Review

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Reviews

Comprehensive Survey of Combinatorial Library Synthesis: 2002

Roland E. Dolle

Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, Pennsylvania 19341

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The sixth annual comprehensive survey on combinatorial chemistry[1] records a total of 388 chemical libraries published in 2002,[2−414] a 25% increase from the previous year. Libraries are divided into two major categories: those with disclosed biological activity (122 entries; Tables 1−5) and those without accompanying biological data (266 entries; Tables 6−10). The screened libraries are segregated by molecular target class: proteolytic enzymes (Table 1), nonproteolytic enzymes (Table 2), GPCRs (Table 3), non-GPCRs (Table 4), and cytotoxics/anti-infectives (Table 5). Scaffold derivatization and acyclic, monocyclic, bicyclic/spirocyclic, and polycyclic ring syntheses compose Tables 6−10, respectively. Each of the latter headings is further subdivided into solid and solution phase. Table 11 covers polymer-supported reagents and scavengers; Table 12 covers new solid-phase linkers, while a new Table (13) is introduced on polymer-supported chiral ligands. There are 67 entries in Tables 11−13, 90% of which come from academic laboratories, indicating that this group continues to be the principal driver for new solid-phase methods development. Overall, academics publishing solid- and solution-phase research outpaced industry by a 2:1 margin. The percentage of published libraries synthesized using solution-phase techniques retreated somewhat from last year to ∼30%, while the average number of compounds in any given biologically active library remained relatively steady (75%, <100 members; 90%, <1000 members).

Iterative library design/synthesis strategies blending solid- and solution-phase protocols in lead optimization increased significantly. Some 20% of the libraries in Tables 1−5 employed multiple streamlined synthesis techniques, suggesting researchers are electing to use all combinatorial tools at their disposal as appropriate to solve optimization problems. Examples include procollagen C-protease inhibitors (library 1.8),[104] caspase-3 inhibitors (library 1.23),[88] $p56^{Lck}$ inhibitors (library 2.4),[74] cyclin-dependent kinase-2 inhibitors (library 2.6),[203] neurokinin-1 antagonists (library 3.16),[41] oxytocin antagonists (library 3.24),[388] and Src SH_2 ligands (library 4.18).[110,111] Tandem resin-solution chemistry was employed to construct nitrile-containing libraries yielding inhibitors of dipeptidyl peptidase IV (library 1.18)[367] and cathepsin S (library 1.21).[374] A clinical candidate emerged from library 1.18.

Therascope AG applied dynamic combinatorial chemistry to identify novel neuraminidase inhibitors.[164] Treating a diamine template with a mixture of aldehydes in the presence of enzyme and borohydride resulted in the amplification of a very small number, from potentially thousands, of transient hemiacetal/imine species that were reduced to give inhibitors with micromolar affinity. A striking illustration of a "privileged" GPCR scaffold was reported by Merck.[380] A 128 000-member mixture library of 2-aryl indoles was active against

* To whom correspondence should be addressed. Tel: 484-495-1024. Fax: 484-595-1551. E-mail: rdolle@adolor.com.

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many families of GPCRs (16 screens), from which a number of highly potent and selective ligands were found following library deconvolution. Four companies, Roche,[73] Merck,[228] Celltech,[229] and Genentech,[64] described libraries targeting VLA-4 ($\alpha_4\beta_1$ integrin). The first three companies started with structurally similar dipeptide antagonist leads possessing poor pharmacokinetic properties. Libraries synthesized to circumvent this problem met with varied results.

Several academic groups published accounts of diversity-oriented synthesis (DOS).[100,173,213,217,218,258,266,276,336] The encoded libraries of Schreiber and co-workers[213,217,218,258,336] for application in chemical genetics are characterized by natural product-type complexity and strive to introduce structural diversity through synthetic "branching points" within the constructs. In one example alone, 18 library compound crystal structures were generated as visual documentation of topological inimitability.

With regard to new methodology, several research groups employed Katritsky's benzotriazole chemistry to create heterocyclic libraries;[193,195,248,249,319,366] a phase-switch protocol for the clean conversion of primary amines to secondary amines was reported by Pellitier;[291] and Hlasta described a traceless, multicomponent solid-phase synthesis of 2-substituted azoles via transient resin-bound azolium ylides.[108] Lindsley created an amide-containing series of fluorous scavengers that, surprisingly, were not retained on the standard Fluoro*Flash* SPE column alone, but required an ion exchange precolumn to fully remove the novel scavengers from reaction mixtures.[233] These and other combinatorial chemical highlights are detailed below.

Nitrile Libraries as Inhibitors of Serine and Cysteine Proteases. Dipeptidyl peptidase IV (DPP-IV) is a serine protease with high substrate specificity cleaving N-terminal dipeptides Xaa-Pro or Xaa-Ala **1** from regulatory polypeptides (Figure 1). In vivo, DPP-IV inactivates glucagon-like peptide-1 (GLP-1), the most potent of the insulinotropic hormones. Selective inhibitors of DPP-IV have been shown to control blood glucose by extending the duration of action of GLP-1 to stimulate insulin secretion, inhibit glycagon release, and slow gastric emptying. In 1999, researchers at the Novartis Institute for Biomedical Research announced the slowly binding DPP-IV inhibitor **9** as a clinical development candidate for type-2 diabetes. Details of the discovery effort were not presented. This past year, it was revealed that combinatorial chemistry played a key role in its discovery.[367] Previous inhibitor design strategies were based on L-amino acids with a protonatable N-terminal primary amine in the enzyme's P2 site. Novartis researchers noted that a P2 *N*-methyl glycine (secondary amine) was recognized as a DPP-IV substrate, suggesting $-HNCH_2CO-Pro-$ as a viable template for inhibitor design. As a result, tandem resin-solution parallel synthesis was carried out to investigate the activity of more complex N-substituted glycines coupled to an electrophilic (2*S*)-cyanopyrrolidine at P1. Resin-bound *N*-bromoacetylproline, **5**, prepared in three steps from Rink resin, was reacted with some 200 amines and cleaved to yield N-substituted Gly-Pro-NH_2 **6**. Library 1.18 (**3**) was obtained upon the solution-phase dehydration of **6** with trifluoroacetic anhydride (TFAA) followed by treatment with NH_3 in MeOH (**6** → **7** → **3**). One of the more potent human plasma DPP-

