultimately found to attach anilines, 2-aminopyridines, and 2-aminopyrimidines to resin with high loading. This was accomplished by pretreatment of a THF solution of the aniline with NaHMDS for 15 min at 25 °C, followed by the addition of resin **93** and shaking the resulting suspension for 3−16 h. Alternatively, a suspension of **93** and 1.7 equiv of aniline in THF is treated with 1.7 equiv of NaHMDS. The latter conditions minimize dimerization that occurs with the 2-amino-5-halopyrimidine substrates. Resin-bound halogen-containing anilines **94**, aminopyridines **95**, and aminopyrimidines **96** were subjected to Suzuki coupling. The purity and yields for some 45 phenyl-substituted aryl and heteroarylamines were reported.

A new family of solid-phase resins was described by Gmeiner (Figure 13).[229] A solution of propargyl ether **97** or **98** was added to a suspension of azide resin **99** in THF and DIEA containing CuI. Shaking the reaction mixture at 35 °C for 16 h afforded functionalized resin products **100** (BAL-type) and **101**, respectively. The 1,3-dipolar cycloaddition reaction was efficient and high-yielding. The "click" backbone linker **100** was reductively aminated, acylated, and then cleaved with TFA to yield a 5 × 5 library of amides (**103**, library 3.2) from which compounds **104** and **105** were identified as dopamine D4 ligands.

Polymer-supported triacetoxyborohydride **107** was introduced by Argonaut Technologies for selective reductive amination of aldehydes and ketones (Figure 14).[32] The more well-known standard reagent, polymer-bound cyanoborohydride, requires moderately strong acidic conditions and is incompatible with acid-labile functionality. In addition, it is restricted to the reduction of preformed imines, because it lacks chemoselectivity, reducing both imine and carbonyl substrate. Sodium triacetoxyborohydride is a preferred reducing agent in solution because of its compatibility with a variety of functional groups, but it suffers from moisture sensitivity and poor solubility in common organic solvents. In contrast, bound triacetoxyborohydride **107** has the advantages of high chemoselectivity under neutral reaction conditions and is largely insensitive to moisture. The reagent, referred to as MP-triacetoxyborohydride (MP = microporous) is quantitatively generated upon heating commercially available MP-borohydride with 3 equiv of glacial acetic acid. The capacity of the new reagent is on the order of 2.0 mmol/g. The isolated resin contains ~10% residue THF, which is critical to maintaining activity and long shelf life. Reducing reactions are performed in THF with 2.5 equiv of **107**. In the case of preparing secondary amines, the corresponding primary amine is used in 20% excess over the carbonyl compound to avoid dialkylation. Excess amine is then scavenged with PS-benzaldehyde. In the case of teriary amine synthesis, the carbonyl compound is the limiting reagent and excess amine scavenged with PS-isocyanate. Excellent yields and product purity were reported for primary amines, cyclic and acyclic secondary amines **109**−**114** in combination with 1,4-cyclohexanedione monoethylene ketal (acid sensitive), acetophenone, and assorted aromatic and aliphatic aldehydes and ketones, **115**−**120**.

Ley employed an interfacial polymerization approach to microencapsulate osmium tetroxide in a polyurea matrix (OS EnCat; Figure 15).[217] This transition metal catalyst is best known for the synthesis of syn diols from olefins. Its toxicity and volatility make operational handling difficult on a large

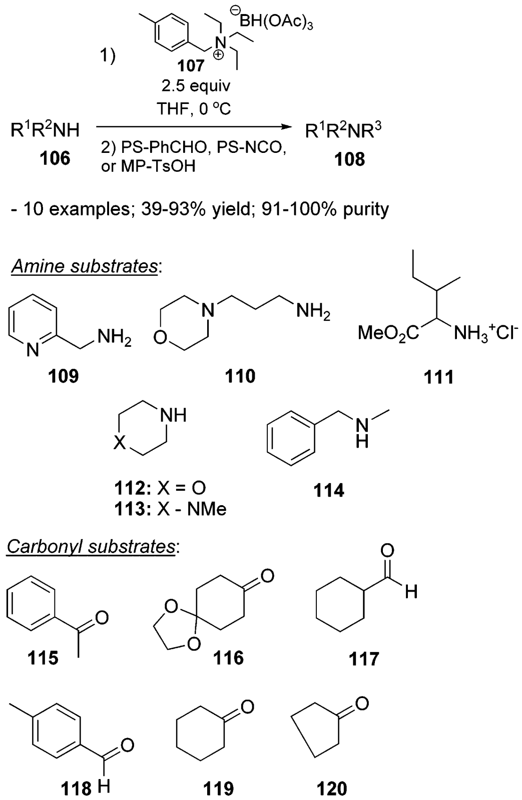


Figure 14. Resin-bound triacetoxyborohydride.[32]

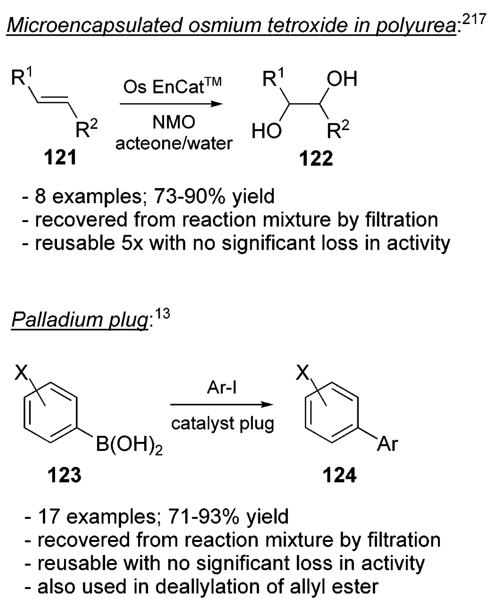


Figure 15. Catalysts in polymer matrixes.[217,13]

scale. An experimental method was given for the preparation of OS EnCat that involves the dispersion of a solution of polymethylene polyphenylene diisocyanate and OsO_4 in an organic solvent (Solvesso 200) into an aqueous mixture containing surfactants. The microemulsion is stirred (cured) for 36 h to yield insoluble OsO_4-containing polyurea microcapsules. Os EnCat was effective in the dihydroxylation of a set of mono-, di-, tri-, and tetra-substituted olefins using 5 mol % (loading based on the amount of metal employed for polymerization) and NMO as co-oxidant in 10:1 acetone/water at 25 °C **(121−122)**. The reagent was recovered by simple filtration and reused five times without significant

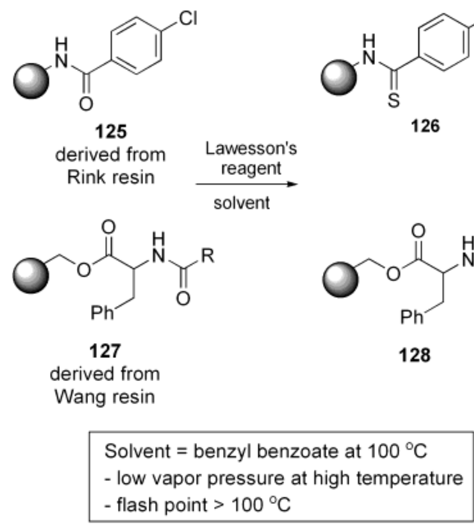


Figure 16. Benzyl benzoate as solvent for high-temperature parallel reactions.[66]

loss in activity. There was no cross-contamination when recycled catalyst dihydroxylated different substrates, nor was there evidence for metal leaching out of the matrix. It is thought that the polyurea backbone may hydrogen-bond to the transition metal, preventing its escape from the microencapsules. Palladium (II) acetate has also been microencapsulated.

Suzuki cross-coupling may be accomplished using a resin plug-bound palladium catalyst (Figure 15). As reported by Bradley,[13] the resin-plug catalyst is easily separated from a reaction mixture and can be recycled. The plug, prepared by sintering high-density polyethylene with Merrifield resin and derivatizing with Ph_2PLi, then exchanging with $Pd(PPh)_4$, is also effective in deprotection of allyl esters.

Alternative solvents for elevated-temperature solid-phase parallel synthesis was investigated by Coats.[66] The impetus for this work was derived from a need to parallel process a large number of amide thionation reactions using Lawesson's reagent (Figure 16). The resulting thioamides were earmarked for preparing resin-bound 1,3 dipoles. Traditional solvents were unsatisfactory due to issues with solvent evaporation and migration and hazards associated with the flash point of escaping vapor, leaking reaction solution/vessel failure, and unnecessary personal exposure. Alternative, albeit less common, solvents were selected on the basis of boiling point (>250 °C), low vapor pressure (<0.01 mmHg at 25 °C), low chemical reactivity, good thermal stability, and reasonable bead-swelling properties. Some 19 solvents were chosen and examined, first on their ability to swell resin, then on the evaluation of their performance in the Lawesson's thionation reaction. Examples included toluene, xylene, silicon oil, corn oil, light mineral oil, diphenylmethane, adiponitrile, bis(2-butoxyethyl)ether, *n*-hexadecane, dibenzyl ether, *N*-benzyl-2-pyrrolidone, benzyl benzoate, and several others. Benzyl benzoate provided high conversion of **125** to **126** and could be performed in an open vessel heated to 100 °C for 1 h (98% yield after TFA cleavage). Similar results were obtained with this nontraditional solvent for a range of amide substrates, including the conversion of ester amide **127** to thioamide **128**.

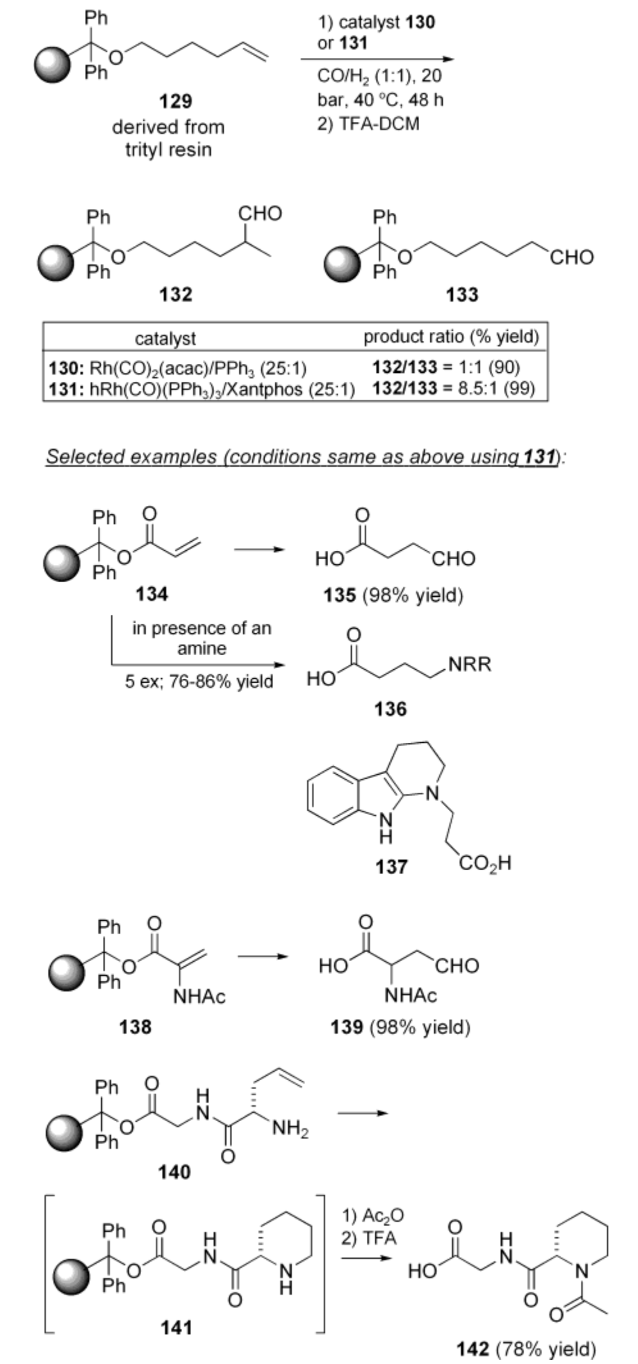


Figure 17. Hydroformylation on solid support.[89]

Taddei and co-workers carried out the first examples of the hydroformylation of resin-bound terminal alkenes (Figure 17).[89] Two catalysts were investigated in initial experiments with hexenol resin **129**. A vial containing beads **129** and catalyst **130** in toluene was placed in a stainless steel autoclave pressurized with syngas (CO/H_2 1:1) at 20 bar. The reaction mixture was stirred at 40 °C for 48 h furnishing a 1:1 mixture of **132** and **133** in 90% yield. Stirring was found to be critical for a successful reaction, and a special "basket in a vial" apparatus was designed to allow agitation of the solution without damaging the beads. The ratio of **132** to **133** was improved to 8.5:1 by switching to rhodium catalyst **131** under the same reaction conditions. Regiochemistry of the hydroformylation was much greater for the acrylate substrates **134** and **138**. When the hydroformylation

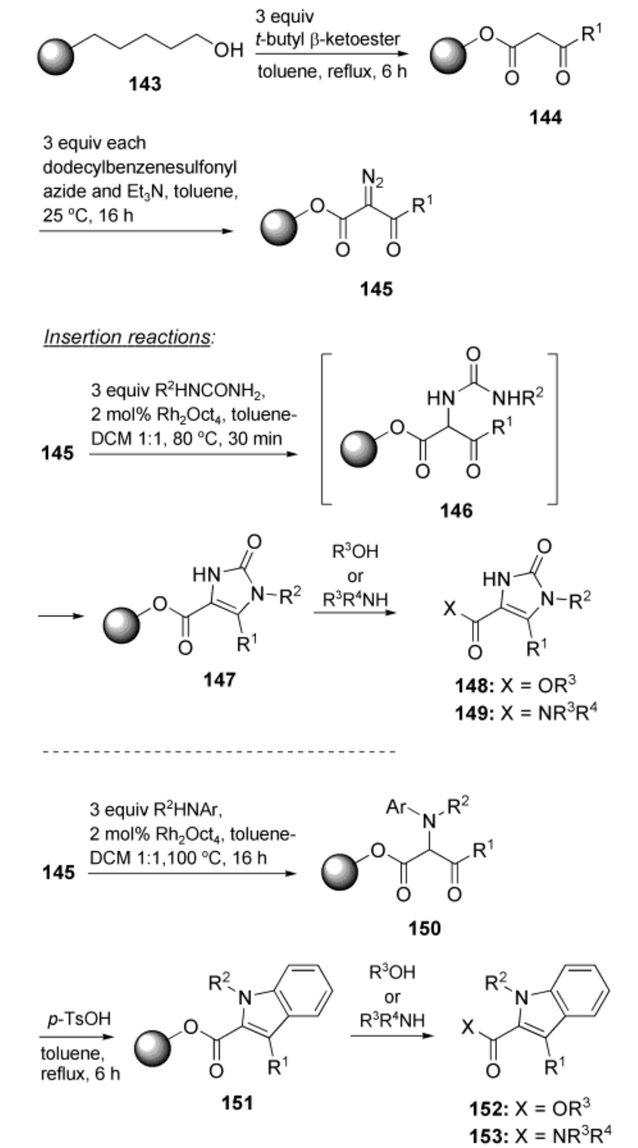


Figure 18. Rhodium carbenoid N−H insertion reactions.[211,212]

of **134** was conducted in the presense of an amine, the corresponding reductive amination products **136** were obtained directly after TFA cleavage. Tryptamine furnished the Pictet−Spengler product **137**. Yields for five amines (primary and secondary) ranged from 76 to 86%. Finally, several intramolecular versions of the hydroformylation/reductive amination were highlighted, including **140** to **142** (78% isolated yield).

Heterocyclic Synthesis. Arrays of imidazolones **148/149** and indoles **152/153** were created by rhodium carbenoid N−H insertion chemistry (Figure 18). In the approach as reported by Janda,[211,212] resin-bound β-ketoesters **144** were converted to the corresponding α-diazo-β-ketoesters **145** using standard diazo-transfer conditions. The pool of β-ketoester starting resins came from the transesterification of *tert*-butyl β-ketoester and hydroxy-functionalized resin **143**. Highly reactive rhodium carbenoid species, generated upon treatment of **145** with 2 mol % Rh_2Oct_4 in toluene/DCM at elevated temperature, inserted into primary ureas or anilines to give insertion products **146** and **150**. Subsequent cyclodehydration of these insertion products afforded imidazolones

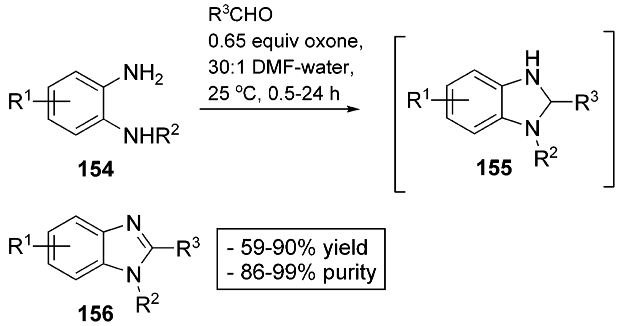


Figure 19. Oxone-mediated benzimidazole synthesis.[25]

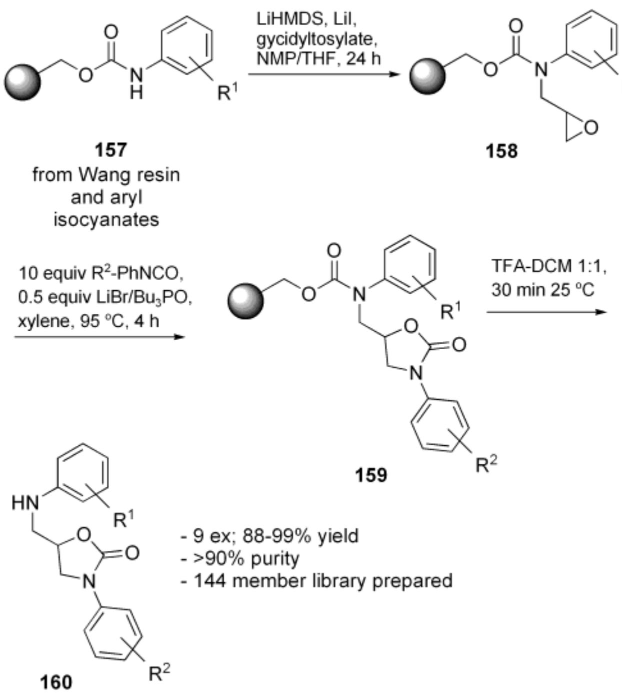


Figure 20. Oxazolidinones by cycloaddition chemistry.[46]

(**146** → → **147** → **148**/**149**) and indoles (**150** → **151** → **152**/**153**). Janda had previously reported application of the chemistry to a solid-phase oxazole synthesis where insertion occurs on an amide NH.[zz]

Beaulieu[25] at Boehringer Ingelheim (Canada) reported an operationally simple and mild method for the high-throughput, solution-phase synthesis of benzimidazoles (Figure 19). Chemistry is accomplished by the addition of oxone to a solution of 1,2-phenylenediamines **154** and an aldehyde in wet DMF at room temperature. Mechanistically, the reaction proceeds through initial formation to a benzoimidazoline **155**, which is then oxidized to give **156**. A wide range of diamine substrates may be used in conjunction with aliphatic, aromatic, and heteroaromatic aldehydes with little restriction to steric or electronic effects. A few aldehydes were found to be sensitive or unstable to oxone (empirically determined) and did not participate in the cyclization chemistry. Crude products are isolated by precipitation or extraction of the reaction mixture and typically do not require further purification. The purity for 15 reported examples was 86−99%, with yields ranging from 59 to 95%. The methodology is also applicable to the preparation of

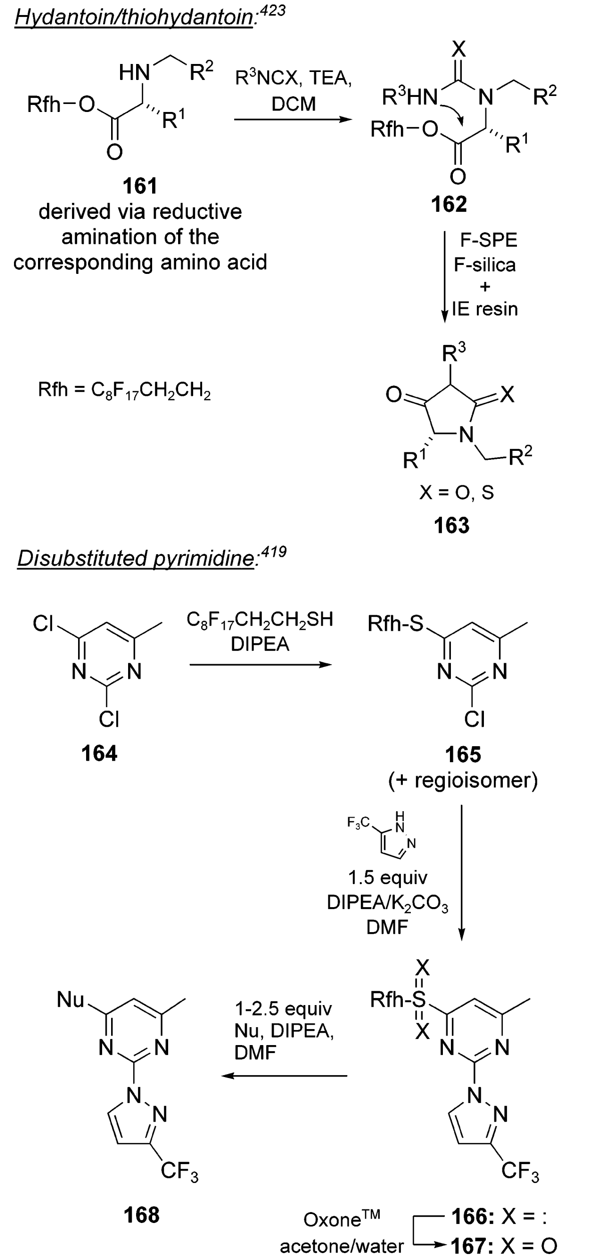


Figure 21. Fluorous synthesis.[419,423]

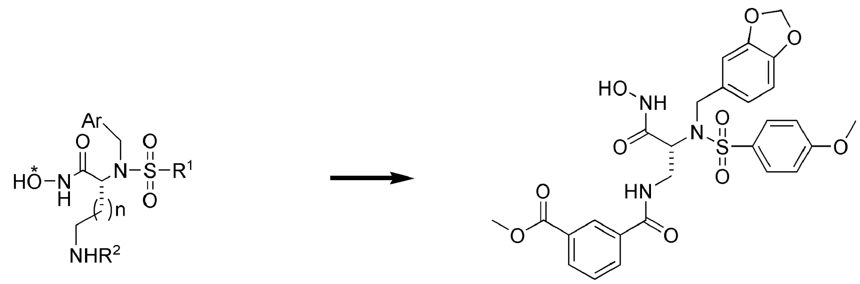
N-*H*-benzimidazoles by the slow addition (syringe pump) of the aldehyde in DMF to the 1,2-aryldiamine in reasonable yield.

N-Aryloxazolidinone is a pharmacophore found in a variety of biologically active compounds. The synthesis of a 144-membered library of substituted 3-phenyl-5-phenylaminomethyloxazolidin-2-ones was reported by Buchstaller[46] and is depicted in Figure 20. The synthesis was achieved by alkylation of resin-bound carbamates **157** with glycidyl tosylate (2 equiv LiHMDS, 10 equiv of glycidyltosylate, 1 equiv of LiI) in *N*-methylpyrollidine/THF at 25 °C under an argon atmosphere to yield resin-bound epoxides **158**. Oxazolidinones were obtained upon heating resins **158** with 10 equiv of an isocyanate in the presence of 0.5 equiv of LiBr/Bu_3PO in xylene at 95 °C for 4 h, followed by TFA-mediated cleavage. Catalytic LiBr is necessary to facilitate epoxide ring opening, and Bu_3PO assists in solubilizing LiBr in

Table 1. Chemical Libraries Targeting Proteases (Asterisk (*), Point of Attachment to Resin)

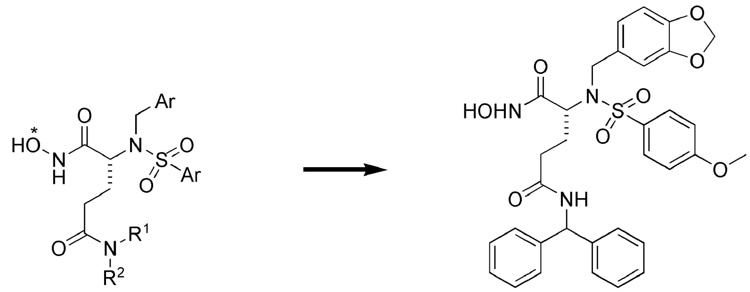
Metallo-proteases

Library: 1.1
Name: Hydroxamate
Size: Several hundred
Reference: Delaet [86]



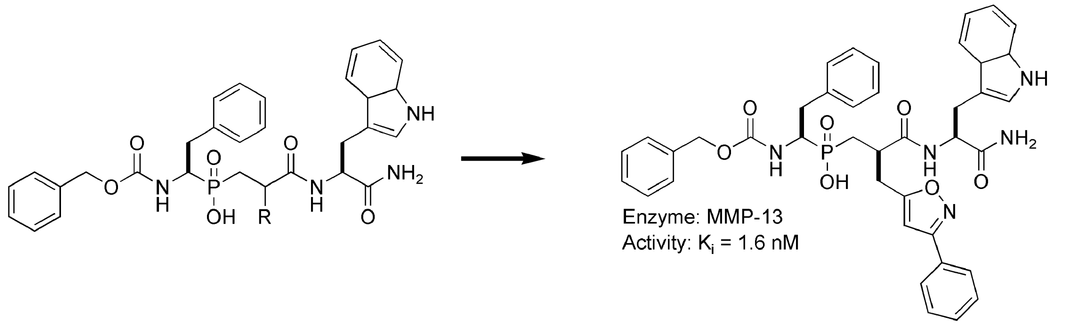
Enzyme: Procollagen C-proteinase
Activity: K_i = 7 nM

Library: 1.2
Name: Glutamic hydroxamates
Size: Several hundred
Reference: Robinson [306]



Enzyme: Procollagen C-proteinase
Activity: K_i = 11 nM

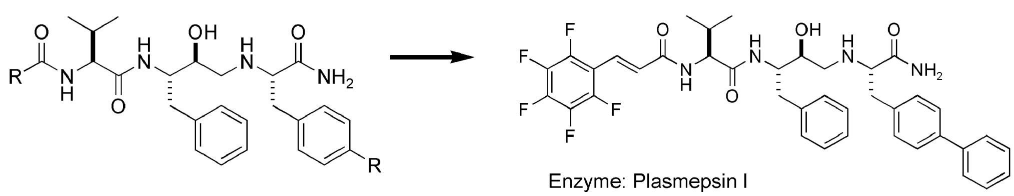
Library: 1.3
Name: Phosphinic peptide
Size: 11 members
Reference: Makaritis [240]



Enzyme: MMP-13
Activity: K_i = 1.6 nM

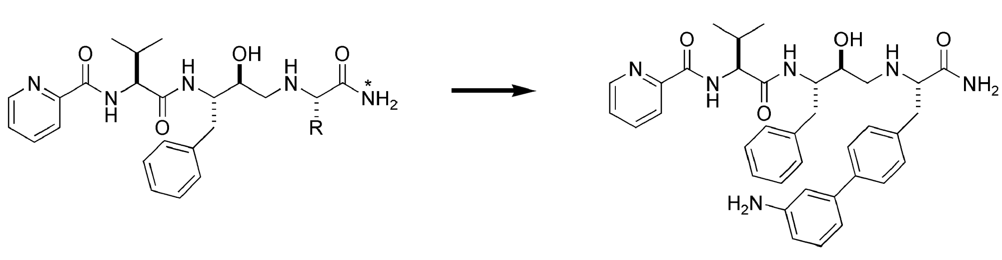
Aspartyl proteases

Library: 1.4
Name: Hydroxyethylamine
Size: *ca.* 30 members
Reference: Noteberg [270]
Note: Three optimization libraries of *ca.* 10 members each.