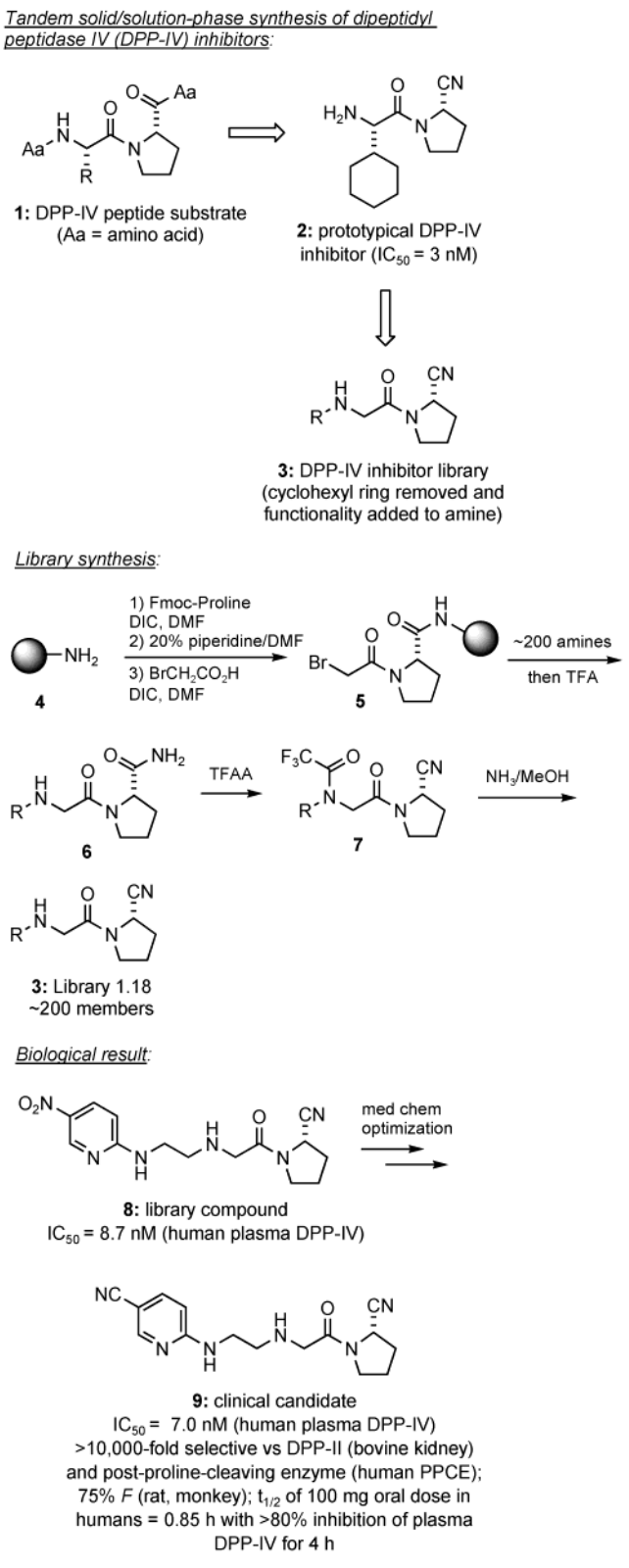


Figure 1. Nitrile library yielding dipeptidyl peptidase-IV (serine protease) inhibitors.[367]

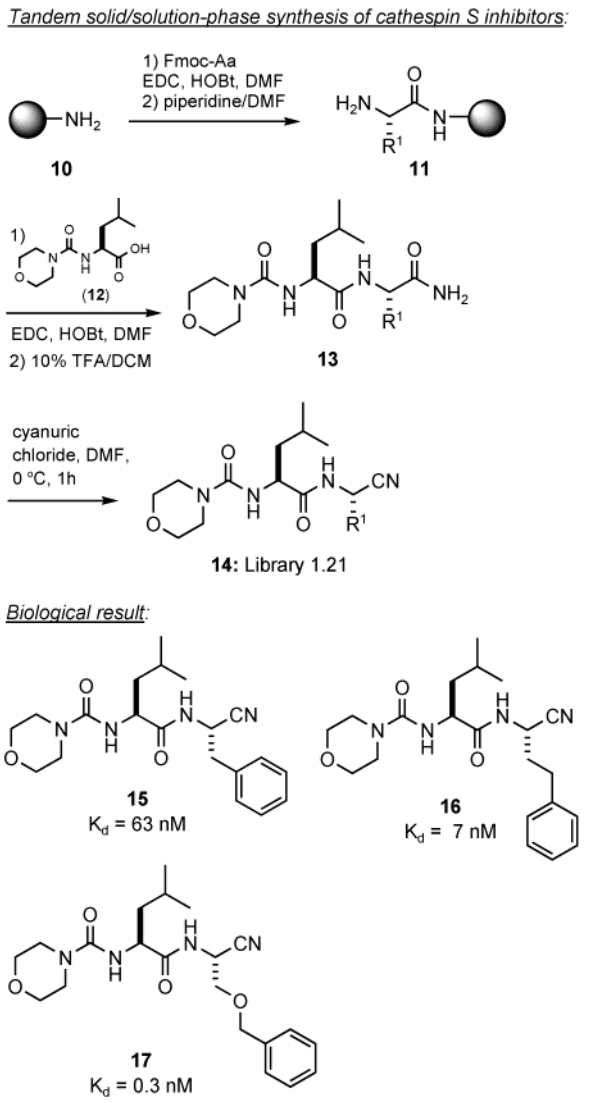


Figure 2. Nitrile library yielding cathepsin S (cysteine protease) inhibitors.[374]

IV inhibitors found in the library was the 5-nitro-aminopyridinyl glycine derivative **8**: $IC_{50} = 8.7$ nM. In a followup medicinal chemistry effort, the potentially toxic 5-nitro group was replaced with a 5-cyano group in the pyridine ring to give orally active **9**, the clinical candidate: $IC_{50} = 7$ nM possessing >10 000-fold selective against closely related proteases, including post-proline-cleaving enzyme (PPCE) and kidney DPP-II. In vivo evaluation of **9** in rats and humans definitively linked DPP-IV inhibition to sustained GLP-1 levels and an improvement in oral glucose tolerance.

Independently, Ward and co-workers at Boehringer Ingelheim developed a tandem resin-solution parallel synthesis of dipeptide-based nitriles as inhibitors of the cysteine protease, cathepsin S.[374] This proteolytic enzyme is intimately involved in immune modulation by processing proteins (final processing step) which are presented as antigenic peptides on the surface of cells. Attenuation of self-antigen presentation via cathepsin S inhibition is of particular therapeutic interest for potential autoimmune disease intervention. Nitrile inhibitors were prepared by three different protocols, including one solid-phase protocol (illustrated in Figure 2) intended to define the preferred P1 specificity requirement for the enzyme. Fmoc-protected amino acids were coupled to piperidine-treated Sieber resin **10**, affoding **11** after protecting group removal. Resin **11** was capped with the morpholino urea derivative of leucine **12** and cleaved from resin yielding amides **13**. Primary amides **13**, in turn, were converted to peptide nitriles **14** (library 1.21) using cyanuric chloride as the dehydrating reagent. Dissociation constants (K_d) increased with extended length of the P1 side chain (**15** → **16** → **17**), with the benzyl-protected serine inhibitor **17** possessing a K_d of 300 pM. An X-ray crystal structure of the inhibitor **17**−enzyme complex confirmed for the first time the putative covalent interaction between the active-site cysteine residue and the nitrile carbon atom, that is, thioimidate bond formation. The dipeptide nitriles prevented processing of the p10 invariant chain fragment (a cathepsin S substrate) in a cellular assay.