Enzyme: Plasmepsin I
Activity: K_i = 2 nM

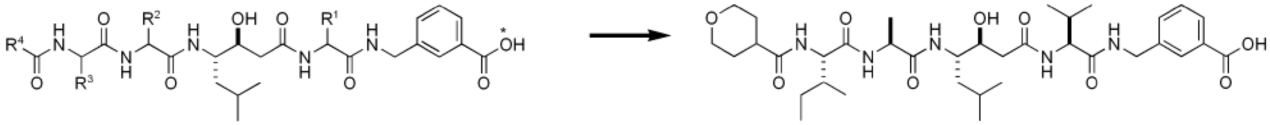
Library: 1.5
Name: Peptidomimetric
Size: Not defined
Reference: Noteberg [269]
Note: Multiple libraries examined.



Target: Plasmepsin I and II (*P. palciparum*)
Activity: K_i = 63 nM, Plm I; K_i = 150 nM, Plm II

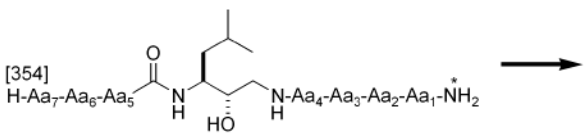
Table 1. (Continued)

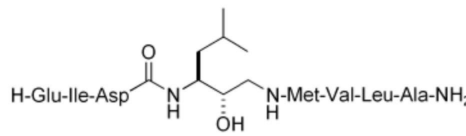
Library: 1.6
Name: Statine peptide
Size: Not defined
Reference: Hu [158]



Enzyme: Human brain B-APP cleaving enzyme (BACE) also know as β-secretase
Activity: IC_{50} = 69 nM

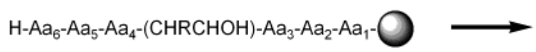
Library: 1.7
Name: Statine peptide
Size: *ca.* 21 members
Reference: Tamamura [354]

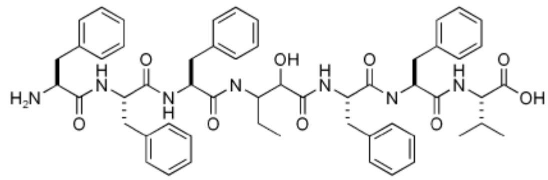




Enzyme: β-secretase
Activity: IC_{50} = 47 nM

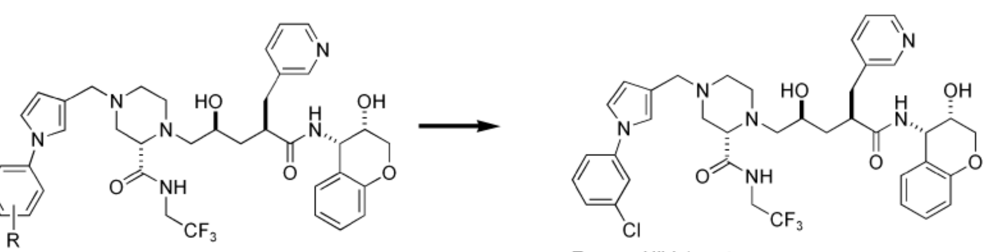
Library: 1.8
Name: Norstatine-type isostere
Size: Up to 2,456,500 members
Reference: Tamamura [392]
Note: One-bead-two-compound library using the nitro aldal reaction on 320,000 beads. Structure identification using MALDI-TOFMS.





Enzyme: Renin
Activity: IC_{50} = 50 nM

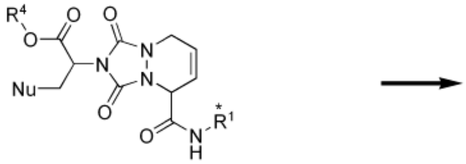
Library: 1.9
Name: Indinavir analog
Size: Not defined
Reference: Willert [184]
Note: Solution-phase synthesis.

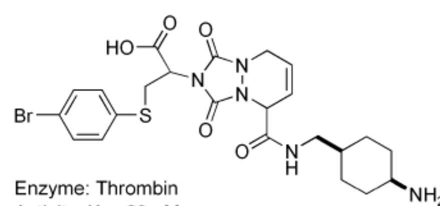


Enyme: HIV-1 protease
Activity: IC_{50} = 50 nM

<u>*Serine proteases*</u>

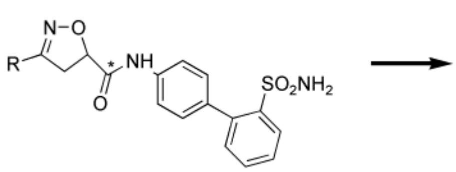
Library: 1.10
Name: Triazolopyridazine
Size: *ca.* 600 members
Reference: Boatman [36]

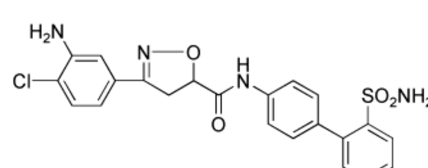




Enzyme: Thrombin
Activity: K_i = 23 nM

Library: 1.11
Name: Isoxazoline
Size: 46 members
Reference: Lam [193]
Note: Two libraries of 22 and 24 members each.

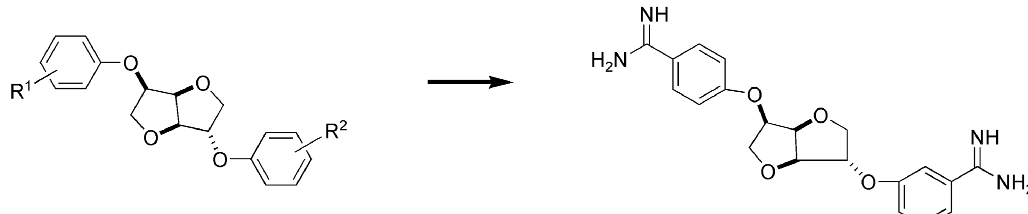




Enzyme: Factor Xa
Activity: K_i = 130 nM

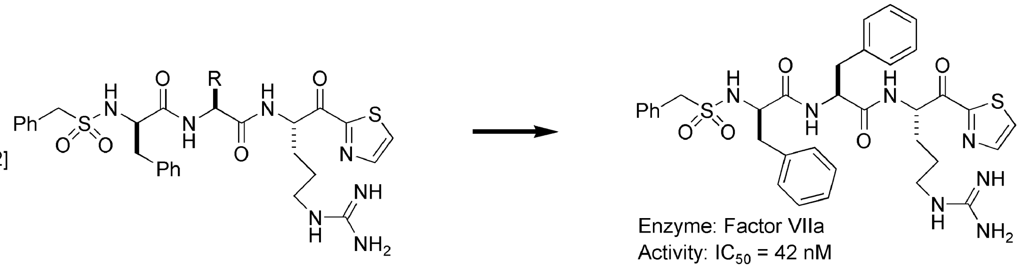
Table 1. (Continued)

Library: 1.12
Name: Dianhydrohexitole
Size: 4 members
Reference: Vogler [376]



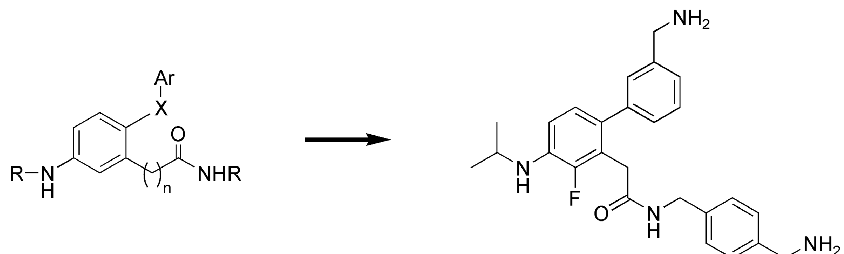
Enzyme: Factor Xa
Activity: IC_{50} = 150 μM

Library: 1.13
Name: α-Ketothiazole
Size: 38 members
Reference: Parlow [283, 342]



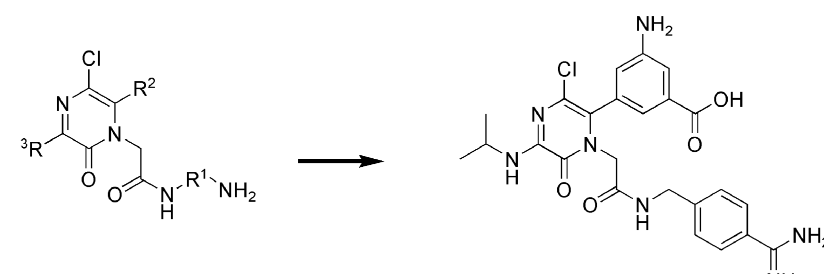
Enzyme: Factor VIIa
Activity: IC_{50} = 42 nM

Library: 1.14
Name: Substituted amide
Size: Not defined
Reference: Parlow [281]
Note: Multi-step synthesis using scavenger resins.



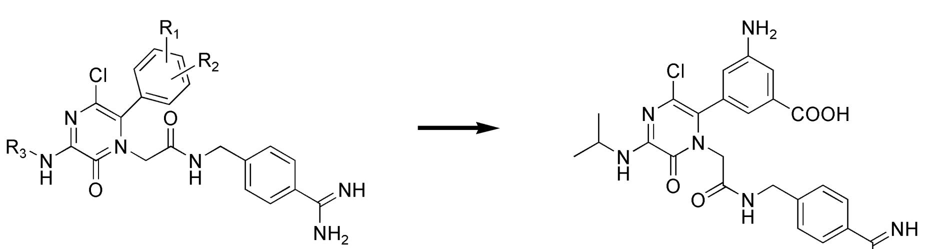
Enzyme: Factor VIIa
Activity: IC_{50} = 340 nM

Library: 1.15
Name: Pyrazinone
Size: Several hundred members
Reference: Parlow [282]
Note: Multi-step sequence using scavenger resins.



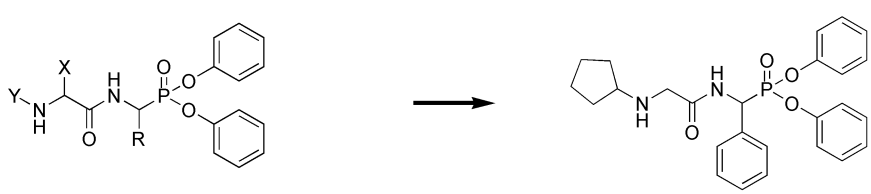
Enzyme: Factor VIIa
Activity: IC_{50} = 16 nM; >10,000x selective versus thrombin and Xa

Library: 1.16
Name: Pyrazinone
Size: Not defined
Reference: South [341]
Note: Polymer-assisted solution-phase synthesis.



Enzyme: Factor VIIa
Activity: IC_{50} = 16 nM

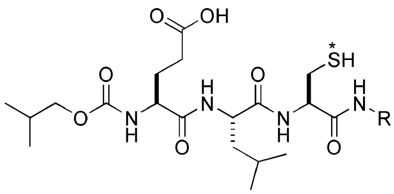
Library: 1.17
Name: Diphenylphosphonate
Size: *ca.* 50 members
Reference: Senten [324]

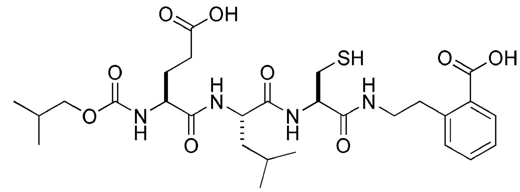


Enzyme: Dipeptidyl peptidase II
Activity: IC_{50} = 3.8 μM

Table 1. (Continued)

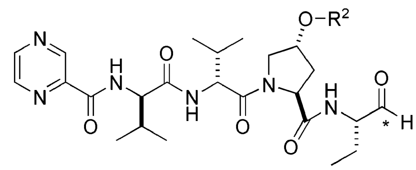
Library: 1.18
Name: Cysteine amide
Size: 5 members
Reference: Perni [67]

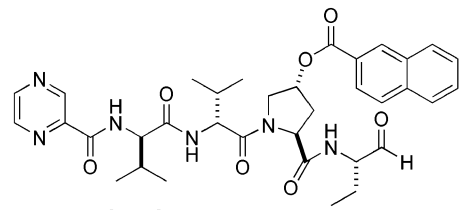




Enzyme: Hepatitus C virus NS3/4A protease
Activity: IC_{50} = 3.2 μM

Library: 1.19
Name:Tetrapeptide
Size: Not defined
Reference: Perni [288]

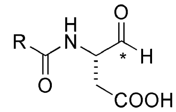


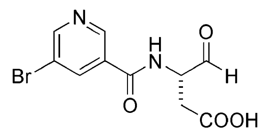


Enyme: HCV NS3-4A
Activity: K_i = 0.4 μM

Cysteine proteases

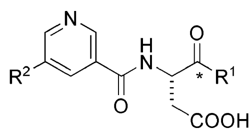
Library: 1.20
Name: Aspartyl aldehyde
Size: Not defined
Reference: Isabel [170]
Note: Semi-carbazone linker used.

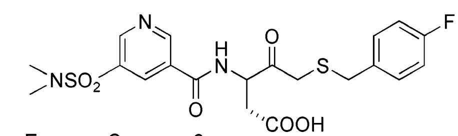




Enzyme: Caspase-3
Activity: IC_{50} = 6 μM

Library: 1.21
Name: Aspartyl ketone
Size: Not defined
Reference: Isabel [170]
Note: Two libraries as follow-up to library **1.X**.

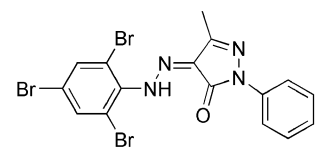




Enzyme: Caspase-3
Activity IC_{50} = 0.13 μM

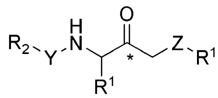
Library: 1.22
Name: Heterocycle
Size: 352 members
Reference: Gosalia [128]
Note: Chemical library in individual nanoliter droplets of glycerol micro-arrayed into glass slides followed by aerosol deposition of reagents.

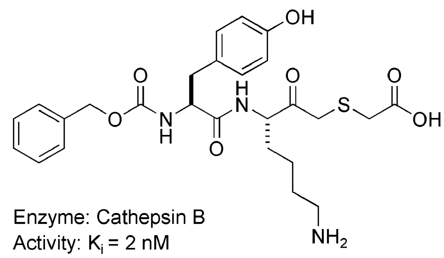
Commercial collection of heterocycles



Enzyme: Caspase 4/LEHD-MCA
Activity: IC_{50} = ca. 0.5 mM

Library: 1.23
Name: Mercaptomethyl ketone
Size: 2016 members
Reference: Wood [395]



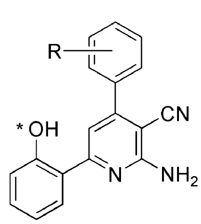


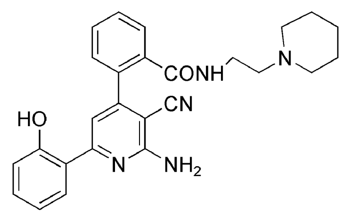
Enzyme: Cathepsin B
Activity: K_i = 2 nM

Table 2. Chemical Libraries Targeting Nonproteolytic Enzymes (Asterisk (*), Point of Attachment to Resin)

Kinases and phosphatases

Library: 2.1
Name: Aminopyridine
Size: 1000 members
Reference: Murata [261]

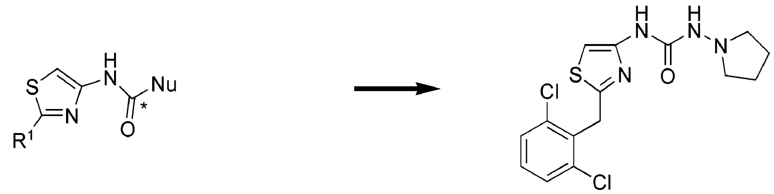




Enzyme: IKK-β serine-threonine protein kinase
Activity: IC_{50} = 0.5 μM

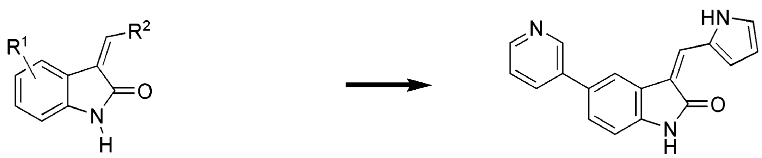
Table 2. (Continued)

Library: 2.2
Name: Acylaminothiazole
Size: *ca.* 250 members
Reference: Larsen [199]



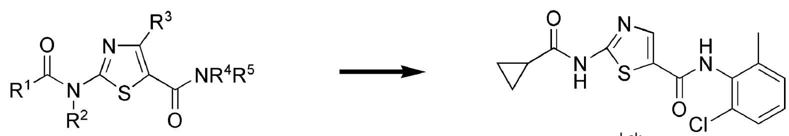
Enzyme: CDK5/p25
Activity: IC_{50} = 3 μM

Library: 2.3
Name: Oxindole
Size: *ca.* 700 members
Reference: Adams [3]



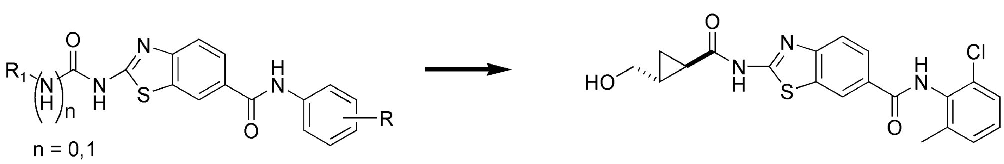
Enzyme: Janus kinase 3 (JAK3)
Activity: IC_{50} = 27 nM

Library: 2.4
Name: Aminothiazole
Size: Not defined
Reference: Wityak [394]
Note: Multiple solution-phase libraries.



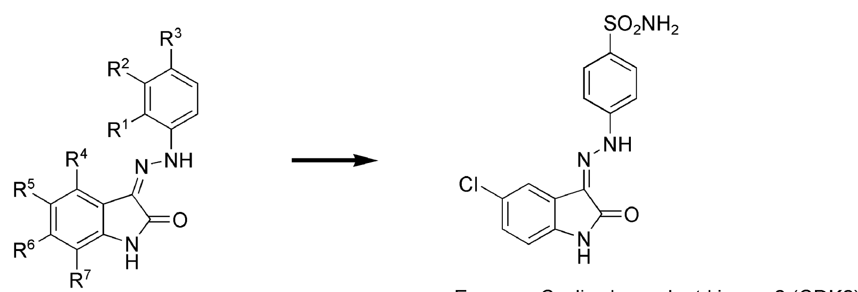
Enzyme: $p56^{Lck}$
Activity: IC_{50} = 35 nM

Library: 2.5
Name: Benzothiazole
Size: Not defined
Reference: Das [81]
Note: Focussed library arrays and discrete analogs. Derived from library 2.4.



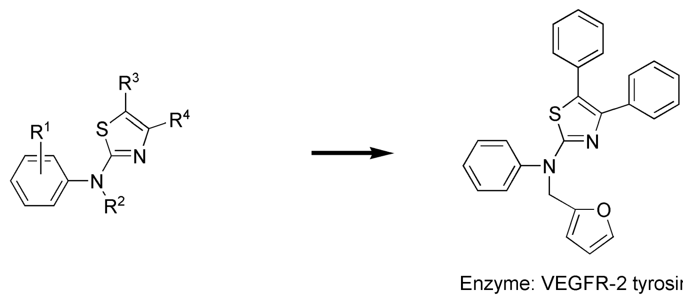
Enzyme: $p56^{lck}$ protein tyrosine kinase
Activity: IC_{50} = 3 nM

Library: 2.6
Name: Oxindole
Size: 30 members
Reference: Congreve [69]
Note: Six isostatins condensed with five hydrazines in presence of CDK2 crystals. Ligands from the dynamic combinatorial library were identified by direct X-ray crystallography.



Enzyme: Cyclin-dependent kinase-2 (CDK2)
Activity: IC_{50} = 30 nM

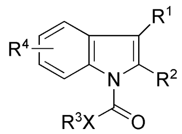
Library: 2.7
Name: Aminothiazole
Size: *ca.* 23 members
Reference: Stieber [346]



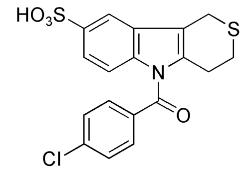
Enzyme: VEGFR-2 tyrosine kinase
Activity: IC_{50} = 7.4 μM; IC_{50} = 44 μM, VEGFR-3; IC_{50} = 9.8 μM, Tie-2; IC_{50} = 8.6 μM, FGFRI

Table 2. (Continued)

Library: 2.8
Name: Indomethacin analog
Size: 197 members
Reference: Rosenbaum [309]
Note: Fisher indole synthesis.

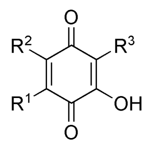


→



Enzyme: Tie-2 tyrosine kinase
Activity: IC_{50} = 3 μM; IC_{50} = 21 μM, VEGFR-2; IC_{50} = 9 μM, IGFIR; IC_{50} = 6 μM, FGFR-1

Library: 2.9
Name: Nakijiquinone C analog
Size: 74 members
Reference: Kissau [187]



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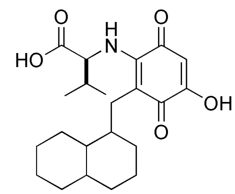
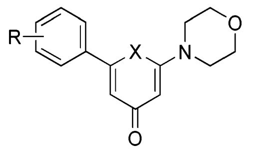


Enzyme: Insulin-like growth-factor 1 receptor tyrosine kinase
Activity: IC_{50} = 0.5 μM

Library: 2.10
Name: Pyranonthiopyran-4-one
Size: Not defined
Reference: Hollick [155]



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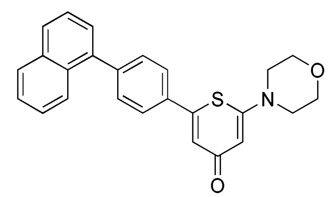
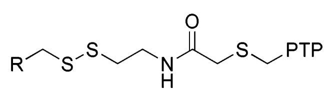


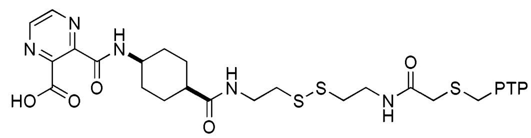
Enzyme: DNA-dependent protein-kinase
Activity: IC_{50} = 190 nM

Library: 2.11
Name: Tethered disulfide
Size: 1500 members
Reference: Elanson [101]
Note: Protein tyrosine kinase modified with active site disulfide probe.



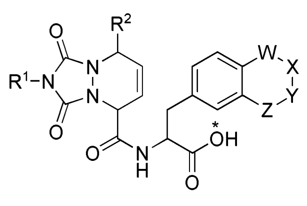
PTP = protein tyrosine phosphatase

→



Enzyme: Protein tyrosine phosphatase (PTP1B)
Activity: K_i = 4.1 mM

Library: 2.12
Name: Triazolopyridazine
Size: Not defined
Reference: Yan [404]



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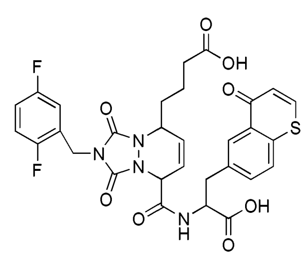
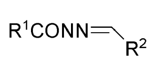


Enzyme: TC-protein tyrosine phosphatase
Activity: 85% inhibition at 10 μM

Library: 2.13
Name: Hydrazone
Size: 440 members
Reference: Bunyapaiboonsri [47]
Note: Dynamic combinatorial library.