Fungal Type-1 Protein Geranylgeranyltransferase (GGTase-1) Inhibitors.[346] The dithiothreitol **18**, a potent inhibitor of *Candida albicans* type I protein geranylgeranyltransferase (GGTase-1), was discovered through random screening at Banyu (Figure 3).[346] GGTase-1 is an enzyme indirectly responsible for essential fungal cell wall biosynthesis via geranylgeranylation of certain G-protein regulatory components of (1,3)-β-D-glucan synthase. GGTase-1 is an α/β heterodimer containing both Mg^{2+} and Zn^{2+} in its active site, and the high affinity of **18** was attributed to the metal chelating properties of the dithiothreitol (DTT) mioety present in **18**. Despite potent action against the enzyme, inhibitor **18** displayed weak antifungal activity (MIC >120 μg/mL). The DTT group was targeted as the barrier to whole cell activity. In an attempt to establish antifungal activity, libraries were designed to remove the DTT liability. For the first iteration, DTT esters were simplified to a single chelating thiol group, furnishing library **19**. Subsequent screening of **19** afforded a new monothiol-containing inhibitor **20** with an $IC_{50} = 240$ nM, albeit ~10 times less potent that the starting lead **18**. Hoping to restore in vitro binding affinity, a second library design/synthesis iteration was carried out in which 3-mercaptopropanol was linked to trityl resin and acylated with a broad array of amino acids (library **21**; 70 members). This led to inhibitor **22** ($IC_{50} = 7$ nM). The naphthylalanine and 1-indane moieties in **22** were essential for high enzyme affinity. Because of the researchers' dissatisfaction with ester thiol chelate, a third library iteration was carried out wherein the 1-indanyl-naphthylalanine groups were kept constant while the 3-mercaptopropanoate was replace by amino acids with side chain functionality capable of metal chelation. From the corresponding library **23** (266 members), D-histidine analogue **24** was identified as a marginally active GGTase-1 inhibitor. The descarboxamide analogue **25** was subsequently prepared as a discrete compound, leading to a 10-fold increase in activity (IC_{50} ~

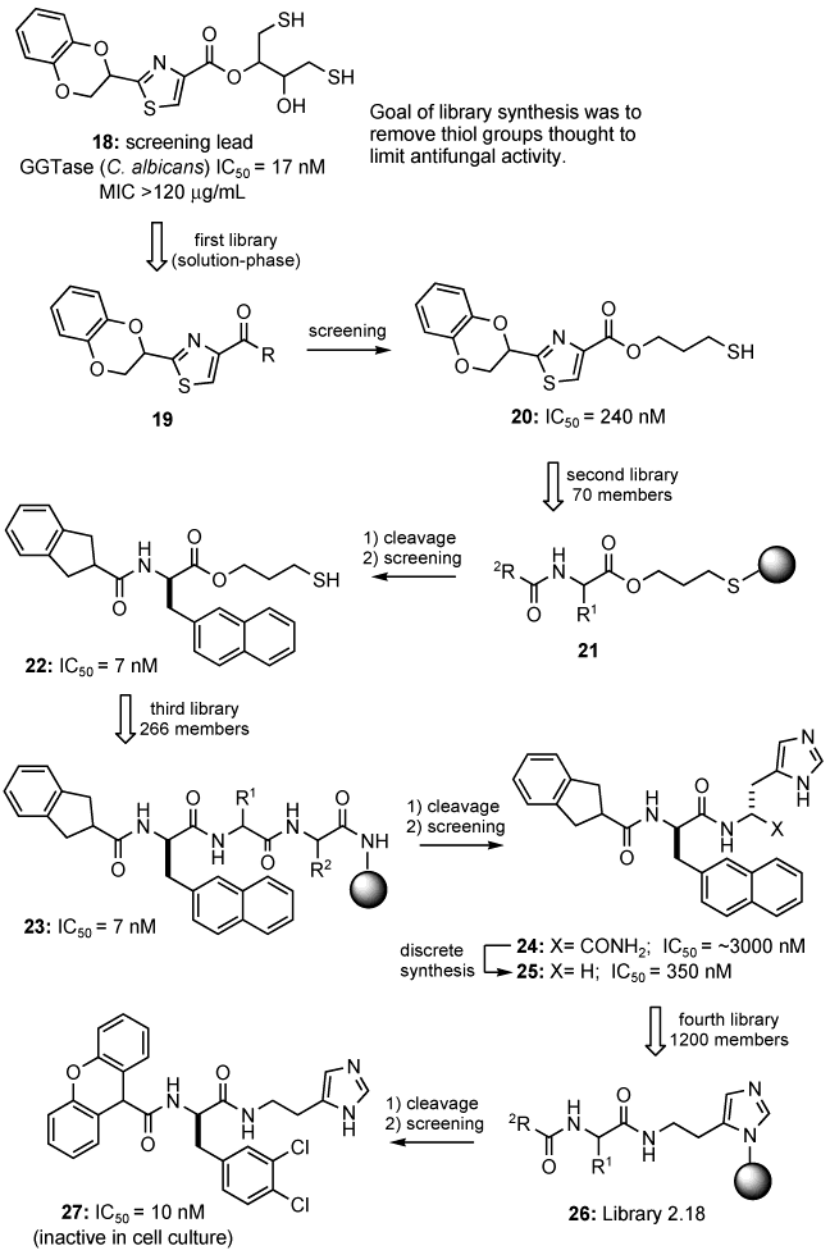


Figure 3. Evolution of imidazole-based geranylgeranyltransferase (GGTase) inhibitors.[346]

3000 nM (**24**) versus IC_{50} = 350 (**25**)). This prompted the final design iteration linking histamine to a solid support and generating some 1200 compounds, as per library 2.18 (**26**). Screening this library revealed D-3,4-dichlorophenylalanine as a surrogate for the D-naphthylalanine, provided the amino acid was capped with a 9-xanthenyl moiety, for example, **27**. The non-thiol-containing inhibitor **27** possessed an IC_{50} of 10 nM, comparable to the starting DTT-containing lead **18** (IC_{50} = 17 nM); however, **27** also lacked antifungal activity against *C. albicans*. The poor in vivo activity was rationalized on the basis of new information that *C. albicans* can sustain growth in the absence of GGTase-1 and, hence, was not a function of inhibitor structure. Although compound **27** no longer contains a thiol group, it was arrived at through a rather circuitous library cascade. Perhaps it would have been more efficient to simply recognize imidazole as a metal-chelating ligand and attach it (histamine) directly to the resin for derivatization negating the need for libraries **19**, **21**, and **23**. No in vitro activity was reported for the obvious analogue of **18** in which DTT-type chelate was exchanged for the histamine-type chelate.

KDR (VEGFR-2) Receptor Tyrosine Kinase Inhibitors. As part of an oncology program directed toward the discovery of antiangiogenesis agents, Merck conducted a high-throughput screening campaign against KDR kinase and identified pyrazolo[1,5-*a*]pyrimidine **28** (IC_{50} = 224 nM) as a novel small molecule lead (Figure 4).[130] KDR is a receptor tyrosine kinase mediating mitogenic signaling of vascular endothelial factor 2 (VEGF-2). VEGF is one of several growth factors that tumors express under hypoxic stress, ultimately triggering an angiogenic response. Chemistry was charged with the goal of improving the activity of **28**. To

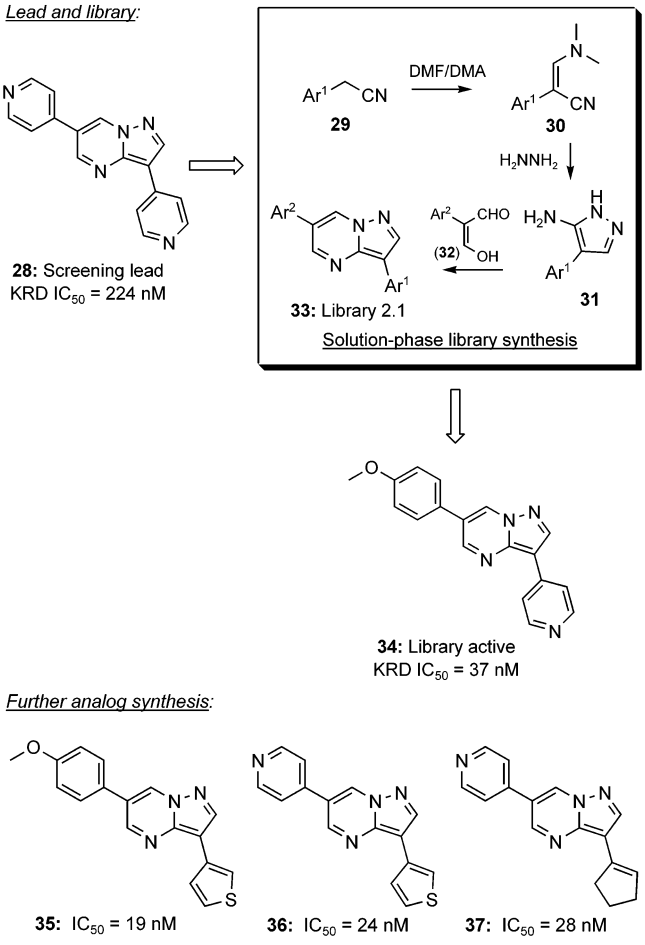
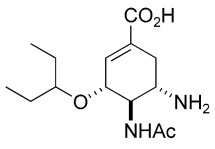


Figure 4. Merck's KDR kinase inhibitors.[130]

this end, a three-step solution-phase synthesis of this compound class was developed. The key step was the condensation of 3-amino-4-arylpyrazoles **31** (prepared in two steps from arylacetonitriles and hydrazine: **29** → **30** → **31**) with commercially available 2-arylmalonates **32**. Heating **31** and **32** in the presence of acetic acid in ethanol and cooling yielded the crystalline 3,6-diarylpyrazolo[1,5-*a*]pyrimidines **33** (library 2.1). SAR obtained from library screening indicated that substitution at the para position of the 6-aryl ring enhanced inhibitory activity (**28** → **34**; ~10-fold increase in affinity). Further analogue synthesis afforded **35**−**37**. In general, these inhibitors were relatively nonselective for KDR versus PDGFRβ, FLT-1, and FLT-4 kinases, but moderately selective versus FGFR-1 and Src kinases. Compound **36** inhibited VEGF-stimulated mitogenesis in human umbilical vein endothelial cells with an IC_{50} comparable to its in vitro KDR IC_{50}.

KDR inhibitors were also identified from a 23-member library of aminothiazoles **45** (library 2.2) synthesized by Waldmann and co-workers, who employed a traceless hydrazine linker strategy (Figure 5).[338] The synthesis initiated with coupling (DIC, HOBt) commercially available nitrophenylhydrazines **39** (two inputs: **46** and **47**) to custom-prepared adipicate-functionalized resin **38**. Bis(Fmoc) protection of the hydrazide nitrogen atom (**40** → **41**) preceded nitro group reduction ($SnCl_2 \cdot H_2O$, DMF). Subsequent reductive amination of **41** proved difficult, but proceeded quantitatively with 10 equiv of R^2CHO (five inputs: **48**−**52**) and $NaCNBH_3$ in THF/AcOH (100:1), with imine formation and reduction occurring in sequential reaction steps. Treatment of the corresponding resin with commercially available Fmoc thioisocyanate followed by global Fmoc deprotection furnished the penultimate intermediate resin **42**. This resin reacted cleanly with α-bromoaryl ketones **43** (three inputs: **53**−**55**) under Hantzsch-type cyclization conditions and gave resin-bound thiazoles **44**. Traceless cleavage (**44** → **45**) was accomplished by treatment with a catalytic amount of $Cu(OAc)_2$ in *n*-propylamine and purging with O_2 to reoxidize Cu^+ generated during the oxidation of the linker group. Copper salts were separated (99.9%) from the product by scavenging with cooper-chelating polyamine resin or through solid-phase extraction. Product purity (81−99%) was sufficient for biological screening. Because it was recognized that 2-aminothiazole derivatives are known inhibitors of cyclin-dependent kinases (CDKs), the library was initially screened against CDK-2 and CDK-4. However, none of the compounds proved active in the assays. Upon considering the high homology of the ATP-binding domain within the class of protein kinases, library **45** was evaluated against several receptor tyrosine kinases. These included epidermal growth factor receptor (EGFR; ErbB-1), ErbB-2 (Her-2/Neu), insulin-like growth factor 1 receptor (IGF1R), fibroblast growth factor receptor 1 (FGFR1), vascular endothelial growth factor receptors 2 and 3 (VEGFR-2 (KDR) and -3), and Tie-2. Inhibitory activity was observed for seven compounds against Tie-2, KDR, VEGFR-3, and FGFR-1. Inhibitor **56** was active against both KDR ($IC_{50} = 7.4\ \mu M$) and Tie-2 ($IC_{50} = 9.8\ \mu M$), while compound **57** ($IC_{50} = 12\ \mu M$) was 3.5-fold selective for KDR versus VEGFR-3 and inactive against Tie-2.

Dynamic Combinatorial Library of Neuraminidase Inhibitors. Researchers at Therascope AG described an elegant application of dynamic combinatorial chemistry to the discovery of inhibitors of the vial enzyme neuraminidase (Figure 6).[164] Tamiflu **58a** is a marketed antiviral that targets influenza A virus neuraminidase. The viral surface enzyme



58a: Tamiflu

catalyzes the cleavage of sialic acid residues terminally linked to glycoproteins and glycolipids and plays an important role in the propagation of the virus. SAR and X-ray crystallographic studies have shown that the carboxylate, amino, and acetamido groups are salient binding elements and that there exists a hydrophobic pocket adjacent to the active site, partly occupied by the alkyl ether of **58a**. A dynamic combinatorial library of potential inhibitors was designed on