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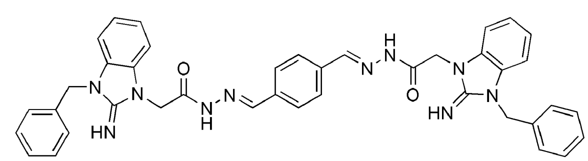
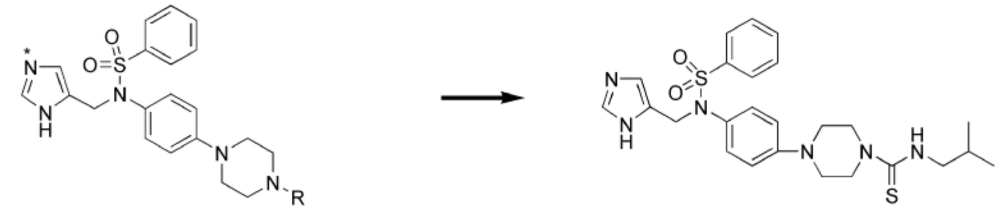


Enzyme: HPr kinase/phosphatase (*B. subtilis*)
Activity: IC_{50} = 17 μM

Table 2. (Continued)

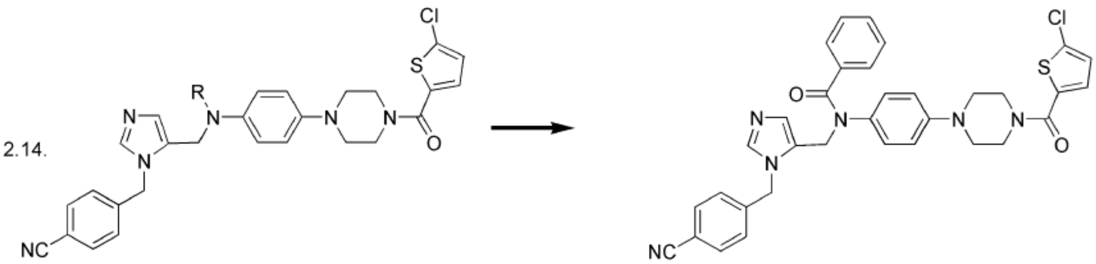
Transferases

Library: 2.14
Name: Imidazole
Size: Not defined
Reference: Perez [287]



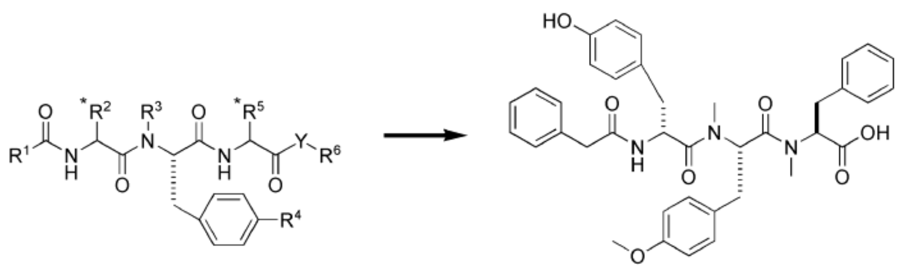
Enzyme: Farnesyl protein transferase
Activity: IC_{50} = 6 nM

Library: 2.15
Name: Imidazole
Size: ca. 80 members
Reference: Perez [287]
Note: Follow-up to library 2.14.



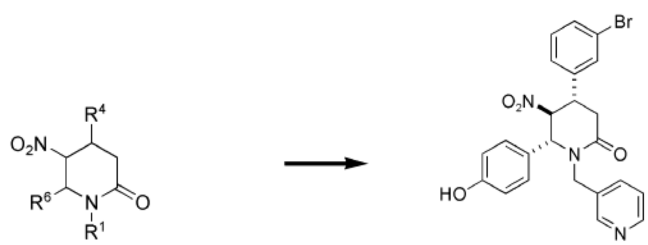
Enzyme: Farnesyl protein transferase
Activity: IC_{50} = 2 μM

Library: 2.16
Name: Pepticinnamin analog
Size: 51 members
Reference: Thutewohl [361, 199]



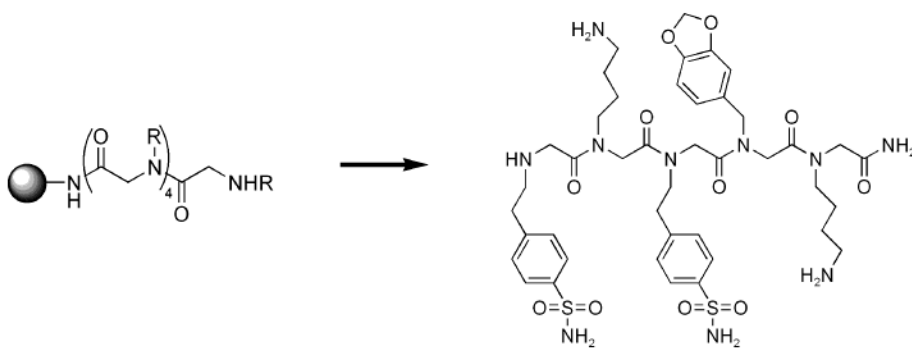
Enzyme: Protein farnesyltransferase
Activity: IC_{50} = 5.0 μM

Library: 2.17
Name: Substituted piperidine
Size: *ca.* 3000 members
Reference: Nara [264]
Note: 3CC solution-phase synthesis.



Enzyme: Farnesyltransferase (FTase; bovine)
Activity: IC_{50} = 420 nM

Library: 2.18
Name: Peptoid
Size: 100,000 members
Reference: Alluri [8]
Note: Three other peptoid libraries also prepared. On-bead screening using Texas Red-labeled protein. Peptoid identity established by Edman sequencing.



Enzyme: Glutathione-*S*-transferase
Activity: K_D = 62 μM

Table 2. (Continued)

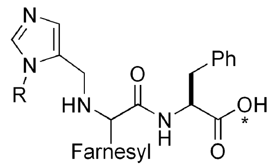
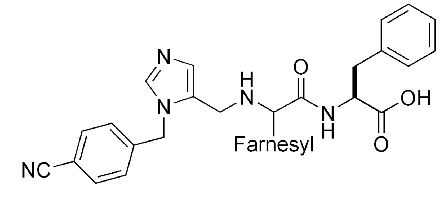
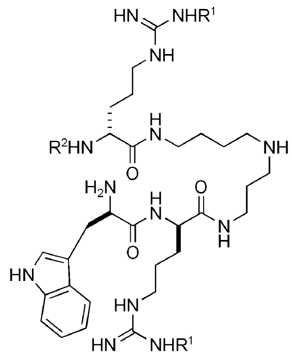
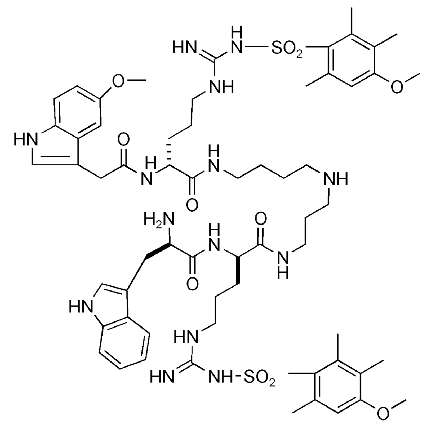
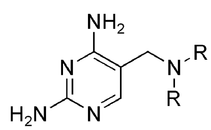
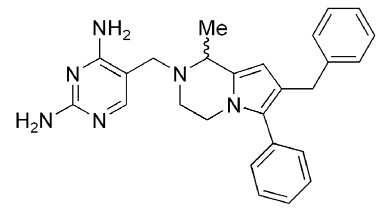
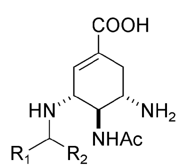
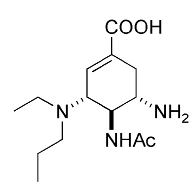
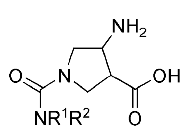
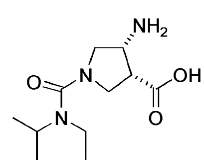
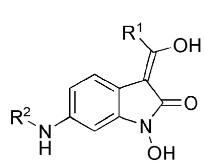
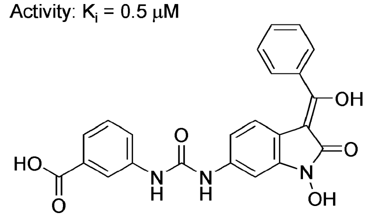
Library: 2.19 Name: Farnesyl amides Size: Not defined Reference: Lannuzel [198]		 Enzyme: Farnesyl transferase Activity: IC_{50} = 91 nM (in vitro)
Reductases		
Library: 2.20 Name: Spermidine conjugate Size: 24 members Reference: De Luca [84]		 Enzyme: Trypanothione reductase Activity: K_i = 530 nM
Library: 2.21 Name: 2,4-Diaminopyrimidine Size: ca. 1200 members Reference: Wyss [402] Note: Structure-based versus diversity-based synthon selection.		 Enzyme: Dihydrofolate reductase (*S. aureus*) Activity: IC_{50} = 42 nM
Viral/bacterial enzymes		
Library: 2.22 Name: Diamine Size: Not defined Reference: Hochgurtel [151] Note: Dynamic combinatorial library of diamine, ketone in the presence of neuraminidase.		 Enzyme: Neuraminidase (viral) Activity: K_i = 85 nM
Library: 2.23 Name: Urea Size: Not defined Reference: Stoll [347]		 Enzyme: Neuraminidase (viral) Activity: K_i = 0.5 μM
Library: 2.24 Name: Tetramic acid Size: 131 members Reference: Parkes [280]		 Enzyme: Influenza endonuclease Activity: IC_{50} = 3 μM

Table 2. (Continued)

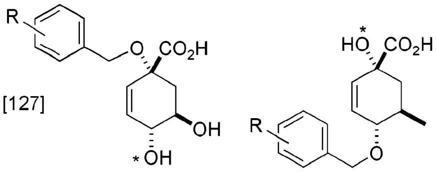
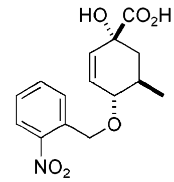
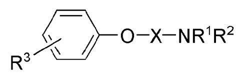
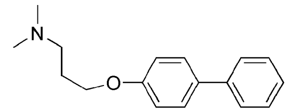
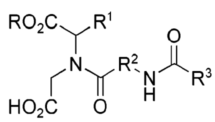
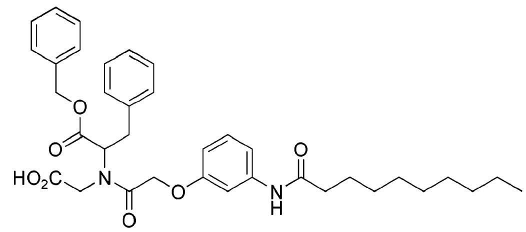
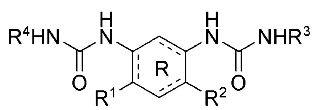
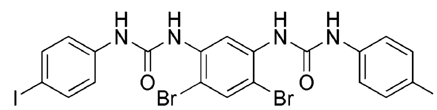
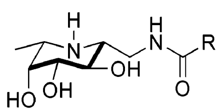
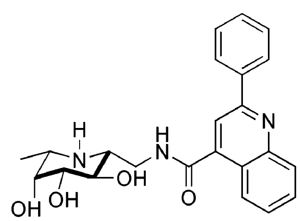
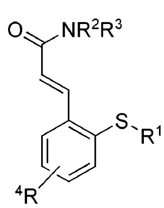
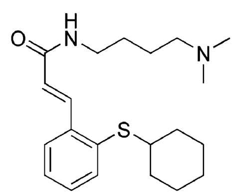
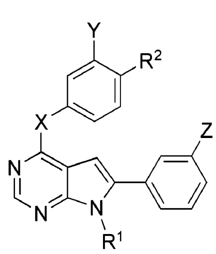
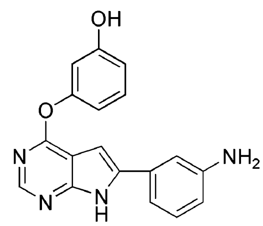
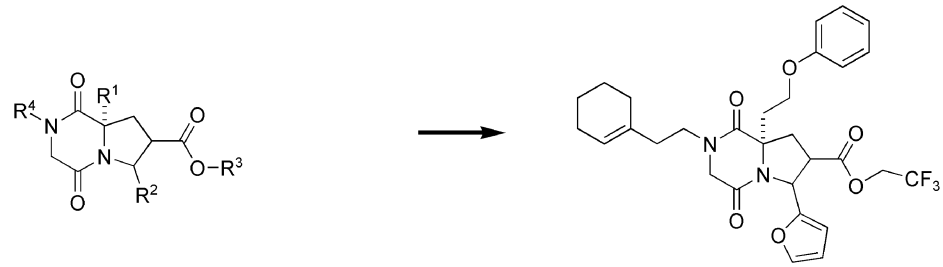
Library: 2.25 Name:Cyclohexenoate Size: 18 members Reference: Gonzalez-Bello [127]		 Enzyme: Type II dehydroquinase (*S. coelicolor*) Activity: K_i = 8 μM
Library: 2.26 Name: Amino phenol Size: 128 members Reference: Hinshaw [149]		 Enzyme: Oxidosqualene cyclase Activity: IC_{50} = 2.5 μM
<u>*Mammalian enzymes*</u>		
Library: 2.27 Name: N-Acyl immodiacetate Size: Not defined Reference: Pei [285]		 Enzyme: Adenine nucleotide translocase (bovine) Activity: EC_{50} = 4.7 μM
Library: 2.28 Name: Bis-urea Size: *ca.* 40 members Reference: Wu [398]		 Enzyme: Cyclophilin Activity: IC_{50} = 590 nM
Library: 2.29 Name: Fuconojirimycin analog Size: 60 members Reference: Wu [396]		 Enzyme: α-Fucosidase (bovine kidney) Activity: K_i = 0.50 nM
Library: 2.30 Name: Arylacrylamide Size: Not defined Reference: Zhang [418]		 Enzyme: Guanylyl cyclase Activity: EC_{50} = 2.9 μM
Library: 2.31 Name: Pyrrolopyrimidine Size: Not defined Reference: Ding [93]		 Enzyme: Glycogen synthesis kinase (GSK-3β) Activity: IC_{50} = 30 nM

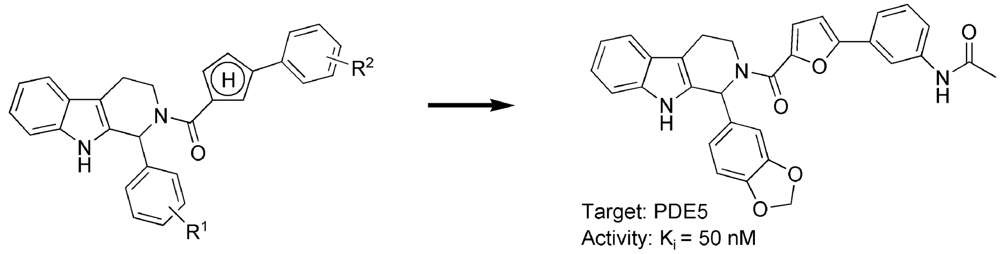
Table 2. (Continued)

Library: 2.32
Name: Pyrrolopyrazinedione
Size: Not defined
Reference: Slee [338]



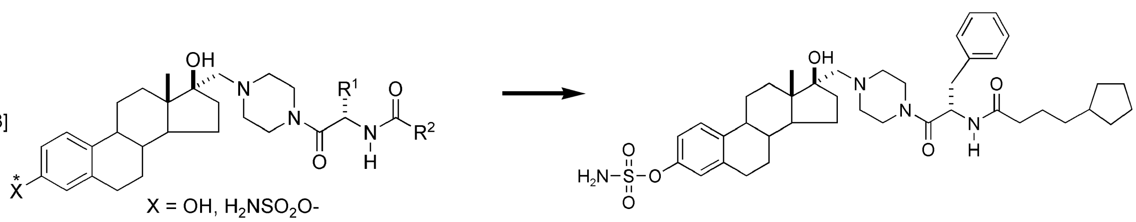
Enzyme: Hormone sensitive lipase
Activity: IC_{50} = 0.12 μM

Library: 2.33
Name: β-Carboline
Size: Not defined
Reference: Sui [348]



Target: PDE5
Activity: K_i = 50 nM

Library: 2.34
Name: Estradiol analog
Size: 50 members
Reference: Ciobanu [63]
Note: Two libraries of 25 members each defined by X.

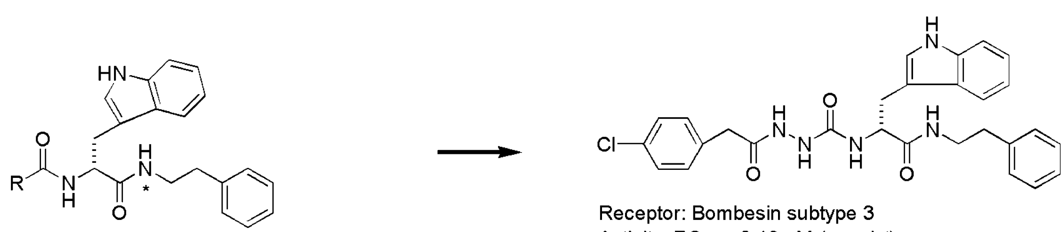


Enzyme: Steroid sulfatase
Activity: 94% inhibition at 1.0 nM

Table 3. Chemical Libraries Targeting G-Protein Coupled Receptors (Asterisk (*), Point of Attachment to Resin)

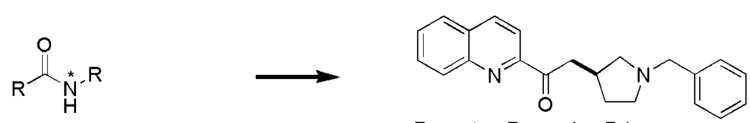
Alphabetical listing

Library: 3.1
Name: Tryptamine
Size: Not defined
Reference: Weber [387]
Note: Multiple libraries.



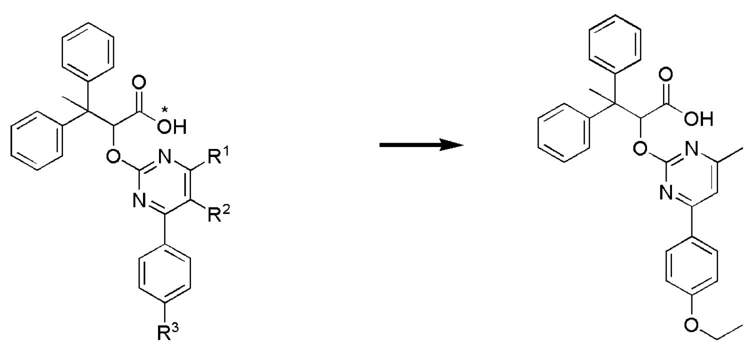
Receptor: Bombesin subtype 3
Activity: EC_{50} = 0.19 nM (agonist)

Library: 3.2
Name: Amide
Size: 20 members
Reference: Lober [229]
Note: Use of "click linker" (1,3-dipolar cycloaddition of PS-N_3 and alkyne-containing substrates).



Receptor: Dopamine D4
Activity: 67% inhibition at 0.1 μM ([^{3}H]spiperone)

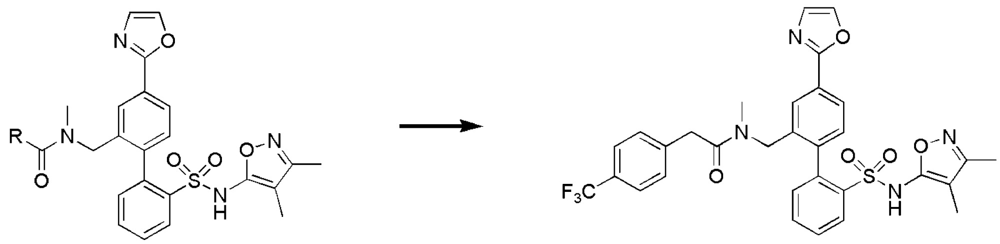
Library: 3.3
Name: Pyrimidine
Size: Not defined
Reference: Lange [197]



Receptor: Endothelin
Activity: K_i (ET_A) = 2 nM;
K_i (ET_B) = 344 nM (antagonist)

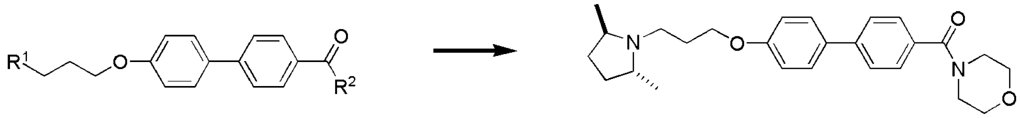
Table 3. (Continued)

Library: 3.4
Name: Biphenylsulfonamide
Size: 160 members
Reference: Murugesan [262]



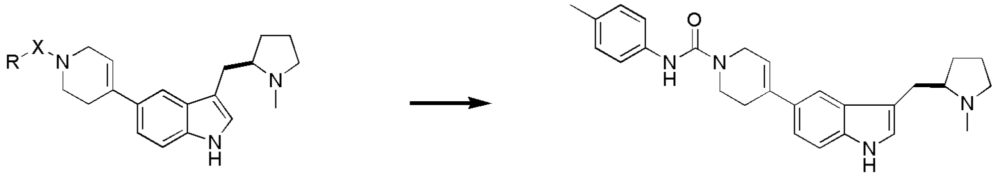
Receptor: Endothelin
Activity: K_i = 1 pM (antagonist)

Library: 3.5
Name: Biphenyl
Size: ca. 49 members
Reference: Faghih [103]



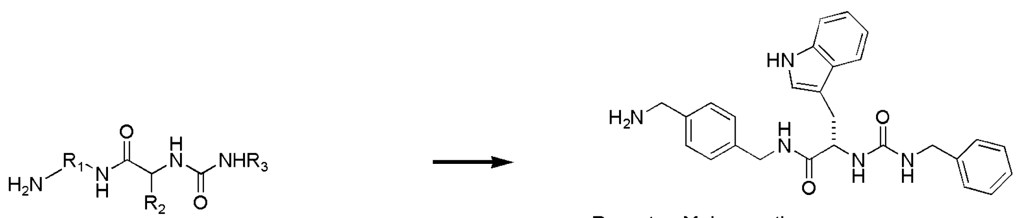
Receptor: Histamine H_3 (human)
Activity: pK_i = 9.31 (antagonist)

Library: 3.6
Name: Indole
Size: 17 members
Reference: Egle [98]



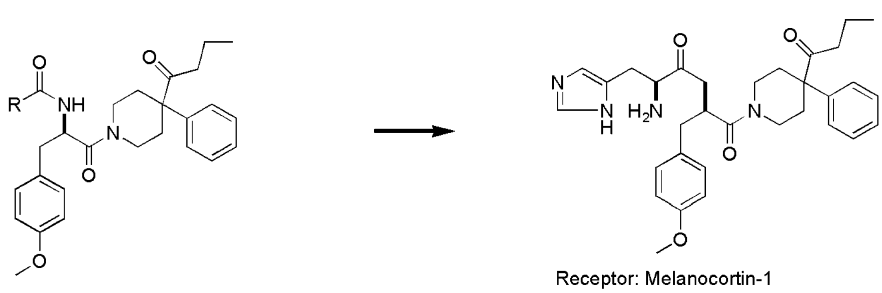
Receptor: 5-HT_{1D} (human)
Activity: K_i = 0.3 nM, 5-HT_{1D};
K_i = 3.0 nM, 5-HT_{1B}

Library: 3.7
Name: Urea
Size: 14 members
Reference: Joseph [179]



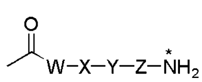
Receptor: Melanocortin
Activity: EC_{50} = 0.4 μM, MC1R; EC_{50} = 10.7 μM, MC3R;
EC_{50} = 0.4 μM, MC4R; EC_{50} = 9.9 μM, MC5R (agonist)

Library: 3.8
Name: Tyrosine derivative
Size: Not defined
Reference: Herpin [148]

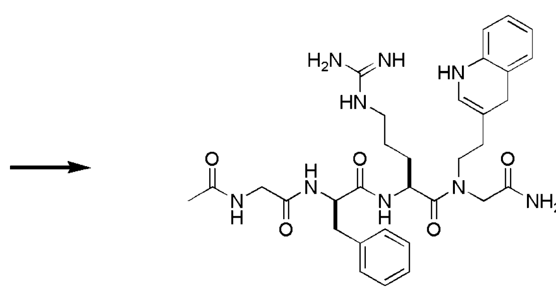


Receptor: Melanocortin-1
Activity: EC_{50} = 0.19 nM (agonist)

Library: 3.9
Name: Peptoid
Size: 9 members
Reference: Holder [154]



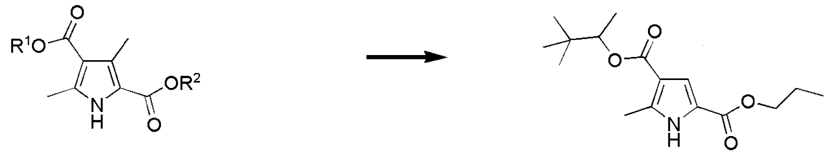
W,X,Y,Z = •dependently amino acid or N-substituted glycine



Receptor: Melanocortin
Activity: EC_{50} = 56 nM, MC5R

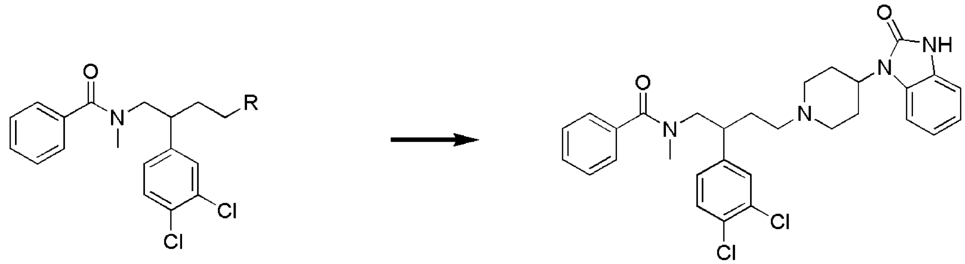
Table 3. (Continued)

Library: 3.10
Name: Pyrrole ester
Size: *ca*. 1600 members
Reference: Micheli [253]



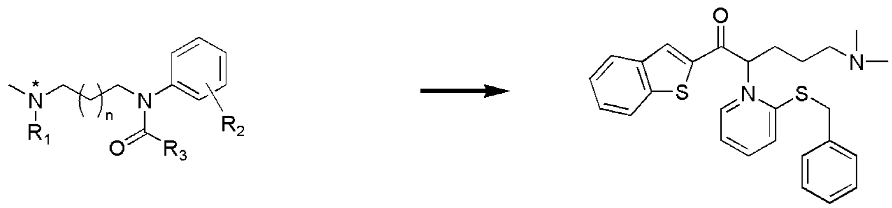
Receptor: mGluR1
Activity: IC_{50} = 16 nM (antagonist)

Library: 3.11
Name: Benzamide
Size: Not defined
Reference: MacKenzie [237]



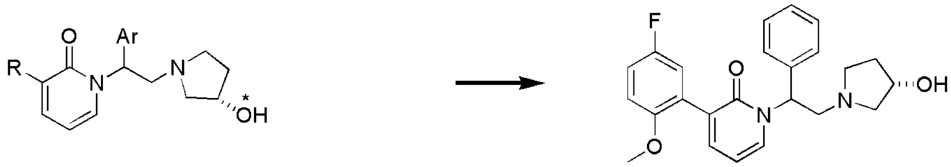
Receptor: Neurokinin-2 (NK_2; human)
Activity: pIC_{50} = 8.9 (antagonist)

Library: 3.12
Name: Diamine
Size: Not defined
Reference: Andres [9]



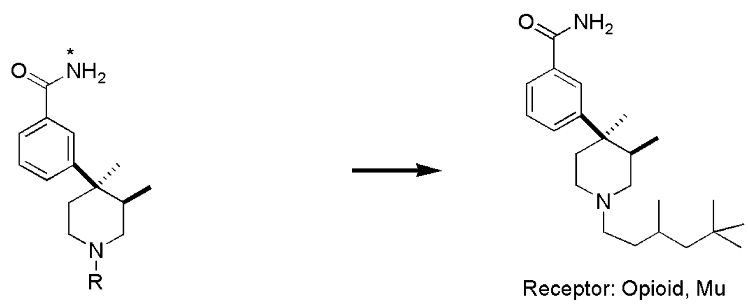
Receptor: Neuropeptide Y_2
Activity: IC_{50} = 450 nM

Library: 3.13
Name: Pyridone
Size: Not defined
Reference: Semple [322]



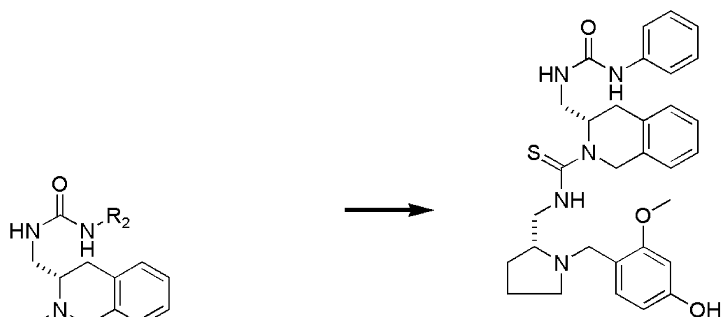
Receptor: Opioid, kappa
Activity: IC_{50} = 5.5 nM (agonist)

Library: 3.14
Name: Peperidine
Size: 80 members
Reference: Le Bourdonnec [204]



Receptor: Opioid, Mu
Activity: K_i = 0.5 μM (antagonist)

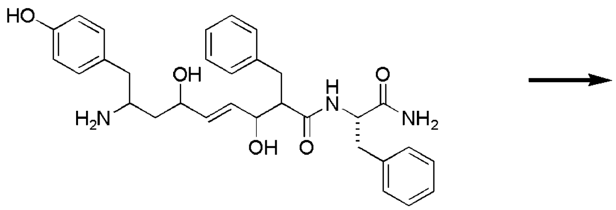
Library: 3.15
Name: Tetrahydroisoquinoline
Size: 500 members
Reference: Page [278]
Note: Solution-phase synthesis.

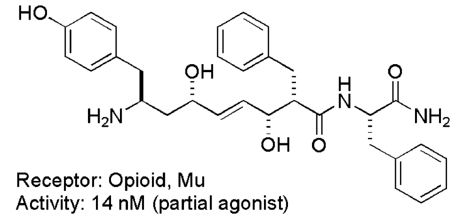


Receptor: Opioid, Mu
Activity: K_i = 1.1 nM, μ (antagonist); K_i = 127 nM, δ; K_i >130 nM, κ

Table 3. (Continued)

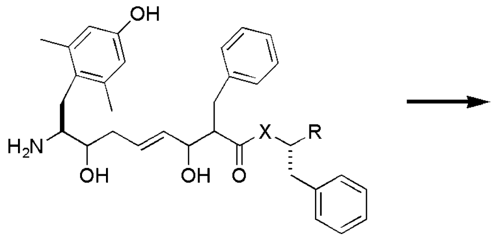
Library: 3.16
Name: 1,4-Enediol
Size: 6 members
Reference: Shi [331]
Note: Exhaustively stereo-diversified library.

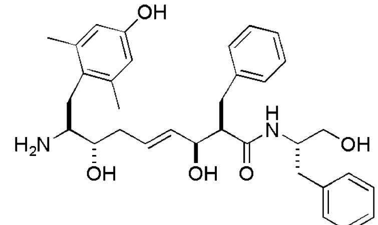




Receptor: Opioid, Mu
Activity: 14 nM (partial agonist)

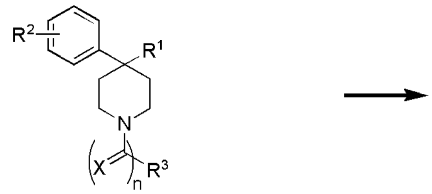
Library: 3.17
Name: Dihydroxy olefin
Size: 6 members
Reference: Harrison [141]

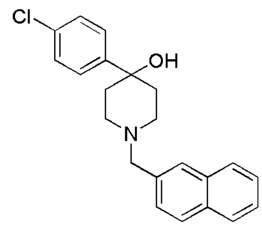




Receptor: Opioid, Mu
Activity: 0.16 nM (partial agonist)

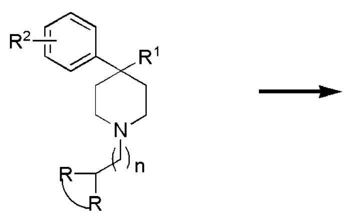
Library: 3.18
Name: Piperidine derivative
Size: *ca.* 150 members
Reference: Chen [58]
Note: Solution-phase synthesis.

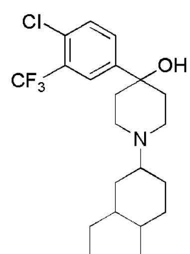




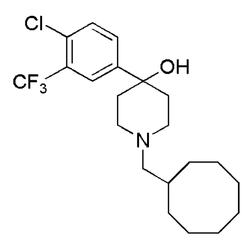
Receptor: Opiod receptor like-1 (ORL-1)
Activity: K_i = 153 nM

Library: 3.19
Name: Piperidine
Size: *ca.* 24 members
Reference: Chen [58]
Note: Follow-up library to library 3.17.



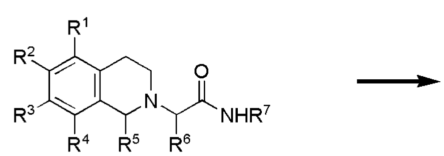


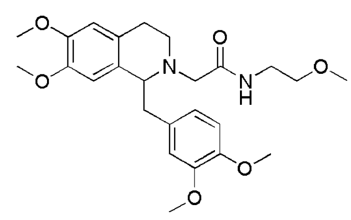
Receptor: ORL-1
Activity: K_i = 12 nM (agonist)



Receptor: ORL-1
Activity: K_i = 47 nM (antagonist)

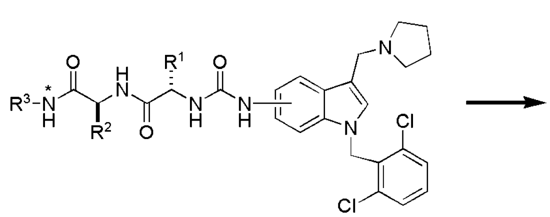
Library: 3.20
Name: Tetrahydroisoquinoline
Size: *ca.* 2000 members
Reference: Koberstein [190]
Note: Multiple libraries produced.

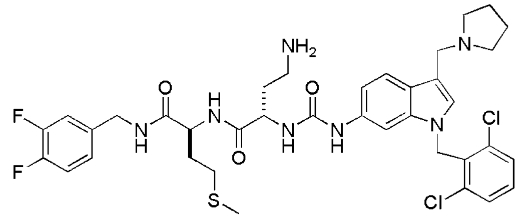




Receptor: Orexin 1 and 2 (human)
Activity: IC_{50} = 8 nM, OX-1; IC_{50} = 109 nM, OX-2

Library: 3.21
Name: Indole peptide mimetic
Size: Not defined
Reference: Zhang [417]
Note: Alternative attachment point at R^2 when a lysine side chain.

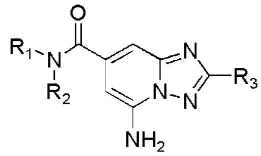




Receptor: Protease-activated receptor-1 (PAR-1)
Activity: IC_{50} = 25 nM

Table 3. (Continued)

Library: 3.22
Name: Triazolopyridine
Size: Not defined
Reference: Schneider [316]



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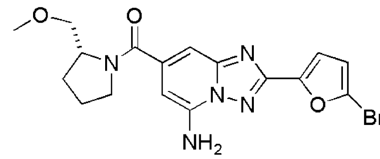
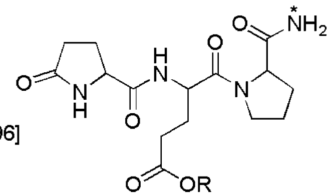


Receptor: Purinergic (A_{2A})
Activity: K_i = 2.4 nM, A_{2A}; K_i = 292 nM, A_1

Library: 3.23
Name: Tripeptide ester
Size: 5 members
Reference: Prokai-Tatrai [296]



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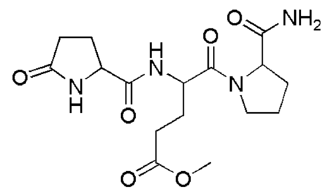
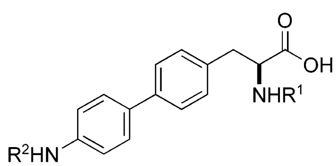


Receptor: Thyrotropin-releasing hormone
Activity: ED_{50} = 2.4 μmol/kg; prodrug for CNS penetration (agonist)

Table 4. Chemical Libraries Targeting Non-G-Protein Coupled Receptors (Asterisk (*), Point of Attachment to Resin)

Integrins

Library: 4.1
Name: Biaryl
Size: 500 members
Reference: Urbahns [369]



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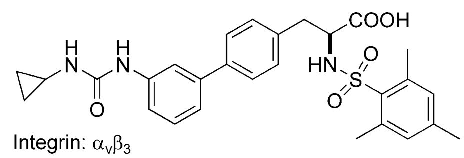
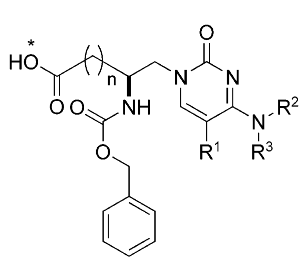
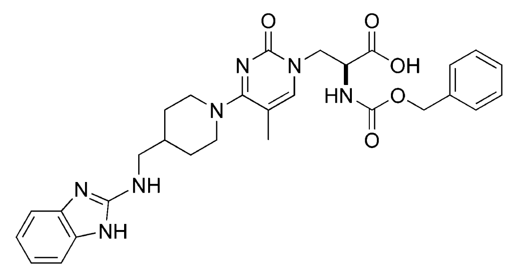


Integrin: $\alpha_v\beta_3$
Activity: K_i = 2.5 nM

Library: 4.2
Name: Pyrimidin-2-one
Size: Not defined
Reference: Zechel [415]

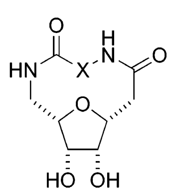


→

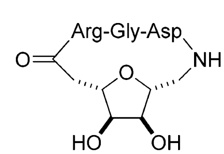


Integrin: $\alpha_v\beta_3$
Activity: IC_{50} = 1.3 nM

Library: 4.3
Name: Furanoid
Size: 5 members
Reference: van Well [370]

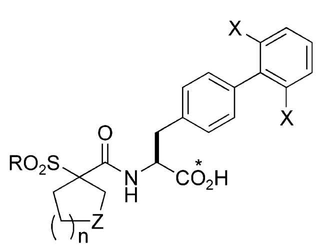


→



Integrin: $\alpha_v\beta_3$
Activity: IC_{50} = 1.5 nM

Library: 4.4
Name: (4-Aryl)phenylalanine
Size: Not defined
Reference: Gutteridge [136]



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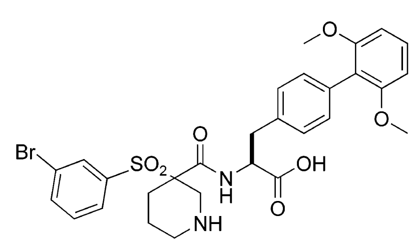
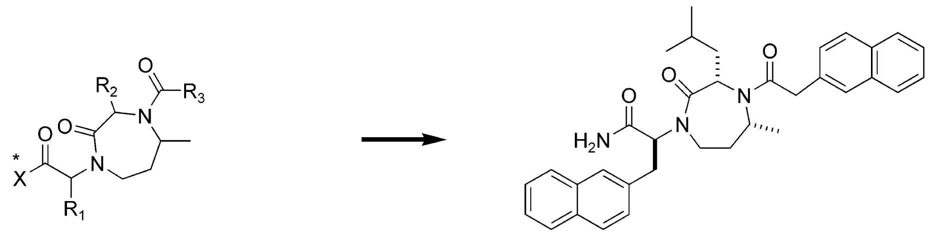


Integrin: VLA-4
Activity: IC_{50} = 0.13 nM (antagonist)

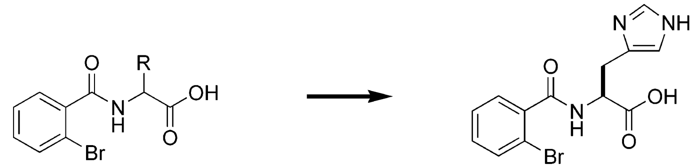
Table 4. (Continued)

Library: 4.5
Name: 1,4-Diazepane-2-one
Size: 90 members
Reference: Wattanasin [385]



Integrin: Lymphocyte function-associated antigen-1 (LAF-1, CD11a/CD18, $\alpha_L\beta_2$)
Activity: IC_{50} = 2.0 μM (antagonist)

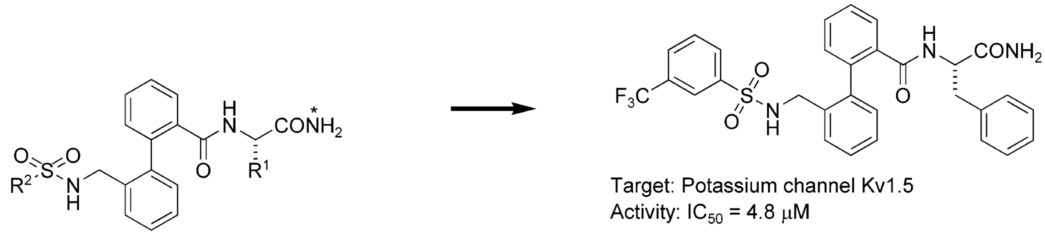
Library: 4.6
Name: Amino acid amide
Size: Not defined
Reference: Burdick [48]
Note: Compounds produced using solution-and solid phase methods.



Integrin: LFA-1/ICAM-1
Activity: IC_{50} = 0.75 μM

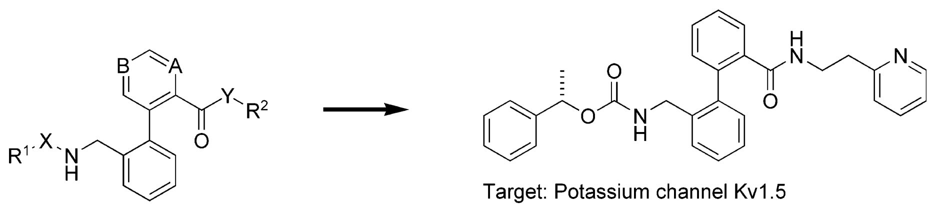
Ion channels

Library: 4.7
Name: Biaryl
Size: Not defined
Reference: Peukert [290]



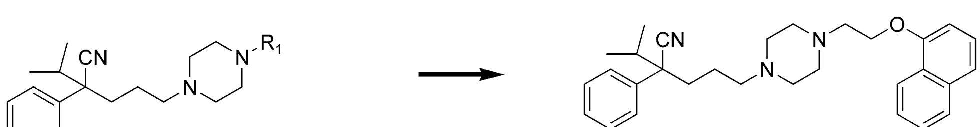
Target: Potassium channel Kv1.5
Activity: IC_{50} = 4.8 μM

Library: 4.8
Name: Biaryl
Size: Not defined
Reference: Peukert [290]
Note: Follow-up to 4.17 using solution-phase methodology.



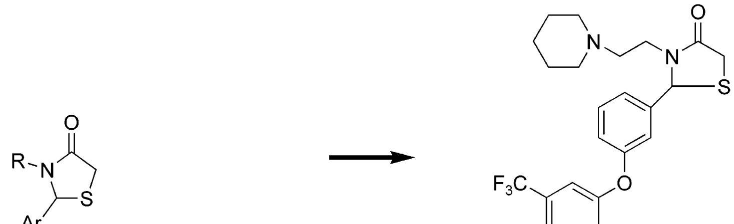
Target: Potassium channel Kv1.5
Activity: IC_{50} = 0.16 μM

Library: 4.9
Name: Emopamil analog
Size: Not defined
Reference: Suzuki [351]



Target: Neuronal voltage-dependent calcium channel
Activity: IC_{50} = 2.5 μM (blocker)

Library: 4.10
Name:Thiazolidinone
Size: 100 members
Reference: Sun [350]

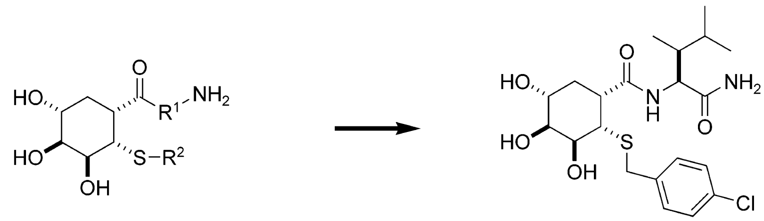


Target: Sodium channel
Activity: K_i = 90 nM (blocker)

Table 4. (Continued)

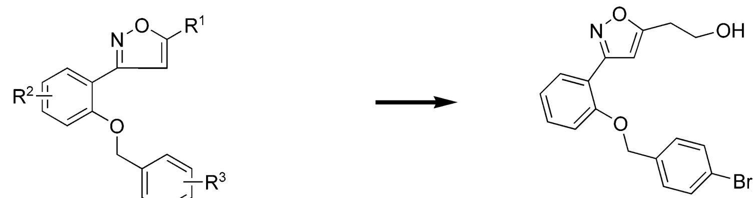
Alphabetical listing

Library: 4.11
Name: Glycomimetic
Size: 192 members
Reference: Schuster [319]
Note: Two libraries of 72 and 120 members each.



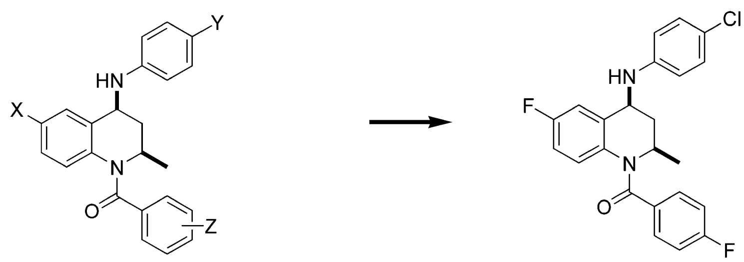
Target: C-type lectin
Activity: IC_{50} = 4 mM

Library: 4.12
Name: Isoxazole
Size: Not defined
Reference: Sammelson [315]



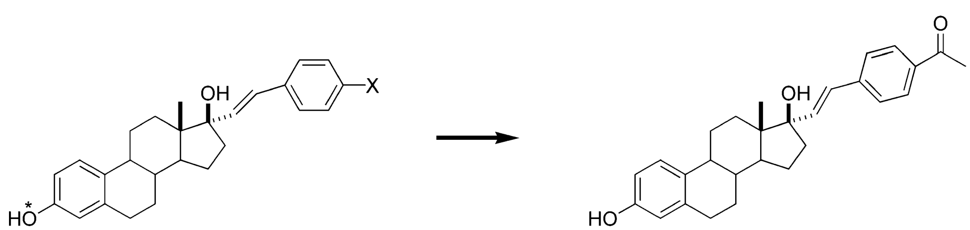
Target: Cystic fibrosis transmembrane conductance regulator
Activity: K_i = 23 μM

Library: 4.13
Name: Tetrahydroquinoline
Size: 35 members
Reference: Smith [339]



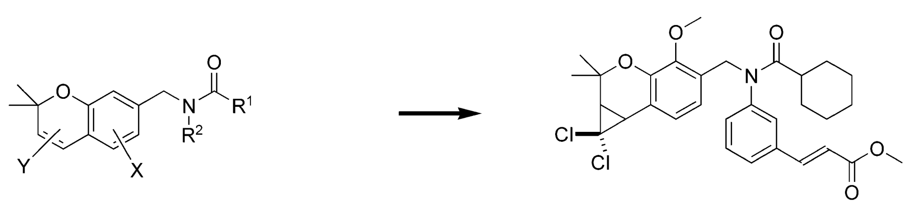
Receptor: Ecdysone nuclear hormone
Activity: EC_{50} = 0.64 μM

Library: 4.14
Name: Estradiol analog
Size: *ca.* 10 members
Reference: Hanson [137]



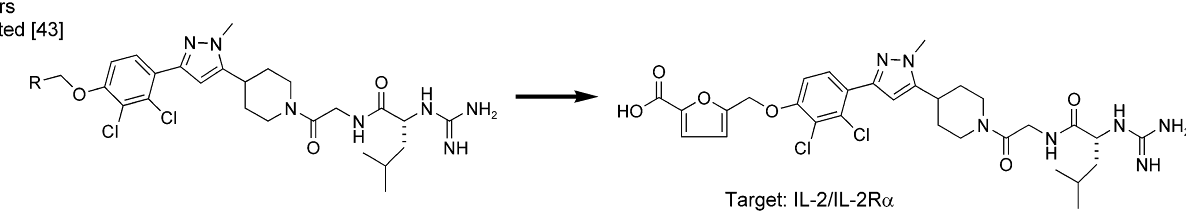
Target: ERα ligand binding domain
Activity: 60% (relative binding to estradiol)

Library: 4.15
Name: Benzopyran
Size: ~ 200 members
Reference: Nicolaou [267]
Note: Multiple solution-and solid-phase libraries.



Target: FXR (farnesoid X receptor)
Activity: EC_{50} = 188 nM

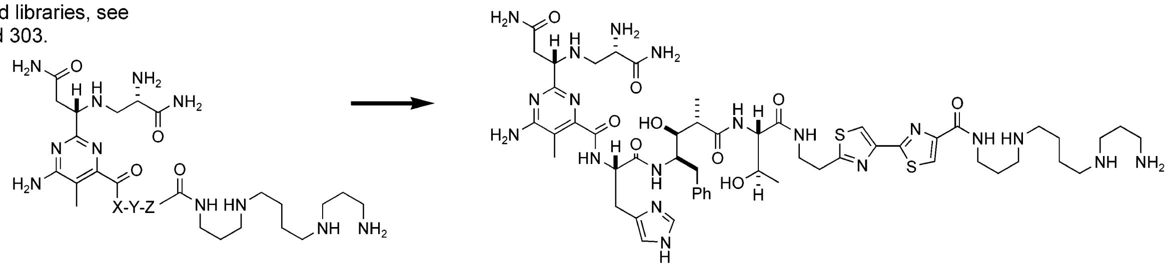
Library: 4.16
Name: Pyrrazole
Size: 20 members
Reference: Braisted [43]



Target: IL-2/IL-2Rα
Activity: IC_{50} = 60 nM

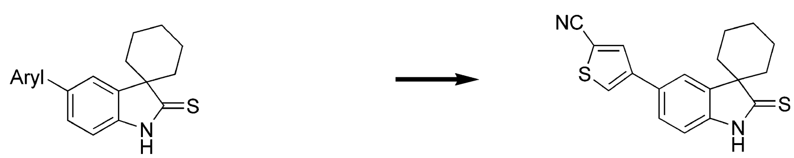
Table 4. (Continued)

Library: 4.17
Name: Deglycobleomycin
Size: 108 members
Reference: Leitheiser [214]
Note: For a related libraries, see references 52 and 303.