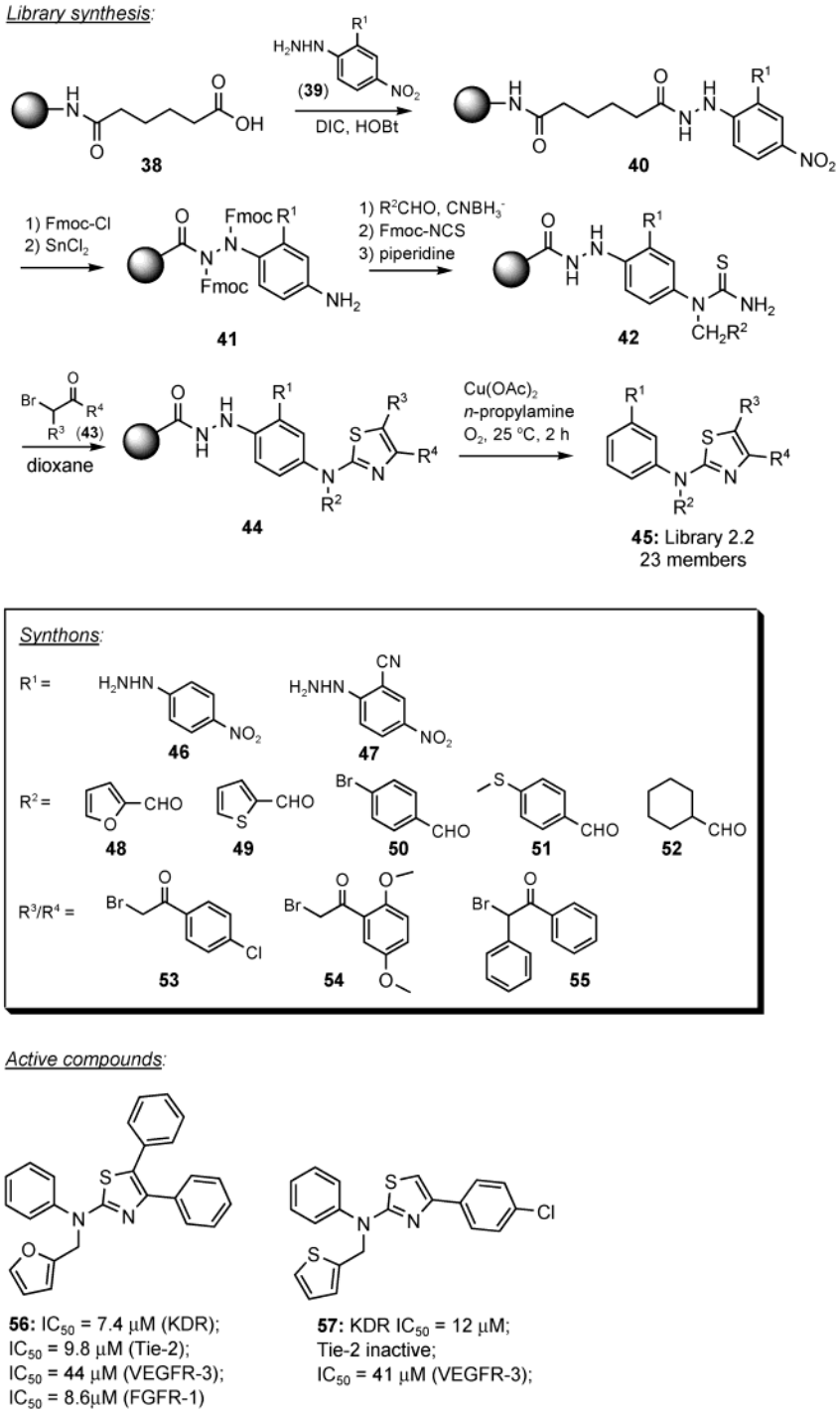


Figure 5. Aminothiozole-based dual active KDR and Tie-2 kinase inhibitors.[338]

the basis of diamine scaffold **58b**, in which the amine functionality was subject to reductive amination with lipophilic aldehydes. This chemistry would give rise to potential inhibitors that may engage the hydrophobic pocket, mimicking the alkyl ether in **58a**. In a control experiment, mixing **58b** with an aldehyde produced an equilibrium mixture of hemiaminal species **59** and **60**, as evidenced by NMR. Upon treatment with tetrabutylammoniumcyanoborohydride, the corresponding mono-, di-, tri- and tetrareductive amination products **63**−**66** were all detected by HPLC/MS. When the reaction was carried out with a mixture of aldehydes in the presence of enzyme, target-biased reequilibration occurred toward species **59**, and amplification of but a few mono-reductive amination products were detected. Resynthesis of the amplified products gave **67**−**69** with micromolar activity against the enzyme. Repeating this chemistry with BSA in place of enzyme did not produce any amplified products, indicating that legitimate target-driven selection/pressure was operating. In further experiments, scaffold **70** was mixed with a set of 20 aldehydes, producing up to 40 000 virtual

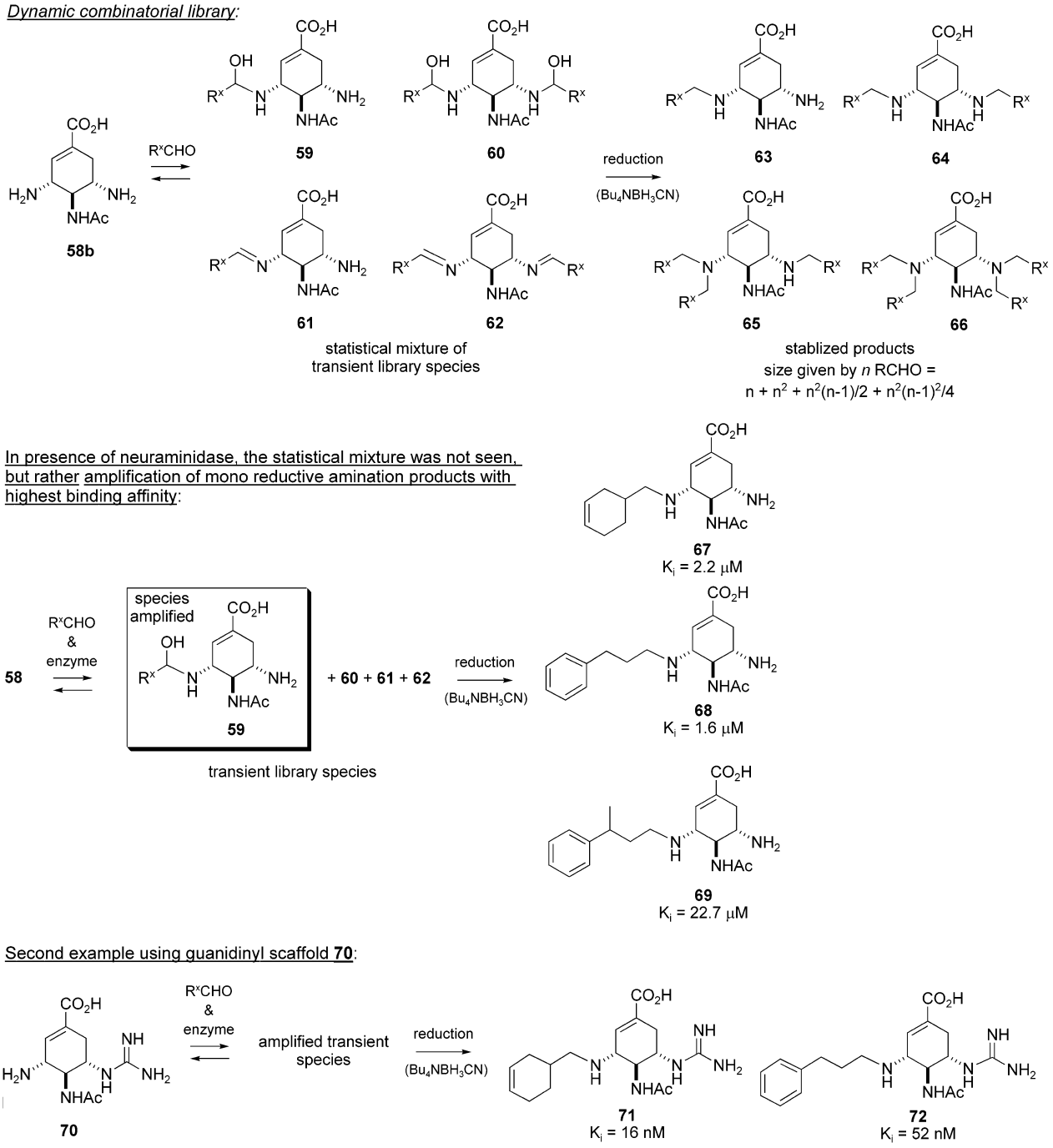


Figure 6. Neuraminidase inhibitors from a dynamic combinatorial library 2.27.[164]

compounds in a single pot from which only a few amplified products were obtained, for example, **71** and **72**. Target-driven self-organizing virtual libraries are envisaged for other systems, provided the target may be obtained in sufficient quantity and reaction conditions developed in aqueous buffer to allow transient equilibrium components to be formed in only trace amounts.