Target: Plasmid DNA
Activity: Supercoiled plasmid DNA relaxation "greater than" parent deglycobleomycin

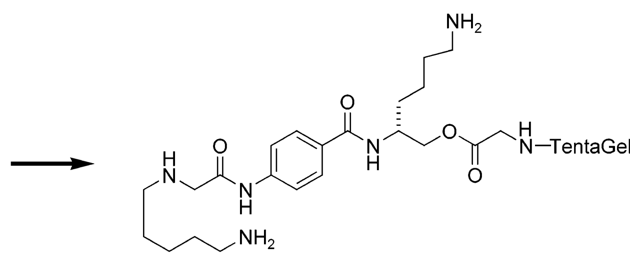
Library: 4.18
Name: Thioamide
Size: Not defined
Reference: Fensome [108]



Receptor: Progesterone
Activity: EC_{50} = 0.3 μM

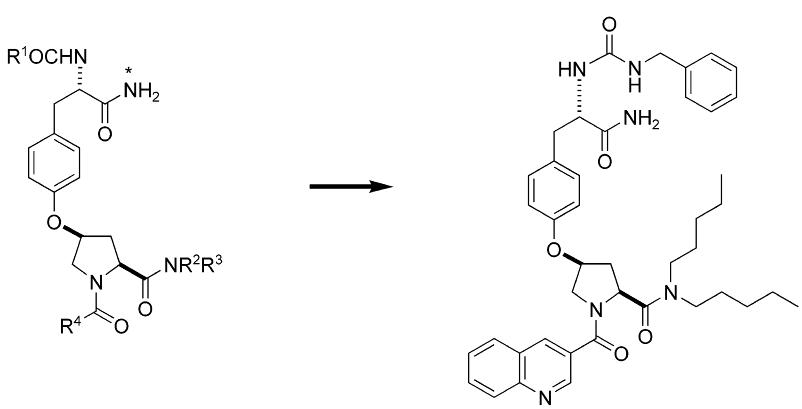
Library: 4.19
Name: Peptidomimetic
Size: 39,304 members
Reference: Hwang [168]
Note: Natural and unnatural amino acids (Aa_x) used.

H-Aa_3-Aa_2-Aa_1-X-TentaGel



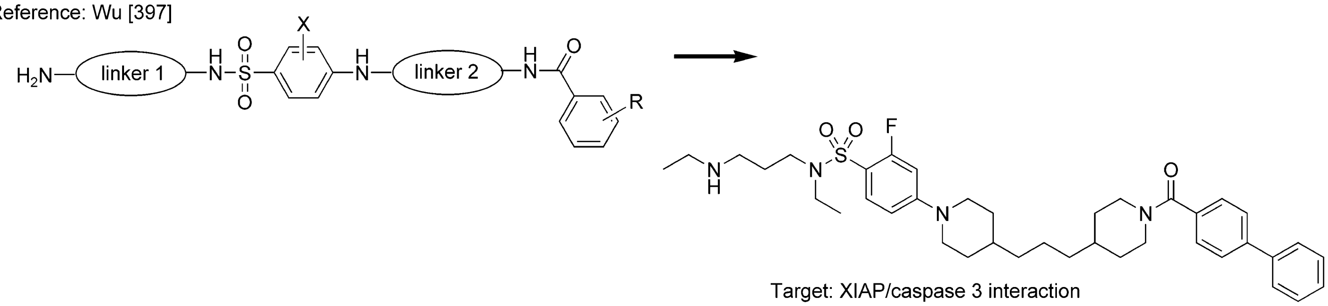
Target: Tat - RNA (HIV-1)
Activity: K_D = 89 nM

Library: 4.20
Name: Tyrosine-proline analogs
Size: 1728 members
Reference: Jackson [174]
Note: Split-pool library.



Target: TNF-α
Activity: IC_{50} = 8.1 mM inhibition of TNF-α induced apoptosis

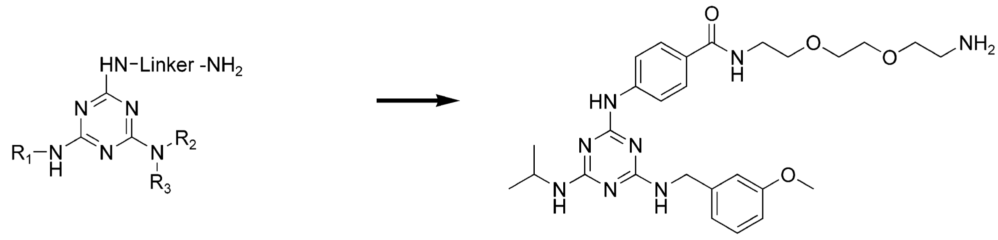
Library: 4.21
Name: Diamine
Size: *ca.* 160,000 members
Reference: Wu [397]



Target: XIAP/caspase 3 interaction
Activity: 80-100% inhibition at 20 μM

Table 4. (Continued)

Library: 4.22
Name: Triazine
Size: 1536 members
Reference: Kheronsky [180]

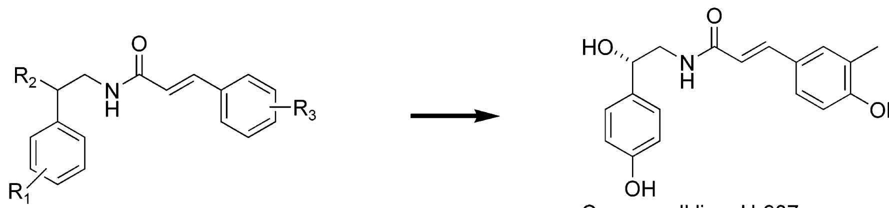


Target: Zebra fish embryo assay
Activity: Brain/eye morphological changes observed at 50 μM

Table 5. Chemical Libraries Yielding Cytotoxic and Anti-infective Agents (Asterisk (*), Point of Attachment to Resin)

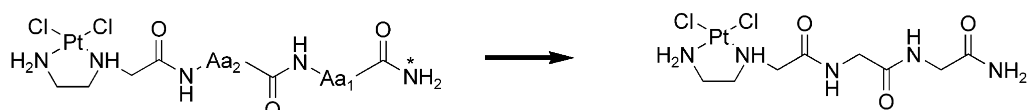
Cytotoxics

Library: 5.1
Name: Cinnamide
Size: 88 members
Reference: Nesterenko [265]



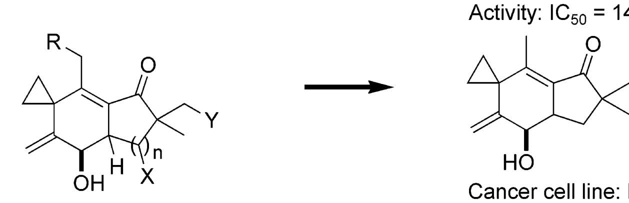
Cancer cell line: U-937
Activity: IC_{50} = 44 μM

Library: 5.2
Name: Peptide platinum complex
Size: 36 members
Reference: Robillard [305]



Cancer cell line: A2780
Activity: IC_{50} = 149 μM

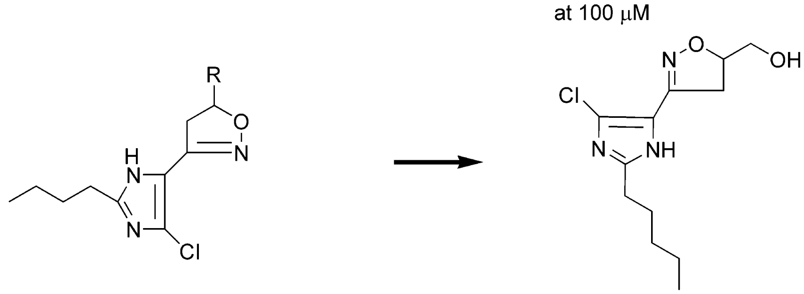
Library: 5.3
Name: Illudinoid analog
Size: 49 members
Reference: Pirrung [292]



Cancer cell line: H460
Cytotoxicity: 100% growth inhibition at 100 μM

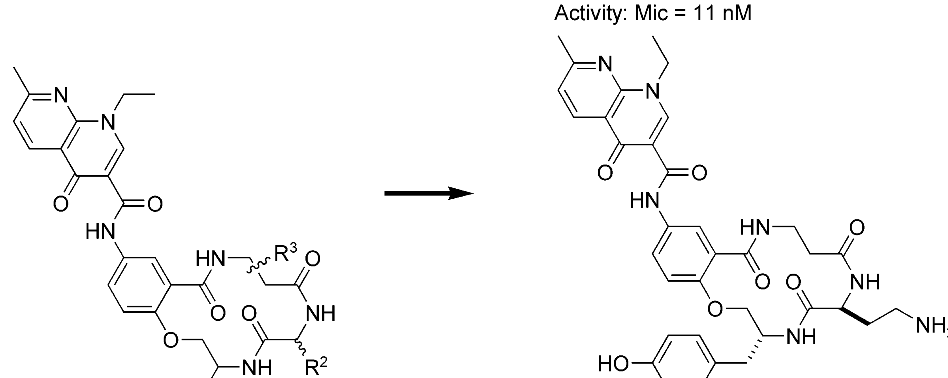
Anti-infectives

Library: 5.4
Name: Isoxazoline
Size: 8 members
Reference: Basappa [19]
Note: Solution-phase synthesis.



Microbe: *A. flavus*
Activity: Mic = 11 nM

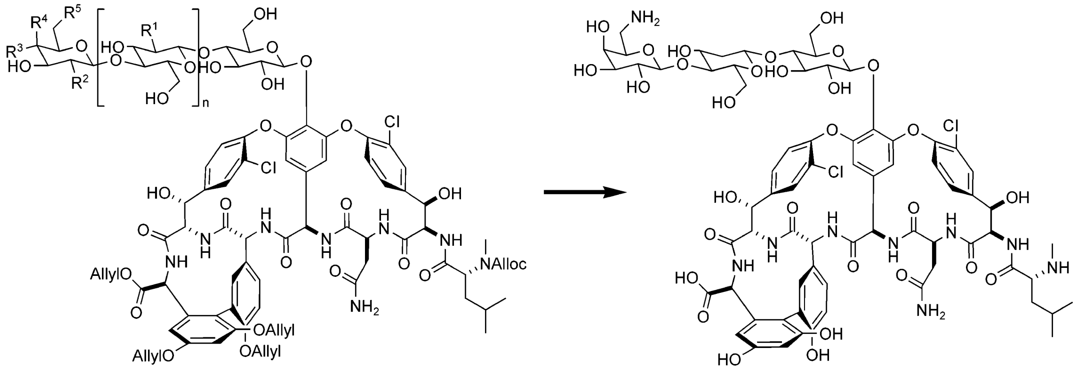
Library: 5.5
Name: Quinolone-macrocycle
Size: 1350 members
Reference: Jefferson [177]



Microbe: *E. coli*
Activity: MIC = 25-50 μM

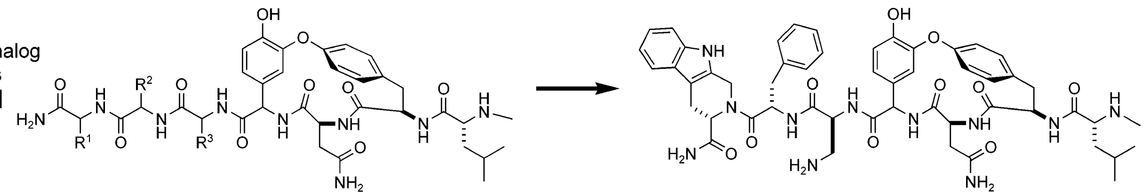
Table 5. (Continued)

Library: 5.6
Name: Vancomycin analog
Size: 6 members
Reference: Ritter [304]



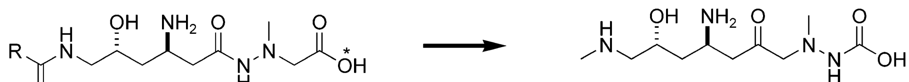
Microbe: *E. faecalis* 29212
MIC = 5 μg/mL

Library: 5.7
Name: Vancomycin analog
Size: 27,000 members
Reference: Ahrendt [7]



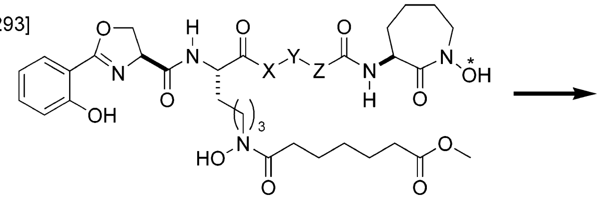
Microbe: Vancomycin resistant *E. faecium*
Activity: MIC = 150 μg/mL

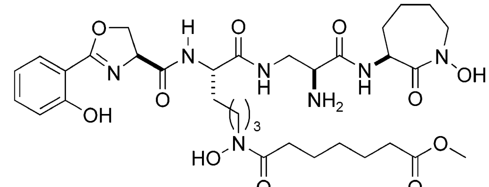
Library: 5.8
Name: Negamycin analogs
Size: Not defined
Reference: Raju [300]



Microbe: *K. pneumoniae*
Activity: MIC = 4 μg/mL

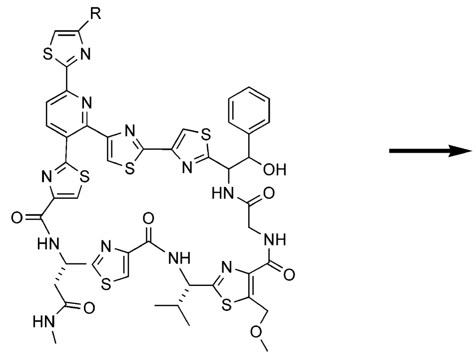
Library: 5.9
Name: Carboxymycobactin T7 analog
Size: 4 members
Reference: Poreddy [293]

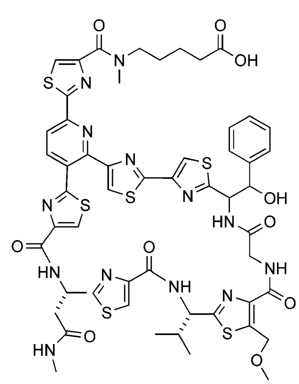




Microbe: *M. avium*
Activity: "high" initial activity diminishing to inactive in 4 weeks in culture

Library: 5.10
Name: Thiazole peptide
Size: 500 members
Reference: Clough [65]
Note: Solution and solid-phase libraries prepared.

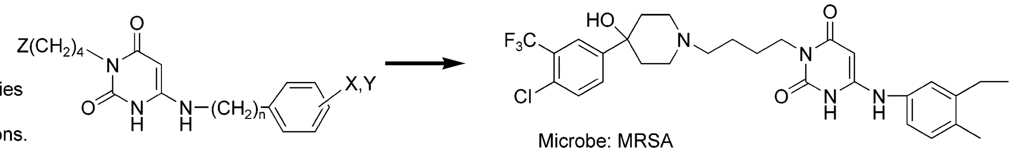




Microbe: MRSA ATTC33591
MIC = 0.125 μg/mL

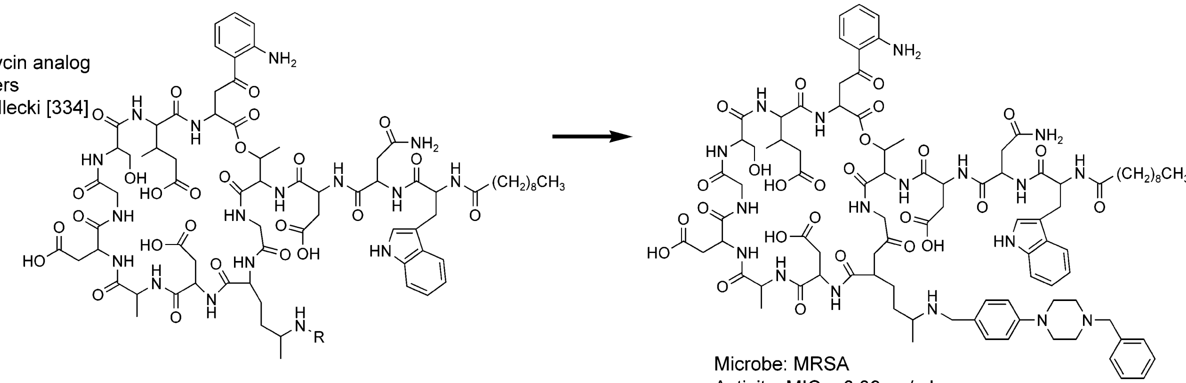
Table 5. (Continued)

Library: 5.11
Name: 6-Anilinouracil
Size: >50 members
Reference: Zhi [424]
Note: Multiple solution-phase libraries using 6-chloro-3-(z-alkyl) substituted uracil as starting synthons.



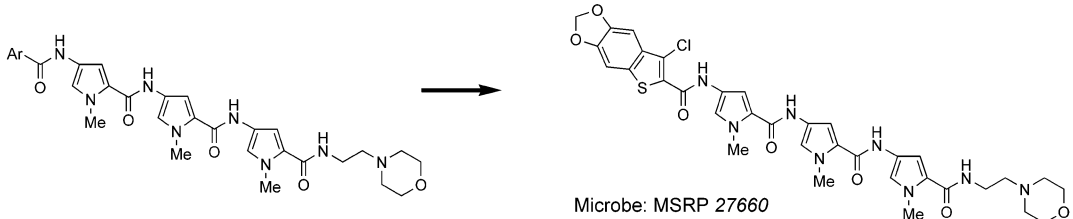
Microbe: MRSA
Activity: MIC = 2.5 μg/mL; inhibition of *B. substilis* DNA polymerase III C: K_i = 32 nM

Library: 5.12
Name: Daptomycin analog
Size: 90 members
Reference: Siedlecki [334]



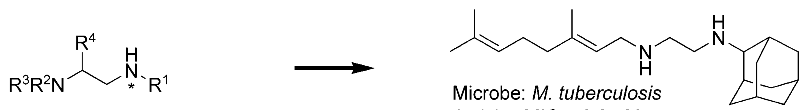
Microbe: MRSA
Activity: MIC = 0.39 μg/mL

Library: 5.13
Name: Distamycin A analog
Size: Not defined
Reference: Kaizerman [180]
Note: Library part of a C- and N-terminal optimization.



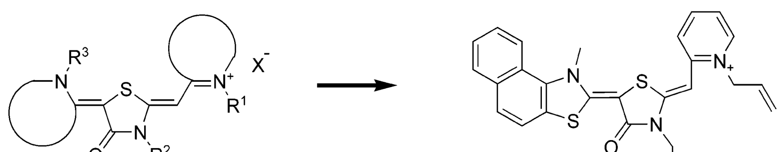
Microbe: MSRP *27660*
Activity: MIC = 0.31 μg/mL

Library: 5.14
Name: Ethambuto analog
Size: 3456 members
Reference: Lee [210]



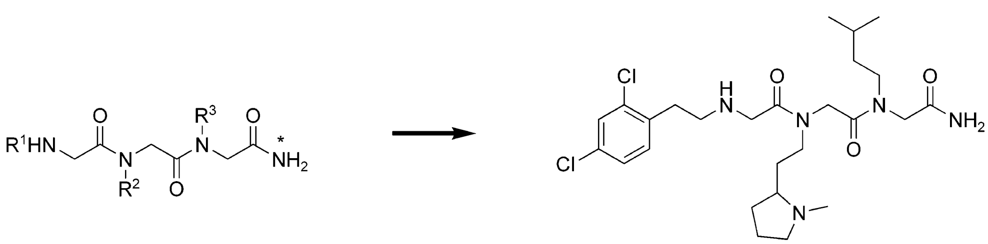
Microbe: *M. tuberculosis*
Activity: MIC = 0.2 μM

Library: 5.15
Name: Rhodacyanine dye
Size: 27 members
Reference: Takasu [353]



Microbe: *P. falciparum*
Activity: EC_{50} = 6 nM

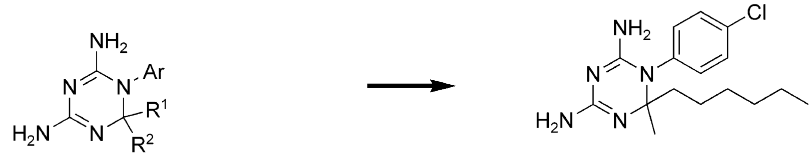
Library: 5.16
Name: Tripeptoid
Size: >10,000 members
Reference: Humet [163]



Microbe: *P. aeruginosa* ATCC 9721
Activity: MIC = 0.25 mg/mL

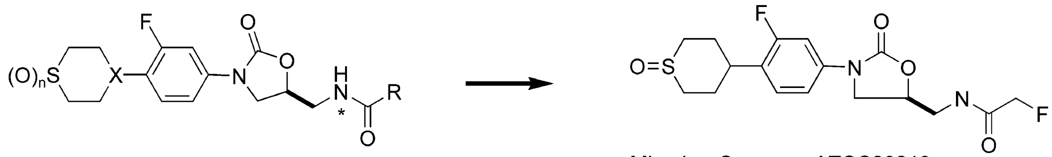
Table 5. (Continued)

Library: 5.17
Name: Dihydrotriazine
Size: 96 members
Reference: Vilaivan [374]



Microbe: *P. falciparum*
Activity: K_i = 0.7 μM

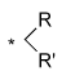
Library: 5.18
Name: Oxazolidinones
Size: 379 members
Reference: Singh [336]



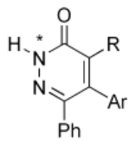
Microbe: *S. aureus* ATCC29213
Activity: MIC = 32 μg/mL

Table 6. Scaffold Derivatization

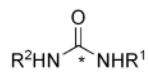
A: Solid-Phase (Asterisk (*), Point of Attachment to Resin)



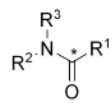
- Bertini [29]
- 7 ex; 0-90%
- reduction of resin-bound dithianes using Na/NH_3 or Bu_3SnH



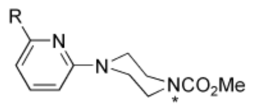
- Sotelo [340]
- 8 ex; 74-86%
- Suzuki-type derivatization of resin-bound halo pyridazinones; R = H, Ar



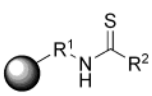
- Fattori [106]
- 12 ex; 69-100%
- amides via Kenner safety-catch linker



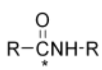
- Humphrey [165]
- 16 ex; 28-100%
- amine acylation using resin-bound O-acyl cyclohexane-1,3-dione



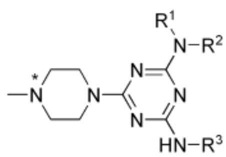
- Louerat [230]
- 8 ex; *ca.* 50%
- assorted Pd-catalyzed C-C bond formation



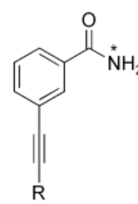
- Coats [66]
- 6 ex; high conversion
- Lawesson's thionation reaction in benzyl benzoate as high temperature solvent



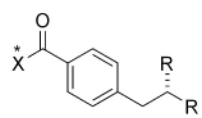
- Byun [51]
- 24 members
- amine acylation with resin-bound pyrazolone active ester



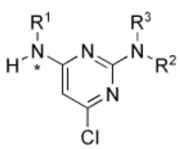
- Maclean [238]
- 4 members
- release of amines following methylation of resin-bound piperazines



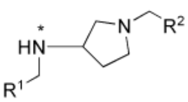
- Erdelyi [100]
- 6 ex; 0-98%
- microwave-assisted Sonogashira coupling of resin-bound aryl iodides and aryl acetylenes



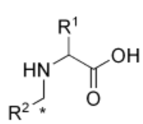
- Oates [272]
- *ca.* 9 ex; 49-99%
- cross-coupling organozinc reagents with resin-bound aryl and acryl iodides



- Montebugnoli [257]
- *ca.* 15 ex; good yield
- from carbamate-linked 4-amino-2,6-dicholorpyrimidine



- Forns [111]
- no specific ex
- release of secondary amines from BAL resin

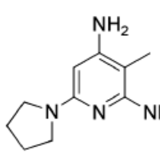


- Forns [111]
- no specific ex
- release of secondary amines from BAL resin

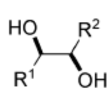
Part B: Solution-phase

Ar-Ar

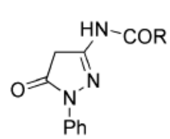
- Atrash [13]
- 17 ex; 71-92%
- Suzuki coupling using resin plug-bound Pd°



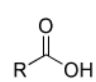
- Menichincheri [251]
- 18 ex; 37-83%
- sequential displacement of F in 4-amino-2,6-difluoro-3,5-dichloropyrimidine then hydrogenolysis



- Ley [217]
- 8 ex; 73-90%
- dihydroxylation of olefins using microencapsulated osmium tetroxide in polyurea



- Fu [112]
- 9 ex; 25-81%
- polymer-assisted acylation of 3-amino-pyrazolinones



- Crosignani [73]
- 14 ex; 89-96%
- esterification of acids with *O*-alkyl isoureas

Table 6. (Continued)

R^1R^2NH

- Schoenleber [318]
- 4 ex; 71-90%
- photochemical release of amines from coumarin chromophore

R^1XR^2

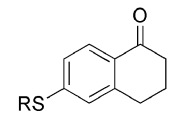
- Lan [195]
- 5 ex; 80-90%
- Mitsunobu reaction using anthracene-tagged phosphine and polymer-bound azodicarboxylate

R-O-R

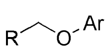
- Choi [61]
- 10 ex; 65-83%
- Mitsunobu reaction using resin-bound triphenylphosphine

R-Br

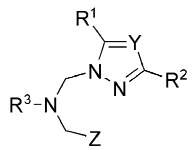
- Choi [61]
- 6 ex; good yields
- bromination of alcohols using Br_2 and resin-bound triphenylphosphine



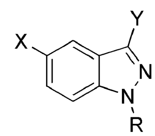
- Zhang [416]
- 4 ex; good yields
- Pd-catalyzed aryl sulfides from aryl fluorous triflate



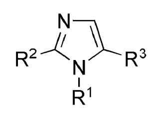
- Ruhland [310]
- 6 ex; 61-100%
- Mitsunobu reaction on tablets of functionalized polystyrene beads



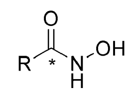
- Touzani [365]
- *ca.* 20 ex; good yield
- condensation of N-alkyl heteroarylamines with N-hydroxymethyl pyrazoles



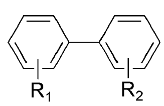
- Menon [252]
- *ca.* 13 ex; 3-62%
- from indazole



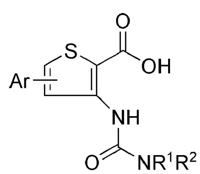
- Sezen [325]
- multiple ex;
- C-H bond functionalization



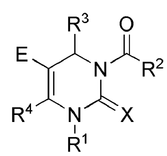
- Devocelle [91]
- 5 ex; 34-100%
- acids + polymer-bound HOBt + NH_2OH or $NH_2OTBDMS$



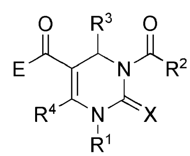
- Lan [196]
- 25 ex; 66-100%
- Suzuki coupling with anthracene-tagged Pd catalyst or tagged arylboronic acids



- Le Foulon [205]
- 20 ex; 84-95%
- from thiaisatoic anhydride



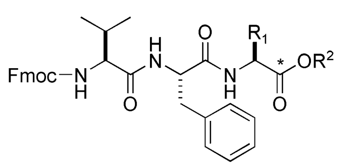
- Dallinger [79]
- 20 members
- microwave-assisted acylation of dihydropyrimidines



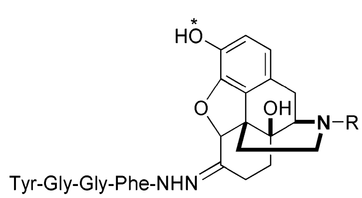
- Dallinger [78]
- 28 members
- *N3*-acylaton of dihydropyrimidines

Table 7. Acyclic Synthesis

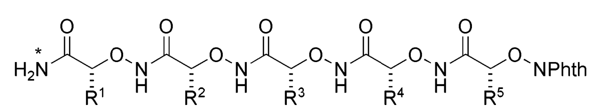
Part A: Solid-Phase (Asterisk (*), Point of Attachment to Resin)



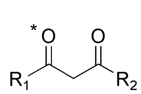
- Peters [289]
- 7 ex; good yield
- peptide esters from hydrazide linker



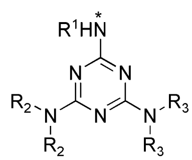
- Wang [382]
- 2 ex; yield not given
- from resin-bound naloxone or naltrexone



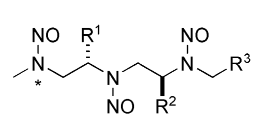
- Lee [209]
- 11 ex; good purity
- step-wise assembly of phthaloyl protected monomers



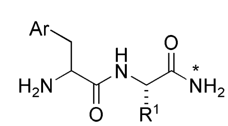
- Park [279]
- 10 ex; 29-66%
- acylation of resin-bound piperidine-based enamine then acid hydrolysis



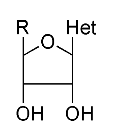
- Bork [41]
- 96 members
- from 2,4-di-Cl_2-6-thiotriazine



- Yu [409]
- 8 ex; 44-56%
- Post cleavage treatment of triamines with EtONO

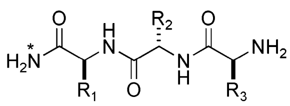


- Doi [96]
- 36 ex; high ee
- reduction of resin-bound dehydro systems with chiral Rh catalyst at 10 psi [H]

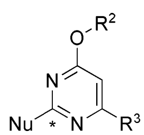


- Epple [99]
- 25,000 members
- nucleoside analogs using 2',3'-acetal linkage for resin attachment

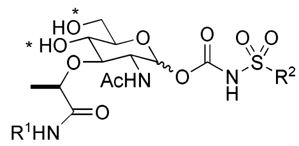
Table 7. (Continued)



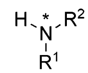
- Kozmin [191]
- 125 members
- novel 3-D array using reaction vessel with 4-sided opening



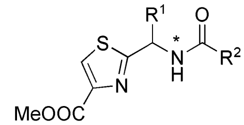
- Font [110]
- 12 ex; 32-72%
- from 2-mercapto-pyrimidin-4-one



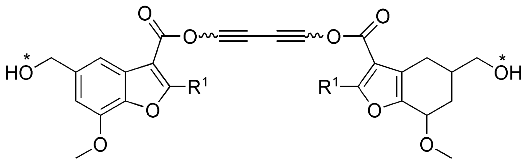
- Maletic [245]
- 9 member
- benzylidene acetal as linkage strategy of protected glycosides



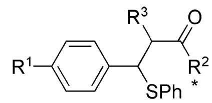
- Congreve [68]
- 16 ex; 21-63%
- 1° and 2° amines from N-Boc-*o*-nitro benzenesulfonamide linker



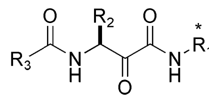
- Henkel [146]
- 24 ex; good yield
- 4cc using Rink amide resin, aldehyde, 3-(N,N-dimethylamino)-2-iso-cyanoacrylate and thio-carboxylic acid



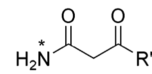
- Liao [221]
- 8 ex; 70-90% purity
- aliphatic acetylenic homo-coupling



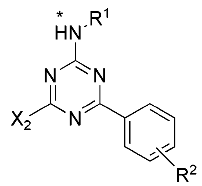
- Senfuss [323]
- 13 ex; 0-70%
- Michael addition of PhSH to resin-bound α,β-unsaturated esters



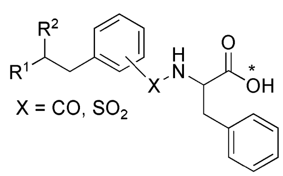
- Basso [21]
- 12 ex; 50-92%
- Passerini 3cc then IBX oxidation



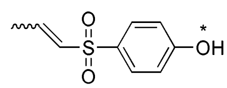
- Gross [132]
- 14 ex; >90%
- reaction of Li enolates with 4-nitrophenyl carbamate resin



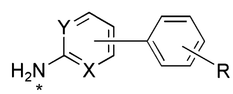
- Bork [40]
- multiple examples
- Pd-catalyzed cross coupling of resin-bound chlorotriazines



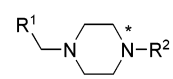
- Ferguson [109]
- 36 ex; good yield
- 9-BBN-mediated Suzuki coupling



- Wang [380]
- 1 ex; good yield
- Horner-Evans condensation of resin bound sufonyl phosphonate and amino acid aldehydes



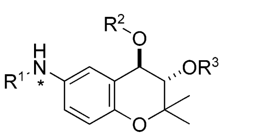
- Zhu [426]
- 45 ex; 17-90%
- attachment of unreactive amines to solid support



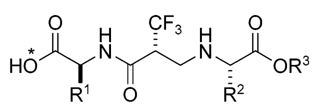
- Salvino [313, 314]
- 12 ex; 55-82%
- borane reduction of resin-bound acylated piperazine cleavage, then derivatization

$HO^*-X-R-CH_2CHO$

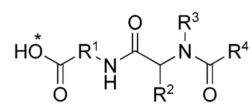
- Dessole [89]
- 5 ex; 90-98%
- hydroformylation of terminal alkenes



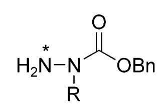
- Gong [125]
- 2000 members
- multi-step sequence from carbamate linked 6-amino-2, 2-dimethylchromene



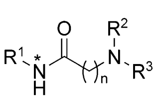
- Volonterio [377]
- 14 ex; high purity
- N-acylation of resin-bound amino acids with 2-CF_3-propenyl chloride then aza-Michael with amino acid esters



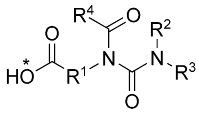
- Henkel [145]
- 24 members
- Ugi reaction using resin-bound isocyano-carboxylates



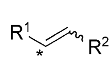
- Mukherjee [260]
- 5 ex; 71-81%
- capture-ROMP-release



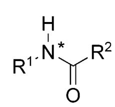
- Shannon [327]
- 60 members
- acylation of resin-bound amines



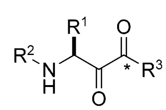
- Ravn [301]
- 14 ex; 30-89%
- multi-step sequence from resin-bound amino acids



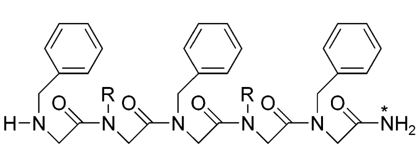
- D'herde [75]
- 2 ex; 25-27%
- reductive elimination of β-benzoyloxysulfones with SmI_2 (Julia-Lythgoe olefination)



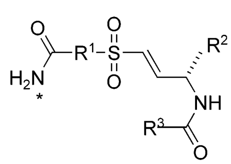
- His [150]
- *ca.* 8 ex; 60-95%
- Beckmann rearrangement of resin-bound ketoximes



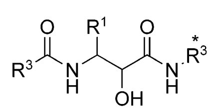
- Weik [388]
- 10 ex; 62-99%
- acylation of a resin-bound phosphorane then cleavage



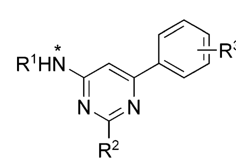
- Burkoth [50]
- *ca.* 12 ex; 53-92%
- R = heterocylic side chains



- Wang [381]
- 30 members
- multi-step sequence: Horner-Emmons olefination of amino acid aldehydes

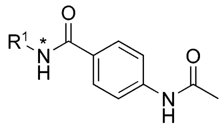


- Banfi [17]
- several ex; good yield
- Passerini-amine deprotectionacyl migration

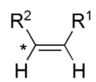


- Wade [379]
- 6 ex; 25-48%
- Suzuki cross-coupling to resin-bound 6-chloro-pyrimidines

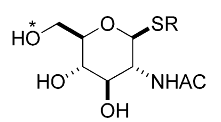
Table 7. (Continued)



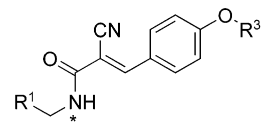
• Luo [234]
• *ca.* 20 ex; 0-92%
• acylation of resin-bound N-alkyl sulfonamides then radical cleavage with $TiCl_4$/Zn



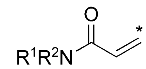
• Sheng [328]
• 10 ex; 70-80%
• Ni-catalyzed coupling of resin-bound vinylic selenides with Grignard reagents; E-isomers also prepared



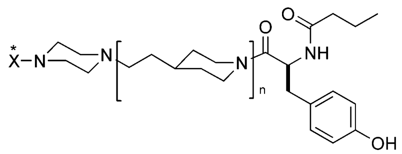
• Hummel [164]
• 1088 members
• from resin-bound N-acetyl-2-deoxy-1-thio-β-D-glycopyranoside



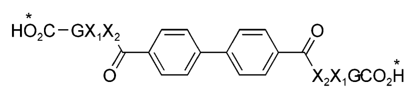
• Guo [134]
• 4500 members
• acylation of resin-bound amines with cyano acetic acid, Knoevenagel condensation with phenolic aldehyde then Mitsunobu coupling



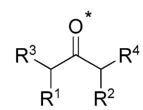
• Sheng [329]
• 9 ex; 85-93%
• from resin-bound β-selenopropanoyl chloride



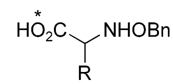
• Olsen [275]
• *ca.* 4 ex;
• alkylation of resin-bound piperidine



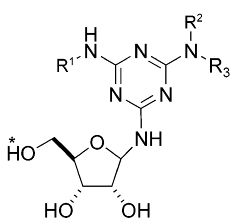
• Ahn [6]
• 81 members
• Suzuki coupling of sub-libraries of soluble polymer-bound tripeptide aryl iodides and tripeptide aryl boronic acids



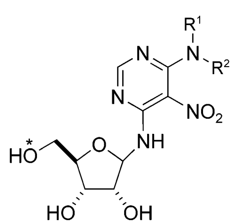
• Lazny [203]
• 18 ex; 32-95%
• alkylation of resin-bound hydrazone then hydrolysis



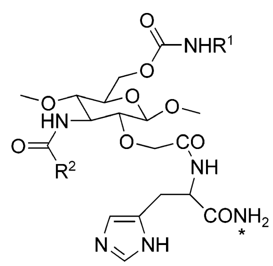
• Miyabe [255]
• 6 ex; high yield
• Et_3B-induced radical addition to resin-bound oxime ethers



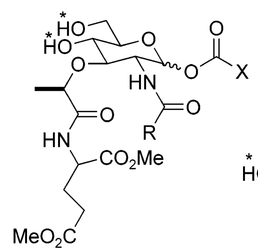
• Varaprasad [371]
• 1152 members
• from resin-bound 1-azido-furanoside and cyanuric chloride



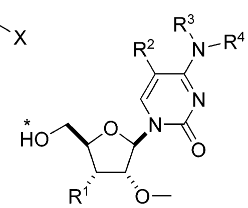
• Varaprasad [371]
• 82 members
• from resin-bound 1-azido-furanoside and 4,6-dichloro-5-nitropyrimidine



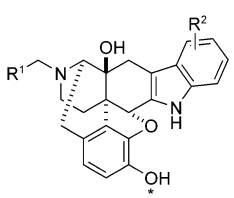
• Jain [175]
• 48 members
• from resin-bound 3-azido-3-deoxy-glycopyranoside



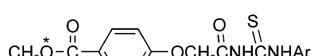
• Maletic [245]
• 5 ex; good yields
• acetal-linked orthoganol protected glycoside



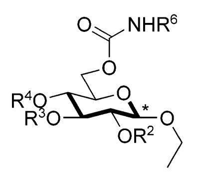
• Ding [94]
• 672 members
• from resin-bound 2'-O-methylcytidine



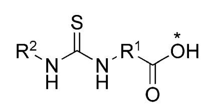
• Tanaka [356]
• 40 members
• from resin-bound Fmoc-protected noroxycodone



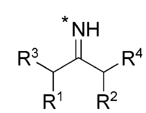
• Li [220]
• 13 ex; high yields
• from resin-bound 4-hydroxybenzoic acid



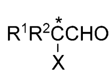
• Opatz [276]
• 36 members
• from an orthoganol protected resin-bound glycoside



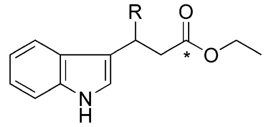
• Boas [35]
• 9 ex; 70-100%
• resin-bound amine treated with CS_2 and PyBOP to give the corresponding isothiocyanate then addition of R^2NH_2



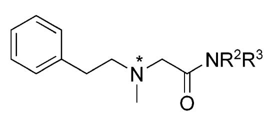
• Lazny [203]
• 18 ex; 22-90%
• alkylation of resin-bound hydrazone then BH_3 reduction



• Sheng [330]
• 7 ex; 74-92%
• reaction of resin-bound α-seleno aldehydes with Br_2 or SO_2Cl_2; X = Cl, Br



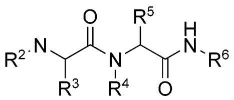
• Liu [228]
• 9 ex; 69-89%
• condensation between indole, polymer-supported cyclic malonic acid ester and aldehyde



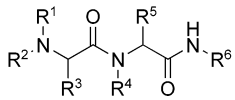
• Morphy [143]
• 10 ex; 5-95%
• REM resin using perfluorous solvent

Table 7. (Continued)

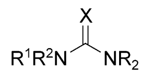
Part B: Solution-Phase



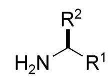
• Portlock [294]
• 9 ex; 30-73%
• tandem Petasis-Ugi multi-component condensation



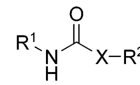
• Portlock [295]
• 11 ex; 22-72%
• Petasis-Ugi multi-component condensation reaction



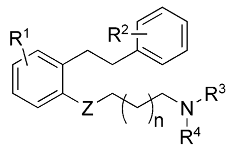
• Cho [632]
• 24 members; high purity
• reacton of amine with isocyanate then scavenging excess amine with self-indicating resin



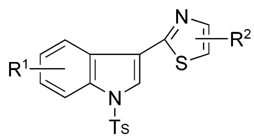
• Mukade [259]
• 10 ex; 72-84%
• chiral α-substituted amines via stereoselective addition of organomagnesium reagents of enantiomerically pure *tert*-butanesulfinyl imimes



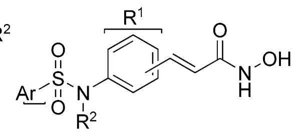
• Lu [231]
• 13 ex; 34-80%
• conversion of RCOOH to carbamates and ureas via polymer-supported di-phenylphosphoryl azide



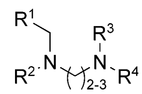
• Husemoen [167]
• > 58 members
• stilbene library first created using Wittig chemistry then hydrogenation and functionalization



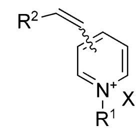
• Zou [427]
• 8 ex; 0-92%
• Suzuki coupling of indoles with chlorothiazole



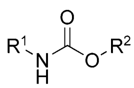
• Vickerstaffe [373]
• 36 members
• multi-step sequence from 4-iodo-aniline



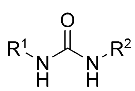
• Dagan [76]
• 600 members
• from amino alcohols



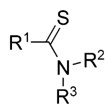
• Rosania [307]
• 276 members
• fluorescent dyes for selective organelle visualization



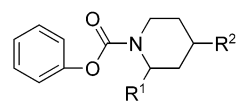
• Lu [231]
• 13 ex; 34-80%
• conversion of RCOOH to carbamates and ureas via polymer-supported di-phenylphosphoryl azide



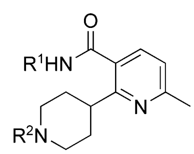
• Lu [231]
• 13 ex; 34-80%
• conversion of RCOOH to carbamates and ureas via polymer-supported di-phenylphosphoryl azide



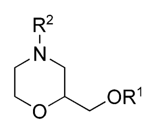
• Zbruyev [413]
• Kindler thioamide synthesis (RCHO, elemental sulfur and amine)



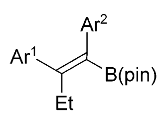
• Wang [383]
• 9 ex; good yield
• Cu-mediated organozinc addition to 1-acylpyridines then hydrogenation of the intermediate dihydropyridines



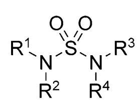
• Bashford [85]
• *ca.* 2100 members
• from the corresponding N-Boc protected pyridine carboxylic acid



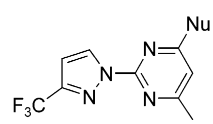
• Lainton [192]
• 7907 members
• from N-benzyl-3-hydrox-methyl morpholine



• Itami [171]
• 15 ex; good yields
• Cu-catalyzed carbo-magnesation across alkynyl-(2-pyridyl)silane



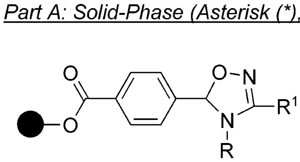
• Beaudoin [24]
• *ca.* 30 ex; up to 90%
• from N,N'-sulfuryldiimidazole



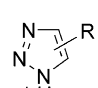
• Zhang [419]
• *ca.* 30 ex; up to 90%
• from fluorous thiol and 2,6-dichloro-6-methyl-pyrimidine

Table 8. Monocyclic Synthesis

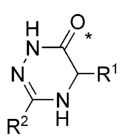
Part A: Solid-Phase (Asterisk (*), Point of Attachment to Resin)



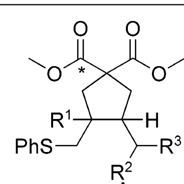
• Shang [326]
• 11 ex; 85-95%
• 1,3-dipolar cycloaddition of resin-bound imine and nitrile oxides



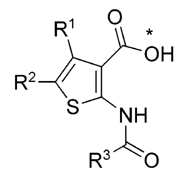
• Garanti [116]
• *ca.* 5 ex; >90%
• cycloaddition of MeOPEG-N_3 and alkynes



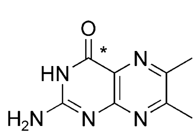
• Boeglin [37]
• 10 ex; 60-92%
• hydrazine-mediated intracyclative cleavage of resin-bound thioamides



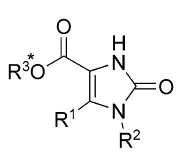
• Harrowven [142]
• 4 ex; *ca.* 65%
• sulfur-mediated cyclization of resin-bound dienes



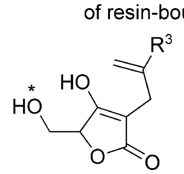
• Hoener [152]
• *ca.* 15 ex; 81-99%
• microwave-assisted Gewald synthesis



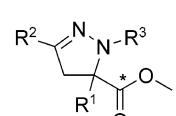
• Gibson [122]
• 5 ex; good yield
• traceless Nu-mediated cleavage of thioether linked aminopyrimidinone



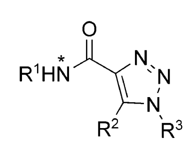
• Lee [211]
• *ca.* 15 ex; 16-79%
• N-H insertion of 1° ureas into rhodium carbenoid intermediates



• Schobert [317]
• 5 ex; good yield
• condensation of resin-bound α-hydroxy esters with Ph_3P =C=C =O

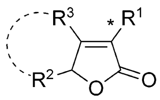


• Wang [384]
• 18 ex; 69-91%
• 3cc of PEG-supported acrylate, R^2CHO, R^2NHNH_2 in the presence of chloramine-T

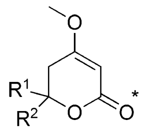


• Blass [33]
• 12 ex; 0-98%
• from alkyl halides and alkynes using polymer supported azide

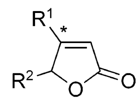
Table 8. (Continued)



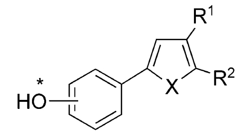
- Huang [159]
- 13 ex; 76-90%
- alkylation of resin-bound α-selenocarboxylic acids and Se elimination



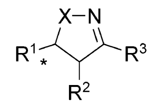
- Pierres [291]
- 21 ex; 20-55%
- hetero-Diels-Alder reaction of resin-bound Brassard diene



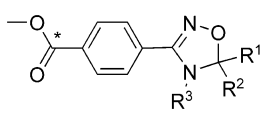
- Fujita [114]
- 5 ex; 41-83%
- intramolecular oxy-selenenylation/de-selenenylation using resin-bound ArSeBr



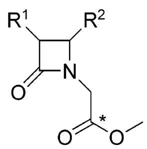
- Raghavan [299]
- *ca.* 16 ex; 65-80%
- from resin-bound 1,4-diketones; X = O, S, N-Ar



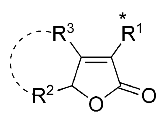
- Chen [57]
- 12 ex; 10-45%
- use of resin-bound benezenesulfinate as a traceless linker; X = O, NR^4



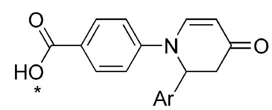
- Lin [225]
- 12 ex; 79-91%
- 1,3-dipolar cyclo-addition of nitrile oxides and amines



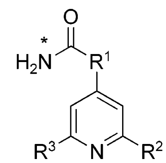
- Delpiccolo [88]
- 16 ex; 40-85%
- Staudinger reaction



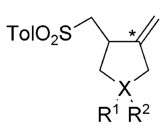
- Huang [159]
- 13 ex; 76-90%
- from resin-bound α-selenocarboxylic acids



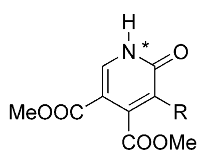
- Guo [135]
- 18 ex; 31-99%
- liquid-phase synthesis; 3cc aza Diels-Alder reaction



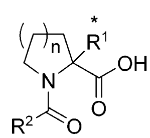
- Fujimori [113]
- 220 members
- Krohnke pyridine synthesis



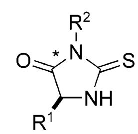
- Qian [297]
- 8 ex; 44-58%
- radical cyclization of 1,6-dienes using resin-bound seleno sulfone then resin cleavage via oxidation/elimination



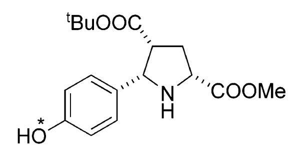
- Kaval [182]
- 2 ex; 27-45%
- Diels-Alder reaction of resin-bound 2(1H)-pyrazinone with DMAD



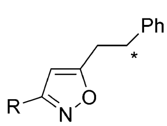
- Scott [321]
- 48 members
- alkylation of resin-bound amino acid aldimines with dihaloalkanes, hydrolysis, intramolecular N-alkylation then cleavage



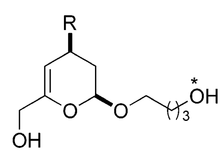
- Lin [224]
- 14 ex; > 85%
- microwave-assisted parallel synthesis from resin-bound Fmoc-protected amino acids