Substituted Indoles as Privileged GPCR Ligands. A mixture synthesis of 128 000-member library **81** (library 3.20) of 3-(amidoalkyl)- and 3-(aminoalkyl)-2-arylindoles was reported by Merck (Figure 7).[380] The rationale for its construction was derived from the common occurrence of indole derivatives in biologically active agents. The indole ring system is regarded as a privileged motif for GPCRs.[415] The design of library **81** was conceptually straightforward: (a) tether a basic amine to the 3-position of the indole ring; (b) introduce small functional group substituents in the 4-, 5-, 6-, and 7-positions; and (c) substitute the 2-position with a variety of aryls. Library construction was initiated by coupling arylketo acids **74** to Kenner safety catch linker **73** (Figure 7a). Condensation of resin **75** with aryl hydrazines **76** under conditions previously reported by the Merck group ($ZnCl_2$, AcOH) furnished the fully substituted indole scaffold **77**. The resin$-SO_2-$NH$-$CO$-$ linkage was alkylated using

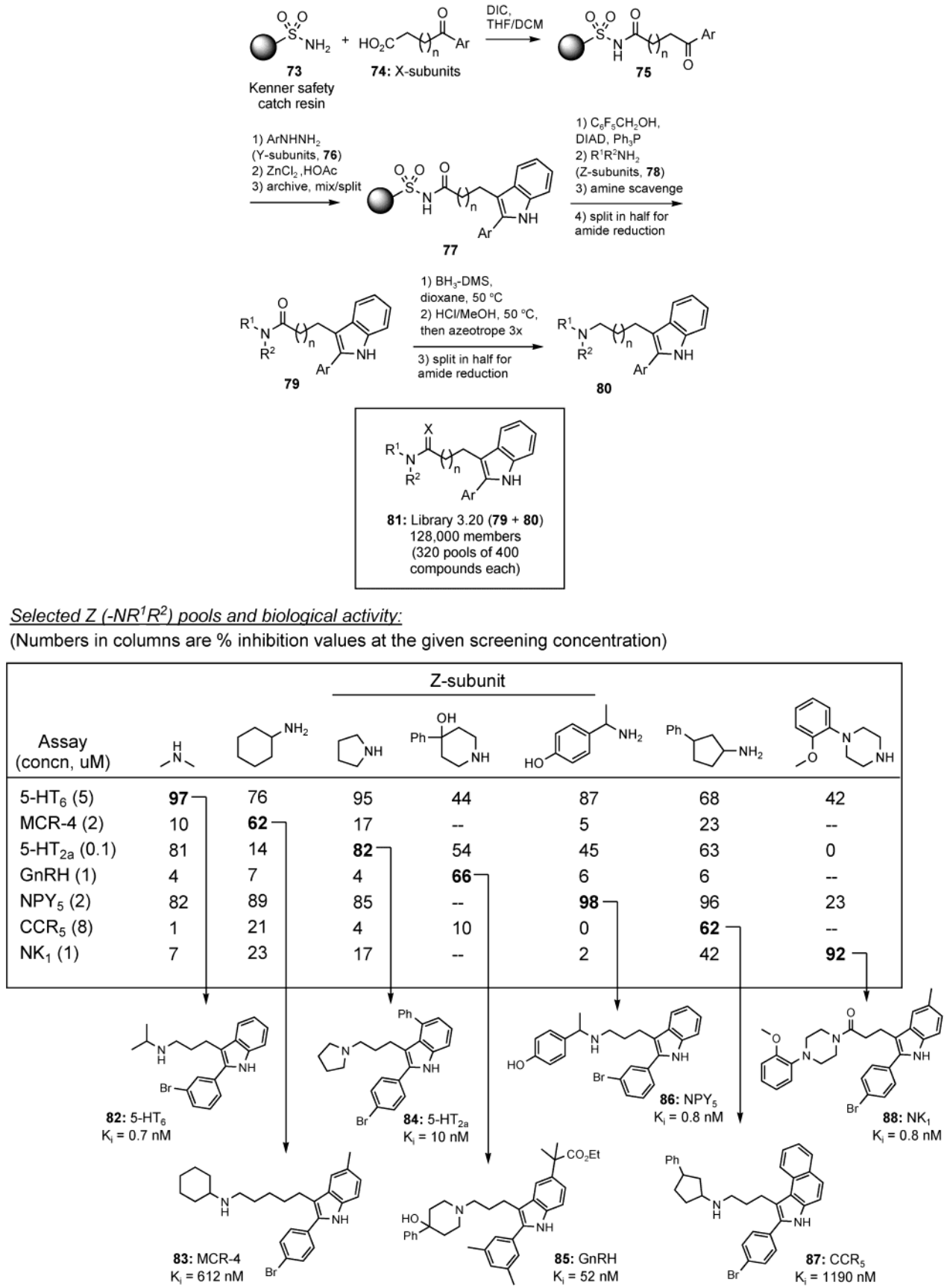


Figure 7. Mixture synthesis and screening results of substituted indoles (library 3.2) as privileged GPCR pharmacophores.[380]

a Mitsunobu protocol (pentafluorobenzyl alcohol, PPh_3, DIAD, THF) and treated with amine nucleophile to afford the 3-(amidoalkyl)-2-arylindoles **79**. The corresponding 3-(aminoalkyl)-2-arylindoles **80** were prepared via post resin

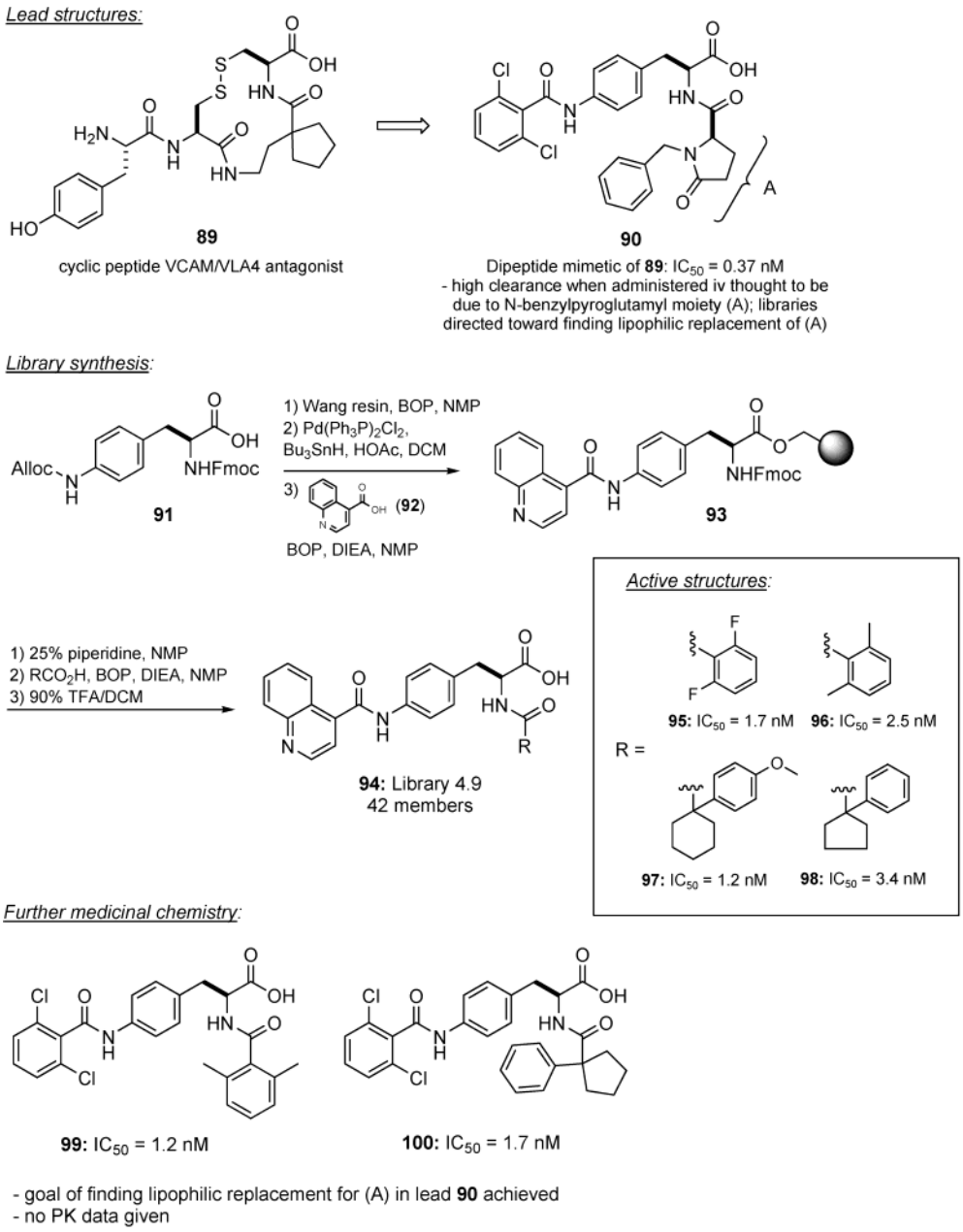


Figure 8. Roche's VCAM/VLA4 antagonists.[73]

amide reduction with borane-dimethyl sulfide complex (BMS, 50 °C) and azeotropic removal (3× with HCl/MeOH 50 °C) of borane byproducts. After each combinatorial step and prior to pooling, a portion of each individual resin was archived for later deconvolution as per standard combinatorial mixture technique. In total, some 128 000 compounds were prepared as 320 pools of 400 compounds.

To exemplify the power of mixture synthesis and the privileged nature of the indole scaffold, the compound pools were screened for biological activity at a single concentration (from 0.1 μM up to 20 μM screening concentration) across a panel of 16 GPCRs, including many receptor subtypes. Activity was observed against every receptor, and selectivity was highly dependent on the pattern of indole substitution. The most active pools from seven representative screening hits were deconvoluted, yielding potent and highly selective ligands (Figure 7b). For example, **88** had an IC_{50} of 0.6 nM against the neurokinin 1 receptor (NK_1), displaying >10 000-fold selectivity versus NK_2 and NK_3. Compound **86**, possessing an IC_{50} of 0.8 nM for neuropeptide Y5 (NPY_5), was similarly >10 000-fold selective versus NPY_1. Impressive, too, were the active compounds deconvoluted against the 5-HT receptors: for example, indole **84** has an IC_{50} of 10 nM against 5-HT_{2a} and was 6-fold selective over 5-HT_{2c}; 60-fold selective over 5-HT_6; and >100-fold selective versus $5HT_{1a}$, $5HT_{5a}$, and 5-HT_7.

VLA-4 ($\alpha_4\beta_1$ Integrin) Antagonists. The very late antigen 4 (VLA-4) is a heterodimeric integrin ($\alpha_4\beta_1$) expressed on many lymphocytes, including T-lymphocytes and eosinophils. VLA-4 mediates cell adhesion, infiltration and activa-

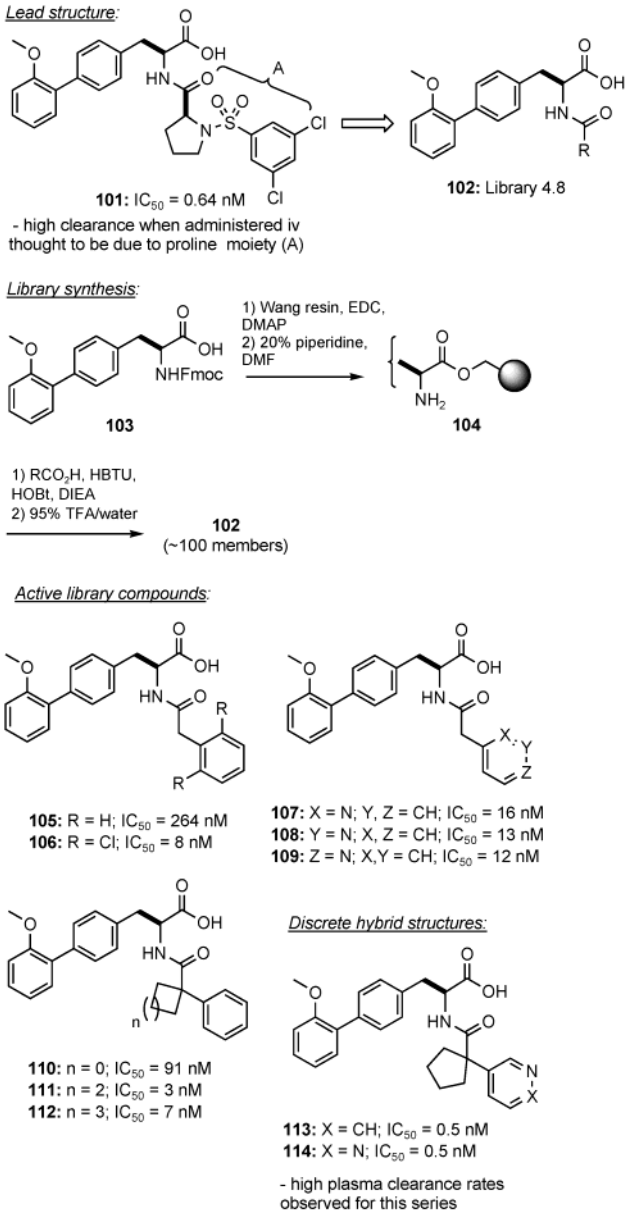


Figure 9. Merck's VCAM/VLA4 antagonists.[228]

tion of these cells when it encounters various receptors, such as vascular cell adhesion molecule-1 (VCAM-1), at sites of inflammation. VLA-4 antagonists are expected to be of significant therapeutic benefit for the treatment of inflammatory diseases. Three companies, Merck,[228] Roche,[73] and Celltech,[299] reported on the synthesis and evaluation of focused libraries for identification of VCAM/VLA-4 antagonists with improved pharmacokinetic properties (lowered clearance). Each company started with structurally similar antagonists displaying high potency and integrin selectivity (Figures 8-10). The lead compounds, **90**, **101**, and **115**, share a derivatized phenylalanine motif as the key pharmacophore. Each company arrived at their lead through screening or structure-based design exercises and had been pursuing VLA-4 antagonists for several years. Finally, leads **90**, **101**, and **115** are rapidly cleared from the blood upon iv administration, and each research group independently hypothesized that the rapid clearance of the compounds may due to the N-acylated functionality (dipeptide-like character); hence, focused libraries were constructed modifying this region of the lead.

The approaches each company took for library synthesis were quite similar. The phenylalanine carboxylate was the functional group handle for solid-phase attachment. In the case of Roche (Figure 8), Wang resin was esterified with the orthogonally protected phenylalanine derivative **91**, and through a series of selective deprotections, they arrived at the 42-member library **94** (library 4.9). The Roche group found *N*-benzylpyroglutamide could be substituted by the less peptidic but more lipophilic 2,6-disubstituted benzamide (e.g., **99**; $IC_{50} = 1.2$ nM) and α,α-spiroalkylphenyacetamide (e.g., **100**; $IC_{50} = 1.7$ nM) moieties. These moieties bear remarkable similarity to the amide replacements that Merck found (see below). No pharmacokinetic data was given, but presumably, these agents were subject to rapid clearance.