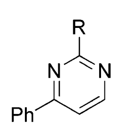
- Chen [55]
- 1 ex; 79%
- catalytic asymmetric [3+4] cycloaddition of azomethine ylide



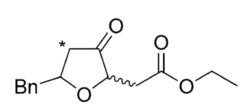
- Huang [160]
- 7 ex; 62-78%
- [3+2] cycloaddition to resin-bound propargyl selenide



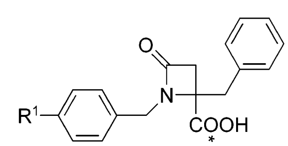
- Arbore [12]
- 5 ex; 10-84%
- hetero Diels-Alder with resin-bound vinyl ethers



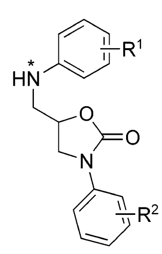
- Spivey [343]
- 16 ex; 27-98%
- condensation of resin-bound dimethylgermyl enaminone and amidines



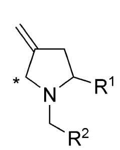
- Berlin [27]
- 1 ex; 55%
- carbonylation/reductive cyclization of resin-bound selenide



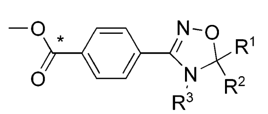
- Gerona-Navarro [120]
- 2 ex; good yield
- lactam ring formation via base promoted intramolecular cyclization of resin-bound N-chloroacetyl amino acids



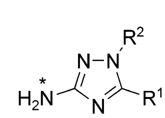
- Buchstaller [46]
- 9 ex; 93-99%
- ring opening of resin-bound epoxides with anilines then treatment with an isocyanate



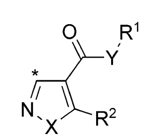
- Brown [45]
- 5 ex; 15-70%
- Pd-catalyzed intracyclative cleavage of carboxylate-linked (2-ethylamino)allylic alcohols



- Lin [226]
- 10 ex; 64-87%
- 1,3-dipolar cycloaddition of resin-bound nitrile oxide and imines

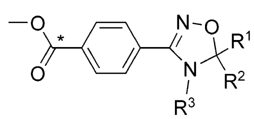


- Yu [410]
- 13 ex; 59-75%
- acylation of S-methylisothioureas then treatment with R^{2}NHNH$_2$

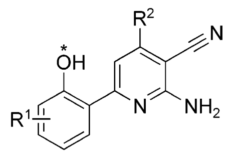


- De Luca [83]
- 38 ex; good yield
- from cellulose-bound enaminones and NH$_2$XH; X = NCONH$_2$, N-aryl, O

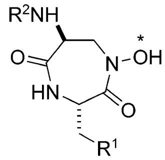
Table 8. (Continued)



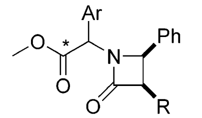
- Lin [227]
- 13 ex; 79-93%
- 1,3-dipolar cycloaddition of PEG-bound nitrile oxide and imines



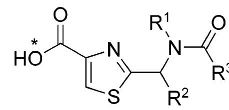
- Shintani [333]
- 18 ex; good purity
- 3CC from resin-bound 2-hydroxyacetophenones, aldehydes and malononitrile



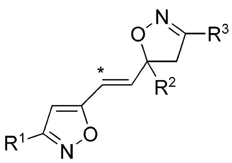
- Lampariello [194]
- 2 ex; good yield
- from resin-bound hydroxylamine resin with amino acid then intramolecular cyclization and cleavage



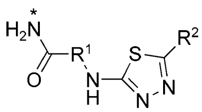
- Le Roy [206]
- *ca.* 3 ex; good yields
- 19F NMR monitored Staudinger reaction of resin-bound imines



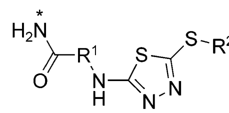
- Henkel [147]
- 25 ex; 26-85%
- 4CC of R^2CHO, R^3COOH, R^1-NH_2 and resin-bound 3-N,N-(dimethylamino)-2-isocyanoacrylate



- Huang [160]
- 7 ex; 62-78%
- 1,3-dipolar cycloadditins and the α-alkylation reaction of selenium resins

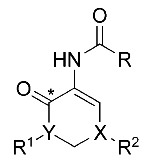


- Kilburn [186]
- 6 ex; 12-74%
- from resin-bound amino acid derived thiosemicarbozide

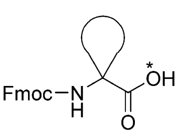


- Kilburn [186]
- 6 ex; 49-75%
- from resin-bound amino acid derived thiosemicarbozide

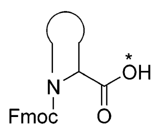
- Harju [138]
- 11 ex; 17-44%
- 1,3-dipolar cycloaddition of resin-bound azide with alkynes



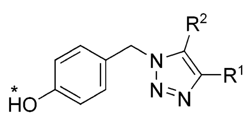
- Westman [391]
- 3 ex; 77-95%
- from resin-bound amino propenoates



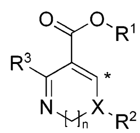
- O'Donnell [271]
- 5 ex; 55-77%
- intramocular alkylation of side chain reactive (alkylhalo)amino acids



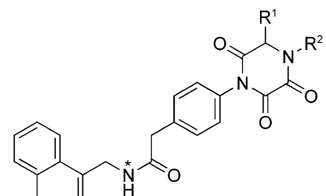
- O'Donnell [271]
- 3 ex; 29-65%
- intramolecular N-alkylation of side chain reactive (alkylhalo)amino acids



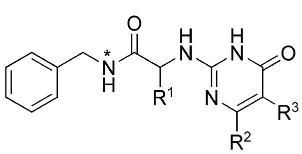
- Harju [138]
- 11 ex; 17-58%
- 1,3-dipolar cycloaddition of resin-bound azide with enamines or alkynes



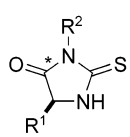
- Westman [391]
- 4 ex; 81-94%
- from resin-bound amino propenoates



- Makino [244]
- *ca.* 25 ex; good yields
- condensation of resin-bound amino acids with oxalyl diimidazole

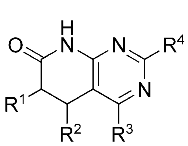


- Zapf [412]
- 4 ex; good yield
- from resin-bound quanidines

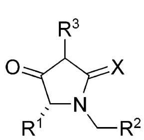


- Lin [224]
- 14 ex; > 90%
- resin-bond amino acids treated with isothiocyanates then intracyclative release all under microwave irradiation

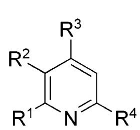
Part B: Solution-Phase



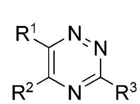
- Mont [256]
- 10 ex; 53-98%
- 3cc of α,β-unsaturated esters, amidines and malononitrile; $R^3 = NH_2$. OH



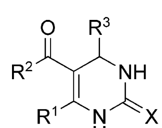
- Zhang [423]
- 10 ex; 46-98%
- fluorous synthesis X = O, S



- Bagley [15]
- *ca.* 7 ex; good yield
- condensation of enamine esters and alkynones

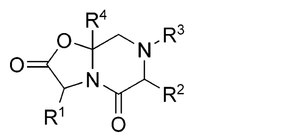


- Zhao [425]
- 12 ex; 64-92%
- microwave-assisted condensation of 1,2-diketones, acylhydrazines and NH_4OAc

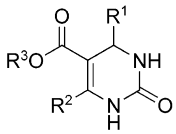


- Sabitha [312]
- 60 members
- VCl_3-catalyzed Biginelli condensation

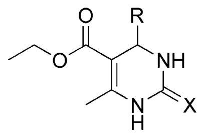
Table 8. (Continued)



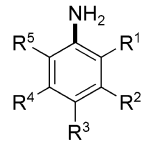
- Lewis [216]
- 12 ex; 22-74%
- base-catalyzed cyclization of *N*-(2-oxoalkyl)-dipeptide esters



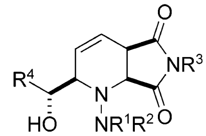
- Adrian [5]
- 64 members
- Ni-catalyzed 3cc of ureas, R^1CHO and β-keto esters



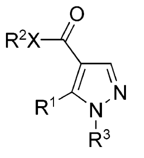
- Maiti [239]
- 17 ex; 72-94%
- 3CC mediated by LiBr; X = O, S



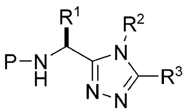
- Neumann [266]
- 10 ex; 44-88%
- 3CC reaction of amide, RCHO and dienophile then dehydrogenation



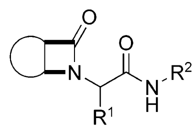
- Toure [364]
- 15 ex; 0-75%
- tandem aza [4+3]/allylboration using 4-borono-hydrazonodienes



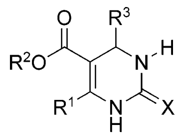
- Giacomelli [121]
- 21 members
- from hydrazines and enamino-β-keto esters and amides



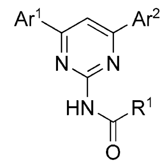
- Boeglin [38]
- 10 ex; 49-80%
- condensation of thioamides and hydrazides



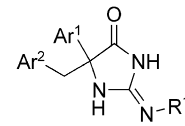
- Gedey [118]
- 135 members
- Ugi 3cc reaction



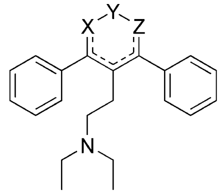
- Bose [42]
- 13 ex; > 70%
- $CeCl_3$-mediated Biginelli condensation X = O, S



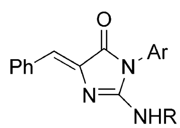
- Varga [372]
- 5 ex; good yield
- from chalcone and guanidine



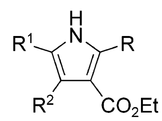
- Varga [372]
- 12 ex; good yield
- from chalcone and guanidine



- Bertozzi [31]
- 5 ex; *ca.* 50%
- heterocyclic structures produced from a multi-component reaction



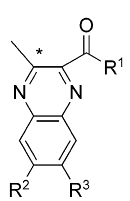
- Ding [92]
- 13 ex; 56-82%
- aza-Wittig reaction of iminophosphorane with aromatic isocyanate to give carbodiimide and subsequent reaction with aliphatic primary amine



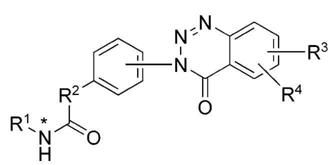
- Yu [407]
- *ca.* 25 ex; 39-91%
- Lewis acid activated donor-acceptor cyclopropanes react with unsaturated nitriles in a cascade [3 + 2] dipolar cycloaddition, dehydration and tautomerization sequence

Table 9. Bicyclic and Spirocyclic Synthesis

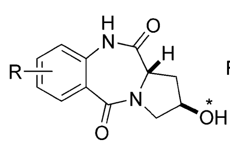
Part A: Solid-Phase (Asterisk (*), Point of Attachment to Resin)



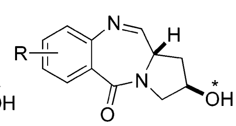
- Attanasi [14]
- 8 ex; 15-38%
- condensation of aryl diamines and resin-bound 1,2-diaza-1,3-butadienes



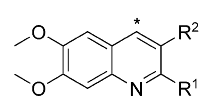
- Okuzumi [271]
- 15 ex; 82-95%
- from resin-bound anilines, anthranylic acids and *t*-butyl nitrile



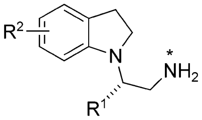
- Kamal [181]
- 3 ex; good yields
- reduction of aryl N_3 or NO_2 and ring closure



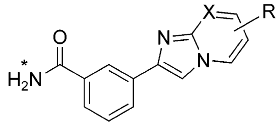
- Kamal [181]
- 3 ex; good yields
- reduction of aryl N_3 or NO_2 and ring closure



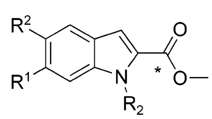
- Patteux [284]
- *ca.* 6 ex; 50-81%
- traceless Friedlander synthesis



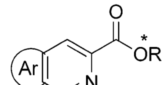
- Yu [408]
- 11 ex; 66-84%
- intramolecular Pd-catalyzed cyclization of resin-bound 2-bromophenylacylated amino acids



- Kazzouli [183]
- 8 ex; 50-80%
- condensation of resin-bound α-bromoketones and 2-amino-pyridine/pyrimidines

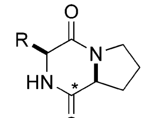


- Yamazaki [403]
- 6 ex; 43-99%
- intramolecular Pd-catalyzed amination of immobilized *N*-substituted dehydrobromophenylalanine



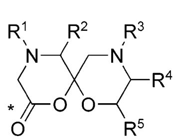
R = H, OMe

- Yamazaki [403]
- 2 ex; 52-56%
- Heck reaction of immobilized de-hydroalanate and 2-bromoaryl carboxylates

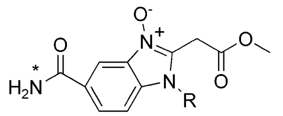


- Sun [349]
- 16 ex; 90-99%
- from PEG-bound proline

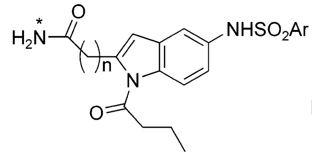
Table 9. (Continued)



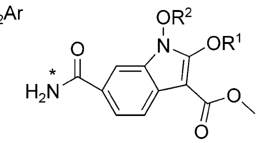
• Trump [367]
• 12 ex; 9-36%
• multi-step sequence from resin-bound amino acid esters



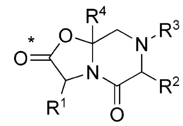
• Wu [400]
• 9 ex; 53-88%
• from resin-bound 4-fluoro-3-nitro-benzoic acid



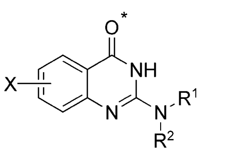
• Dai [77]
• 12 ex; 65-82%
• Pd^{2+} or Cu^{2+}-mediated ring closure of resin-bound 2-alkynylanilides



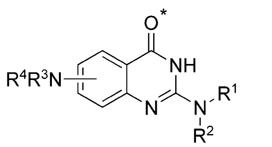
• Wu [399]
• 64 members
• from 4-fluoro-3-nitro benzoic acid



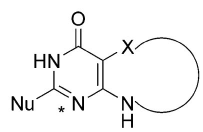
• Lewis [216]
• *ca.* 9 ex; good yields
• base-catalyzed cyclization of N-(2-oxoallyl)-dipeptide esters



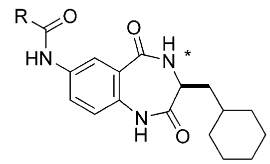
• Weber [386]
• 11 ex; 78-91%
• from 2,4,6- and 2,4,7-trichloroquinazolines and benzyl alcohol type linkers



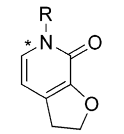
• Weber [386]
• 17 ex; 57-71%
• from 2,4,6- and 2,4,7-trichloroquinazolines and benzyl alcohol type linkers



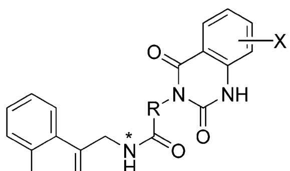
• Gibson [123]
• 5 ex;
• from thioether-linked pyrimidine



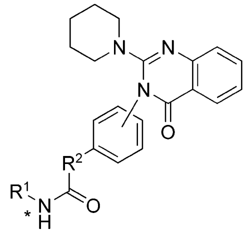
• Ettmayer [102]
• 4 ex; good yield
• from resin-bound 5-nitro anthranilyl amino acid esters



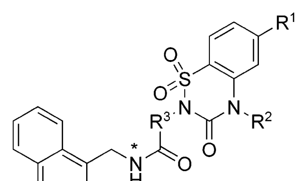
• Kaval [182]
• 2 ex; 16-79%
• intramolecular Diels-Alder reaction of resin-bound 2(1H)-pyrazinone



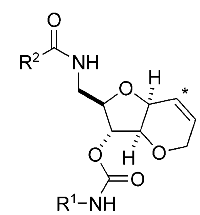
• Okuzumi [274]
• *ca.* 12 ex; 80-100%
• coupling resin-bound anilines to anthranilic acids, cyclization with CDI then release



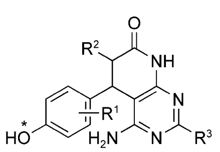
• Makino [241]
• 9 ex; 84-95%
• condensation of resin-bound anilines and aryl isocyanates and piperdine



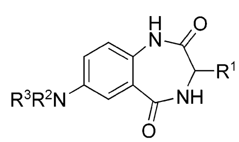
• Makino [242]
• *ca.* 20 ex; good yield
• reduction of resin-bound 2-nitro-benzene sulfonamides then cyclization with CDI



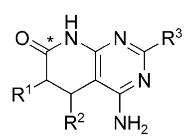
• Timmer [362]
• 9 members
• cleavage from resin via RCM reaction



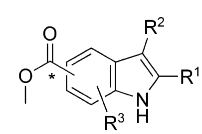
• Falco [104]
• 32 members
• multi-step sequence from resin-bound cinnamates



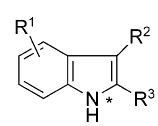
• Migihashi [254]
• 400 members
• acylation of resin-bound amino acid esters with 5-fluoro-2-nitrobenzoic acid, amine displacement of F, NO_2 reduction, intracyclative cleavage



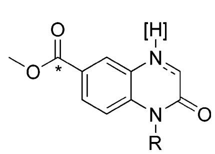
• Falco [105]
• 40 members
• reaction of resin-bound unsaturated esters with malononitrile the cleavage with amidines



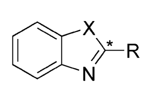
• Knepper [189]
• 16 ex; 11-37%
• Bartoli indole synthesis



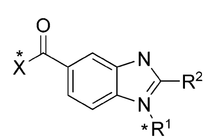
• Rosenbaum [308]
• 11 ex; 7-39%
• traceless Fischer indole synthesis



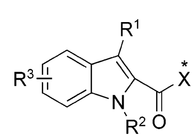
• Chang [54]
• 13 ex; 76-99%
• from resin-bound diamino benzoic acids and $ClCH_2COCl$



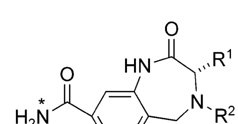
• Matsushita [250]
• *ca.* 30 ex; 0-99%
• resin-bound esters treated with 2-aminothiophenols or 1,2-phenylenediamines in the presence of a Lewis acid



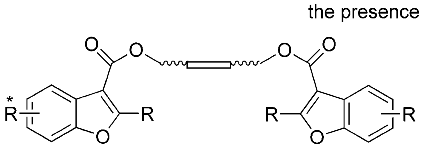
• Vourloumis [378]
• *ca.* 40 members
• from 4-fluoro-3-nitro-benzoic acid; resin attachment at either R^1 or X



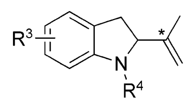
• Lee [212]
• 33 ex; 0-67%
• Bischler indole synthesis (N-H insertion of N-alkylanilines into a resin-bound Rh carbenoid intermediate; X = OR, NRR



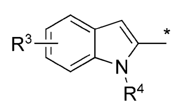
• Wu [401]
• 21 members
• from 4-bromo-3-nitrobenzoic acid



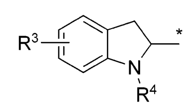
• Liao [222]
• 8 ex; 76-80%
• multi-step sequence from resin-bound 2-iodophenols



• Nicolaou [268]
• *ca.* 10 ex;
• cycloaddition of substituted *o*-allyl and *o*-prenyl anilines to selenyl bromide resins, functionalization and cleavage

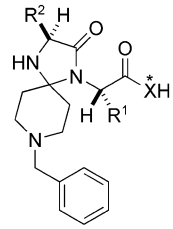


• Nicolaou [268]
• *ca.* 10 ex;
• cycloaddition of substituted *o*-allyl and *o*-prenyl anilines to selenyl bromide resins, functionalization and cleavage

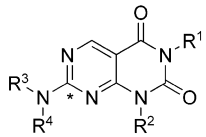


• Nicolaou [268]
• *ca.* 10 ex;
• cycloaddition of substituted *o*-allyl and *o*-prenyl anilines to selenyl bromide resins, functionalization and cleavage

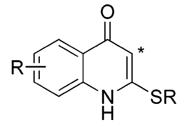
Table 9. (Continued)



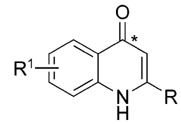
- Feliu [107]
- 180 members
- multi-step sequence from Fmoc-amino acids bound on Syn Phase lanterns



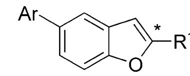
- Graveleau [129]
- 200 members
- treatment of thio-linked 4-amino-2-thio pyrimidine-5-carboxylate with isocyanates then intra-molecular ring closure, alkylation then cleavage



- Tang [357]
- 9 ex; 60-86%
- resin-bound cyclic malonic acid ester reacted with aryl isothiocyanate and alkyl halides to afford arylthio-aminomethylene cycle malonic ester; thermal intracyclative cleavage

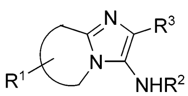


- Tang [358]
- 11 ex; 38-73%
- from resin-bound bis-methylthiomethylene cyclic malonic acid ester and arylamines

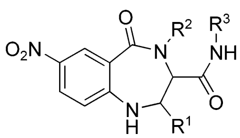


- McKiernan [236]
- 3 ex; good yield
- TFA-mediated cyclization of resin-bound enols ethers (prepared from Schrock carbenes and alkylidenate resin-bound esters)

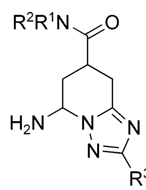
Part B: Solution-Phase



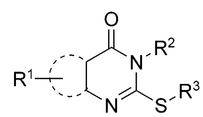
- Ireland [169]
- 10 ex; 33-93%
- microwave-assisted 3cc of amidines, isocyanide, aldehydes



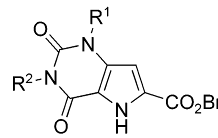
- Tempest [360]
- 80 member library
- 4cc/S_NAr reaction



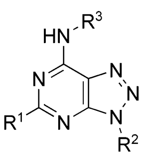
- Brodbeck [44]
- 500 members
- from 2,6-dichloro citracinic acid



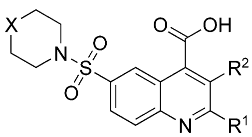
- Adams [4]
- 48 member library
- P-BEMP mediated catch and release synthesis



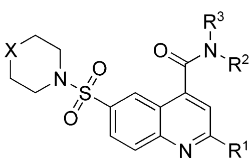
- Marcotte [249]
- 9 ex; good yield
- from 4-oxo-N-protected proline benzyl ester



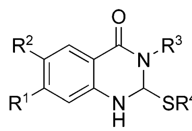
- Baindur [18]
- 80 members
- multi-step solution synthesis using scavenging resins



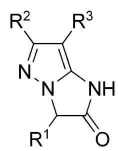
- Ivachtchenko [172]
- 11 members
- multi-step sequence from 5-sulfamoylisatins



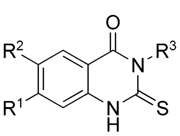
- Ivachtchenko [172]
- 48 members
- multi-step sequence from 5-sulfamoylisatins



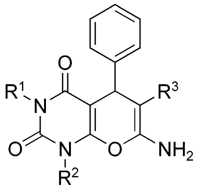
- Ivachtchenko [173]
- 1823 members
- S-alkylation of 4-oxo-2-thioxo-1,2,3,4-tetrahydro-quinazolines



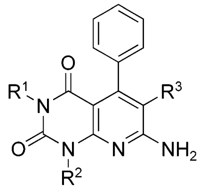
- Blass [34]
- 8 ex; 16-69%
- condensation of hydrazino acids with malononitriles then intramolecular cyclo-dehydration



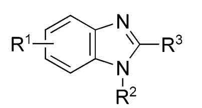
- Ivachtchenko [173]
- 380 members
- cyclization of substituted methyl anthranilates with isothiocyanates, or cyclization of substituted 2-(methylcarboxy) benzeneisothiocyanates with primary amines or hydrazines



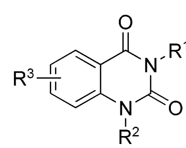
- Devi [90]
- 4 ex; good yields
- microwave-assisted 3CC of barbituric acid with benz-aldehyde and alkyl nitriles



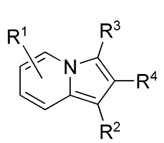
- Devi [90]
- 4 ex; good yields
- microwave-assisted 3CC of 6-hydroxyaminouracils with benzaldehyde and alkyl nitriles



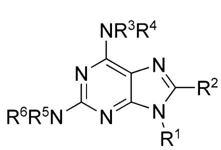
- Beaulieu [25]
- *ca.* 15 ex; 59-95%
- reaction of RCHO, 1,2-phenylenediamine and oxone



- Schwinn [320]
- 16 ex; good yield
- multi-step sequence using perfluoro-tagged benzyl alcohol



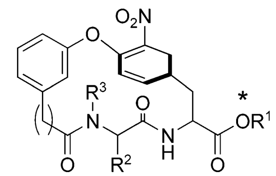
- Chai [53]
- 20 ex; good yield
- from substituted pyridines and 2-bromoketones



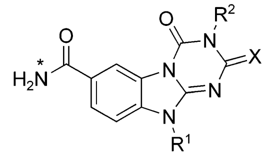
- Hammarstrom [140]
- 4 ex; good yield
- from 4,6-dichloro-2-(methylthio)-5-nitropyrimidine

Table 10. Polycyclic Synthesis

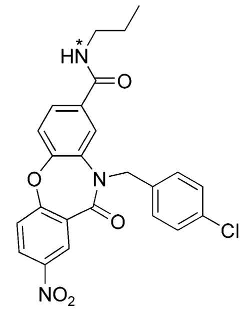
Part A: Solid-Phase (Asterisk (*), Point of Attachment to Resin)



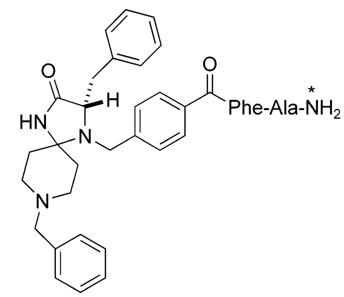
- Cristau [71, 72]
- 6 ex; 4-48%
- Ugi 4cc reaction then intramolecular S_NAr



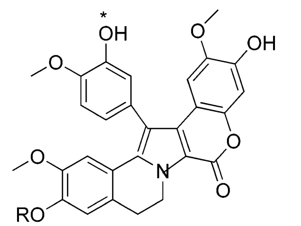
- Hoesl [153]
- 12 ex; good yield
- from resin-bound iminophosphoranes and aryl isocyanates; X = O or NR^2



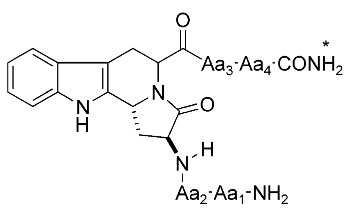
- Hone [156]
- 1 ex; 64%
- from resin-bound 2-fluoro-5-nitrobenzamide



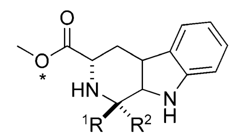
- Bedos [26]
- 1 ex; 90%
- condensation of piperidine with resin-bound α-amino amide



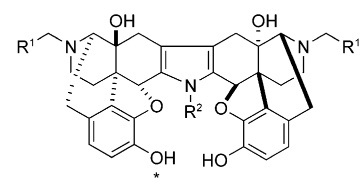
- Cironi [64]
- 2 ex;
- Lamellarins U and R prepared by multistep sequences; intramolecular [3 + 2] cycloaddition of a 3,4-dihydroisoquinolinium salt and alkyne



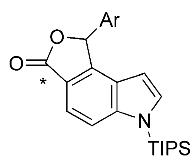
- Grimes [131]
- 576 members
- Pictet-Spangler reaction



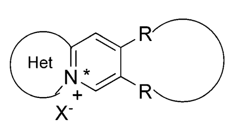
- Yeh [406]
- 28 ex; 50-98%
- classical synthesis using soluble PEG-OH support



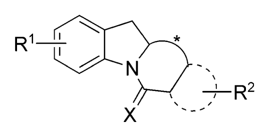
- Tanaka [355]
- 120 members
- homo coupling of resin-bound ketone with hydrazine and sequential N-alkylation



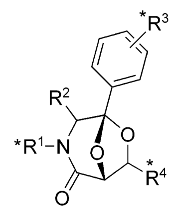
- Tois [363]
- 5 ex; 23-36%
- ortho-lithiation of resin-bound5-carboxyindole, quench with Ar CHO then intracyclative cleavage



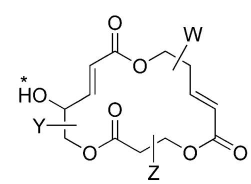
- Delgado [87]
- 16 ex; 64-98%
- Westpal reactin via resin-bound azolium or azinium acetates and 1,2-diketones



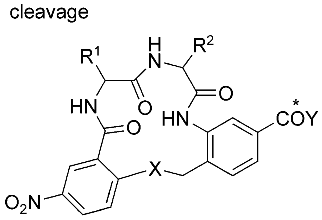
- Nicolaou [268]
- *ca.*10 ex;
- cycloaddition of substituted *o*-allyl an *o*-prenyl anilines to selenyl bromide resin, functionalization and cleavage



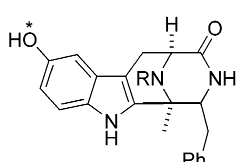
- Trabochi [366]
- *ca.*10 ex; good yield
- prepared from amines, α-halo-acetophenones and tartaric acid or sugar derivatives; multiple attachment points on resin



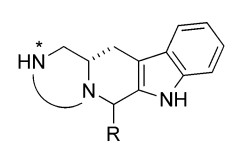
- Takahashi [352]
- 129 members
- 3CC and Pd-catalyzed carbonylative ring closure



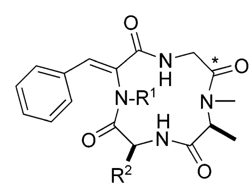
- Lee [207]
- 9 ex; 43-80%
- from 3-nitro-4-bromomethyl benzoic acid



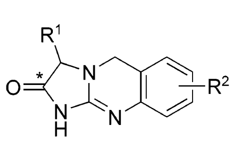
- Orain [277]
- 2 ex;
- Dakin-West/Pictet Spengler using resin-bound tryptophan-containing dipeptide



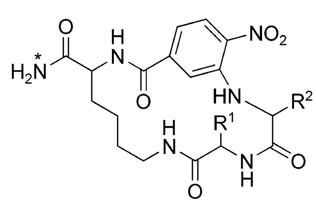
- Klein [188]
- ca. 5 ex; good yield
- Pictet-Spengler then intramolecular cyclization chemistry to create appended ring



- Jimenez [178]
- 7 members
- multi-step sequence to Tentoxin analogs



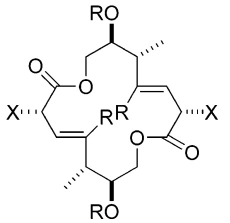
- Srivastava [344]
- 15 ex; 95-99%
- from resin-bound α-amino acids and 2-nitrobenzaldehyde



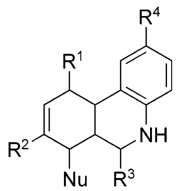
- Giulianotti [124]
- 9 ex; good purity
- ring formation via intramolecular S_NAr

Table 10. (Continued)

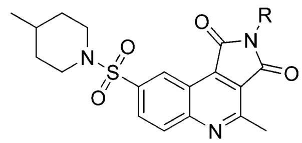
Part B: Solution-Phase



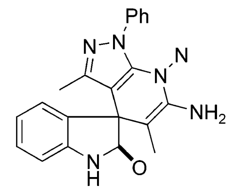
- Su [298]
- 9 ex; 45-84%
- cyclodimerization of C7 and C8 hydroxy esters yielding 14 to 22-membered macrodiolides (16 membered ring shown here)



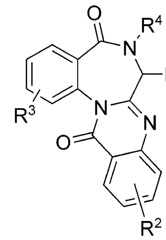
- Lavilla [200]
- 5 ex; good yield
- 3CC then [4 + 2] cycloaddition



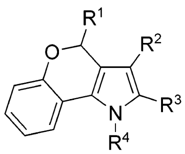
- Ivachtchenko [172]
- 6 members
- multi-step sequence from 5-sulfamoylisatins



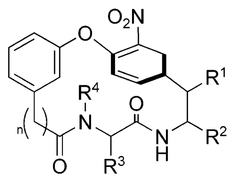
- Dandia [80]
- 4 ex; good yield
- from dicyanomethylene indole-2-one



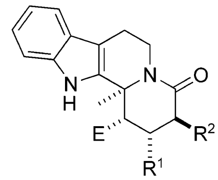
- Grieder [130]
- 162 members
- multi-step sequence from anthranilic acids



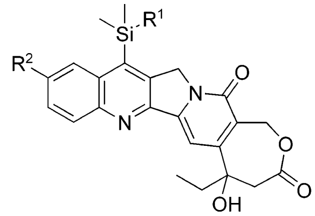
- Bashiardes [20]
- *ca.* 12 ex; 54-96%
- MnO_2-mediated [3+2] intra-molecular [3+2] cycloaddition of imines derived from amino acids and *o*-propargylic salicylaldehydes



- Cristau [72]
- 8 ex; 55-90%
- Ugi 4CC reaction then intramolecular S_NAr

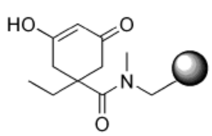


- Abelman [2]
- 3 ex; 40-79%
- these and other related heterocyclic systems via *N*-acyliminium ion

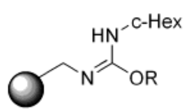


- Gabarda [115]
- 115 members
- multi-step sequence

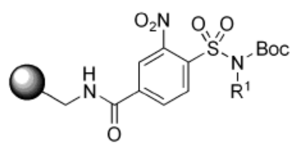
Table 11. Polymer-Supported Reagents and Scavengers



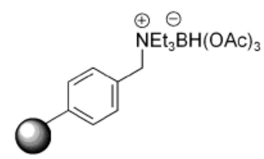
- Humphrey [165]
- O-acylation gives acyl transfer reagents for amine derivatization



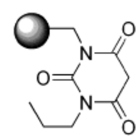
- Crosignani [73]
- carboxylic acid esterification reagent



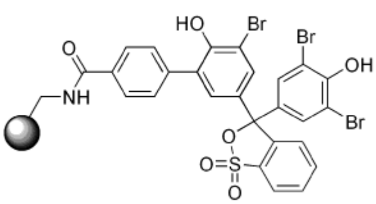
- Congreve [68]
- release of 1° and 2° amines



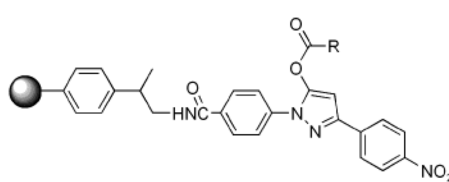
- Bhattacharyya [32]
- triacetoxyborohydride for reductive amination



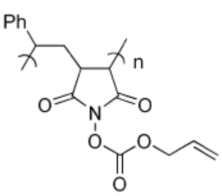
- Tsukamoto [368]
- deprotection of allyl derivatives under Pd-catalysis



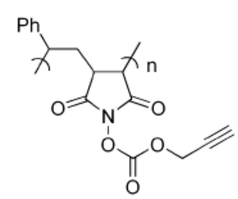
- Cho [60]
- resin-bound bromophenyl blue as a self indicating resin for amines



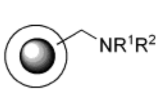
- Byun [51]
- polymer-bound pyrazolone-type active esters



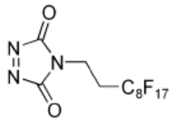
- Chinchilla [59]
- alloc transfer reagent (Alloc-P-OSu)



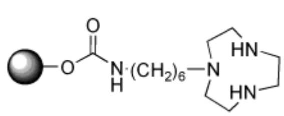
- Chinchilla [59]
- propargyl transfer reagent (Proc-P-OSu)



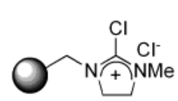
- Wisnoski [393]
- high loading Rasta resin for scavenging



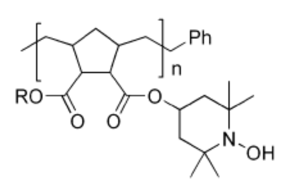
- Werner [390]
- fluorous diene scavenger



- Bonora [39]
- recyclable catalyst for phosphodiester hydrolysis

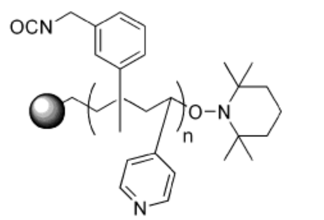


- Disadee [95]
- dehydrating reagent for esterification and amidation

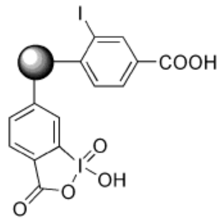


- Tanyeli [1639]
- TEMPO Catalyst

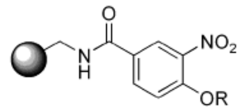
Table 11. (Continued)



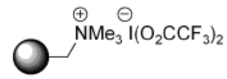
- Wisnoski [393]
- high loading Rasta resin containing isocyanate and "internal" base for amine scavenging



- Lei [213]
- oxidation

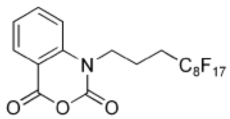


- Lee [208]
- activated ester and sulfonate for amine derivatization

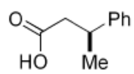


- Jaunzems [176]
- anomeric activation of thioglycosides

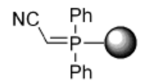
- Zhang [422]
- fluorous electrophilic scavengers



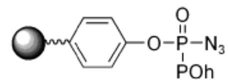
- Zhang [422]
- fluorous electrophilic scavengers



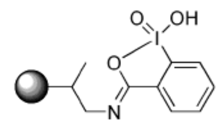
- Humphrey [166]
- O-acylation yields ester substrates for lipase-catalyzed kinetic resolution



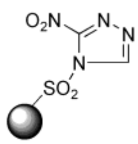
- Weik [388]
- 10 ex; 62-99%
- acylation of a resin-bound phosphorane then cleavage (acyl anion equivalent)



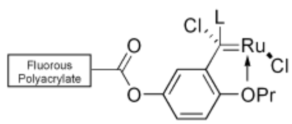
- Lu [231]
- polymer supported phosphorylazide



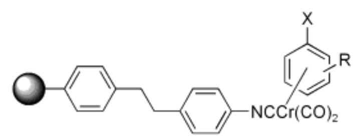
- Chung [62]
- oxidation



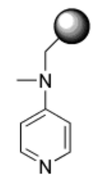
- Zander [411]
- esterification of amino acids



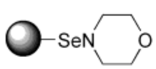
- Yao [405]
- fluorous Ru catalyst for RCM



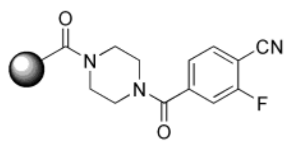
- Baldoli [16]
- haloarene $(Cr(CO)_3$ complex 5 on isonitrile resin yielding aryls activated toward Nu substitution



- Corma [70]
- resin-bound DMAP for Baylis-Hillman reaction



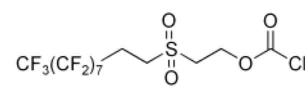
- Sheng [330]
- reacts with R^1R^2 CHCHO in DCM at reflux to give resin-bound α-seleno aldehydes



- Lepore [215]
- reacts with oximes to give aryloximes as a means to attach ketones to solid support

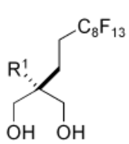
Amberlite IRA-400(BrO_3)

- Sikdar [335]
- solid-phase oxidation of allylic and benzylic alcohols

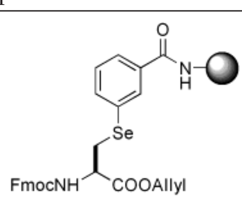


- de Visser [139]
- base-labile fluorous amine protecting group

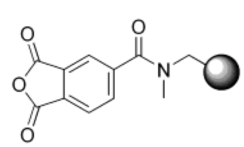
Table 12. Polymer-Supported Linkers



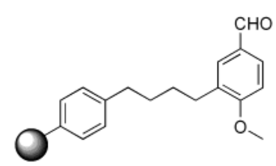
- Read [302]
- preparation of fluorous tagged acetals and ketals



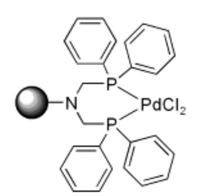
- Nakamura [263]
- Selenyl linker for dihydropeptide synthesis



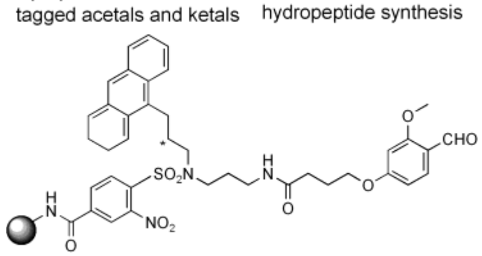
- Bauer [22]
- TAL-linker for immobilization of primary amines



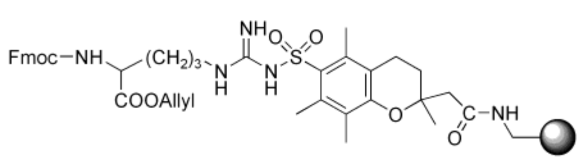
- Gu [133]
- stable backbone acid-cleavable linker



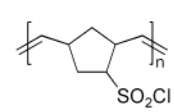
- Gonthier [126]
- catalyst for Sonogashira coupling



- Andrews [10]
- acid-cleavable linker as new analytical construct to aid library chemistry optimization; * = CH_2:CD_2 (1:1)

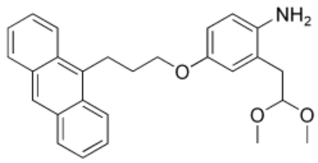


- Garcia [117]
- linker for side-chain anchoring of arginine

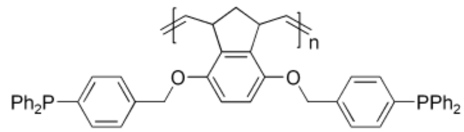


- Moore [258]
- amine scavenging agent

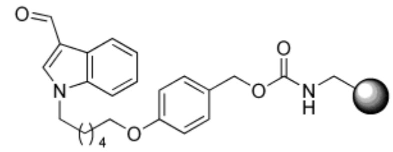
Table 12. (Continued)



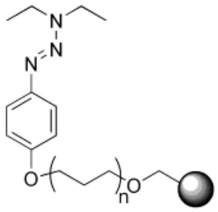
- Li [218]
- anthracenyl tagged protecting group for phase-switching applications in parallel synthesis



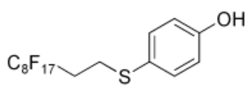
- Yang [232]
- Pd-catalyzed Heck, Soinogashira Negishi reactions



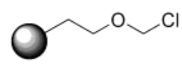
- Vitre [375]
- "head-to-tail" linkers for recycling solid supports



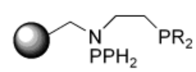
- Lazny [201, 202]
- immobilization of amines



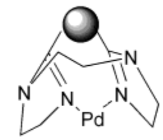
- Chen [56]
- fluorous version of Marshall resin



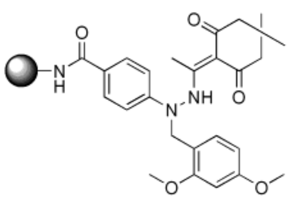
- Ruhland [311]
- attachment of indoles to solid-phase



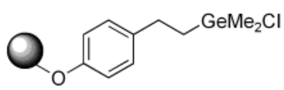
- Mansour [248]
- assorted phosphorous ligands for Heck reaction



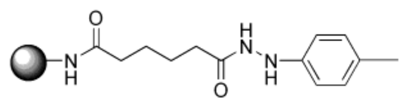
- Lin [223]
- Pd - catalyst for Heck reactions



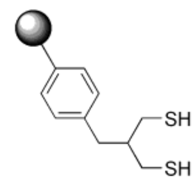
- Berst [28]
- safety-catch linker for synthesis of ketopiperazines



- Spivey [343]
- use in traceless SPS of 2-pyrimidines

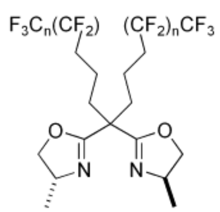


- Stieber [345]
- traceless phenylhydrazide linker

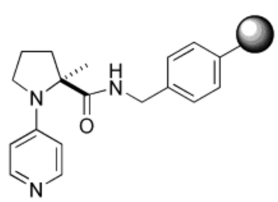


- Bertini [29, 30]
- linker yields 1,3-dithiane derivatives with carbonyl compounds

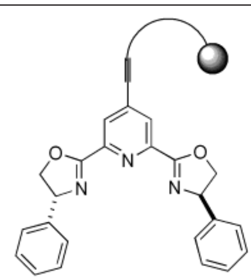
Table 13. Polymer-Supported Chiral Ligands



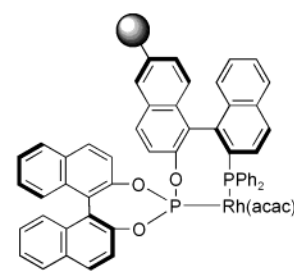
- Bayardon [23]
- chiral fluorous bisoxazoline for asymmetric alkylation



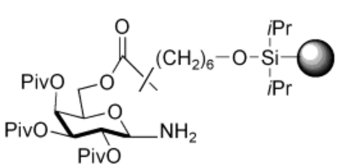
- Pelotier [286]
- kinetic resolution of alcohols



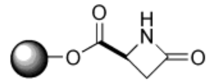
- Lundgren [233]
- corresponding Ytterbium complex as asymmetric silylcyanation of Ph CHO



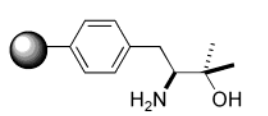
- Shibahara [332]
- asymmetric olefin hydro-formylation catalyst



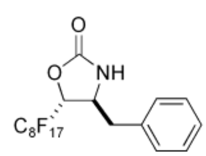
- Zech [414]
- immobilized galactose auxilliary



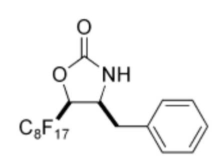
- Doyle [97]
- corresponding rhodium catalyst for asymmetric cyclopropanation



- Hulme [162]
- enantiselective addition of Et_2Zn to Ph CHO

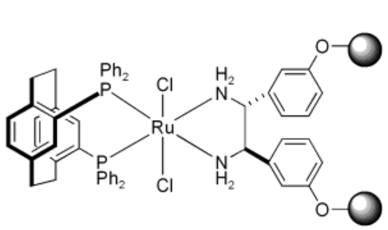


- Hein [144]
- asymmetric aldol reactions

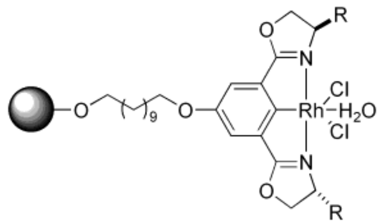


- Hein [144]
- asymmetric aldol reactions

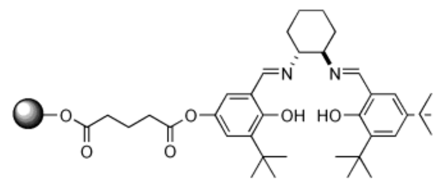
Table 13. (Continued)



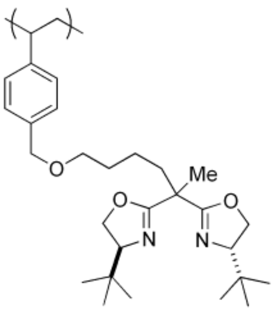
• Li [219]
• asymmetric hydrogenation of ketones



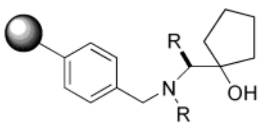
• Weissberg [389]
• Phe Box ligands or enantioselective allylation of aldehydes



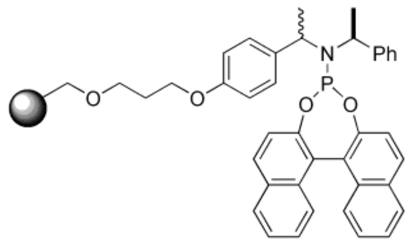
• Anyanwu [11]
• asymmetric addition of Et_2Zn to RCHO



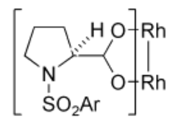
• Mandoli [246]
• enantioselective heterogeneous cyclopropanations



• Burguete [49]
• enantioselective addition of $ZnEt_2$ to PhCHO



• Mandoli [247]
• Cu-catalyzed enantioselective 1,4-addition of $ZnEt_2$ to 2-cyclohexenone



• Davies [82]
• asymmetric C-H activation

xylene. Yields and product purity exceeded 85% for nine fully characterized examples. For the large library, purities exceeded 90% for >70% of the products.

Fluorous Chemistry. Fluorous Technologies Inc. (FTI), a company commercializing fluorous-based reagents, scavengers, and protecting groups,[420,421] developed new fluorous syntheses of hydantoins[423] and pyrimidines[419] (Figure 21). For the former chemistry, perfluoroalkyl-tagged esters **161** were reacted with isocyanates in solution, followed by Et_3N-mediated intramolecular cyclization to urea and concomitant tag release. Product purification was performed by solid-phase extraction over Fluoro*Flash* cartridges. No fluorous solvent was involved in either the reaction or separation processes. Thiohydantions were prepared similarly. A fluorous "catch-and-release"-type strategy was devised for a disubstituted pyrimidine synthesis. In this instance, a fluorous thiol reacts with a 2,4-dichloro-5-substituted pyrimidine, affording a 3:1 mixture of regioisomers. After reaction of **165** (major isomer) with a nitrogen nucelophile (**165** → **166**), the fluorous tag is oxidized with oxone to sulfone **167**. The sulfone is then displaced with a second amine or other nucleophile, releasing the tag **(167 → 168)**. The fluorous tag acts as a phase tag for intermediate and product purification over Fluoro*Flash* SPE cartridges. Also reported by FTI and affiliates were fluorous electrophilic scavengers,[422] a fluorous version of the Marshall resin,[56] the synthesis and reactions of fluorous-Cbz-protected amino acids,[74] and application of fluorous separation technology in the preparation of aryl sulfides.[416] Fluorous-based chemistries published by researches not directly affilitated with FTI include fluorous versions of Evan's chiral auxiliary,[144] fluorous chiral bisoxazolines for asymmetric allylic alkylation,[23] a fluorous diol for acetal/ketal synthesis,[302] a fluorous-based quinazoline 2,4-dione synthesis,[320] fluorous dienophiles,[390] and a fluorous Ru catalysis for ring-closing metathesis.[405]

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