From earlier studies, Merck observed that the 2-methoxyphenyl group in lead **101** was quite optimal for integrin antagonism (Figure 9). The biphenyl moiety substantially reduces the peptide character relative to the Roche series (4-amido linkage in **90** removed) and is arguably a better starting point for pharmacokinetic optimization. In an effort to reduce molecular weight and improve clearance, library 4.8 (**102**) was prepared. Wang resin was coupled with the Fmoc-protected 4-(2-methoxyphenyl)phenylalanine **103**. Following Fmoc deprotection (**103** → **104**) and acylation (**104** → **102**), the ∼100 member library **102** was obtained. Surrogates for the sulfonated proline residue included 2,6-disubstituted phenylacetamides (e.g., **106**; $IC_{50} = 8$ nM), heteroarylacetamides (e.g., **109**: $IC_{50} = 12$ nM), and α,α-spiroalkylphenyacetamides (e.g., **111**; $IC_{50} = 3$ nM). Hybrid structures **113** and **114** ($IC_{50} = 0.5$ nM, each), combining elements of both heteroaryl and α,α-spiroalkyl groups and synthesized as discrete compounds based on library SAR, were the most potent VLA-4/VCAM1 antagonists. Despite a reduction in molecular weight, these agents still displayed unfavorably high clearance.

Celltech took a slightly different tack from Merck and Roche and sought an isosteric replacement for the thiazolidinecarboxamide in lead **115** (Figure 10). In particular, the researchers were interested in incorporating the amino acid isostere, 3,4-diamino-3-cyclobutene-1,2-dione. Library construction began with acylation of Wang resin with Fmoc-protected 4-nitrophenylalanine **117**. Nitro reduction proceeded smoothly to yield the corresponding resin-bound 4-aminophenylalanine, which was acylated with 3,5-dichloropyridine-4-carboxylic acid chloride **118** (**117** → **119**). After Fmoc deprotection, resin-bound amine was reacted with 3,4-dimethoxycyclobuten-1,2-dione **120** to give the penultimate intermediate **121**. Treatment of **121** with primary and secondary amines followed by cleavage with 60% TFA/DCM, and HPLC purification furnished a series of libraries, **116a**−**c**, defined by the amine nucleophile (primary un-

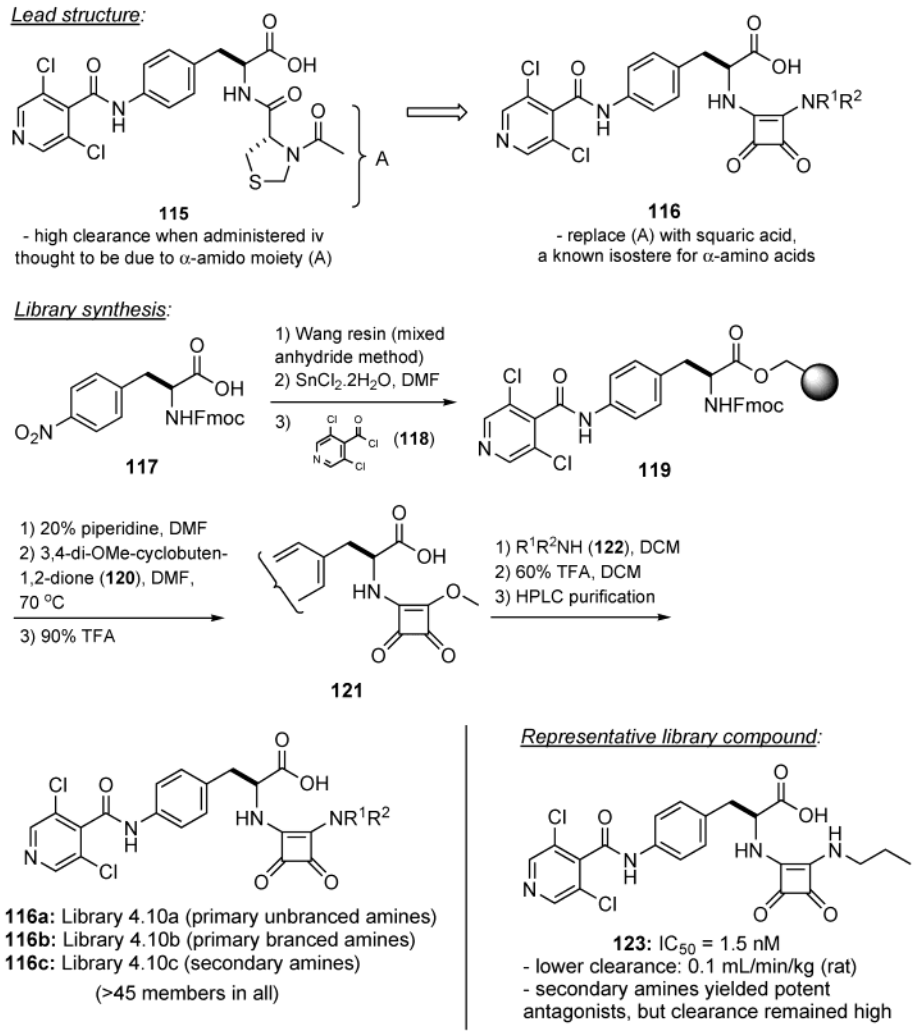


Figure 10. Celltech's VCAM/VLA4 antagonists.[299]

branched, primary branched, or secondary amine). In general, the squaric acid derivatives displayed good potency, again demonstrating their utility as amino acid surrogates. Of special interest was *N*-propyl analogue **123** (IC_{50} = 1.5 nM (protein-based assay); IC_{50} = 120 nM (whole cell assay), which showed high potency and reduced iv clearance (0.1 mL/min/kg (rat)). Interestingly, Celltech prepared a squaric acid analogue of Merck's 2-methoxyphenylphenylalanine-containing antagonist **101** and was found to have diminished potency by a factor of ~10 (whole cell assay), suggesting a unique SAR for the squaric acid series.

Diversity-Oriented Synthesis (DOS). There were several architecturally sophisticated DOS libraries originating from the laboratories of Stuart Schreiber at the Harvard Institute of Chemistry and Cell Biology.[213,217,218,336] This group has been developing encoded split synthesis of stereochemically complex and diverse small molecules. The libraries are not necessarily intended to be druglike in terms of overall physiochemical properties or yield drug leads per se, but rather, they are natural product-inspired designed to explore cellular and organismal pathways vis a vis chemical genetics. Chemistries are typically carried out on high-capacity macrobeads (500 μm; capacity of 100 nmol per bead), providing a sufficient amount of compound after cleavage and formulation as a "one bead/one stock" solution for screening in many assays. A recurring linker theme is the immobilization of functionalized alcohol- or phenol-containing building blocks by way of a silyl ether bond (macrobead-alkylsilyl triflate). After single bead arraying, release of library compounds is achieved by exposure to HF-pyridine. Excess reagent is removed by the addition of TMSOMe, followed by concentration under reduced pressure. All library members therefore possess a hydroxyl group in their structure. Compound identity and purity is ascertained by LCMS analysis of a small portion of cleaved material, or in those cases in which libraries are encoded, GC analysis of the unique set of electrophoric tags revealing the bead's chemical reaction history. Encoded split synthesis library **136** of 29 400 discrete, polycyclic compounds relied on differential dienophile reactivity with resin bound trienes to achieve skeletal diversity (Figure 11).[218] Some 14 X-ray crystal structures of library compounds were determined as a visual aid to reveal skeletal diversity. Ferrier and Pauson−Khand reactions on a glycal template led to a 2500-member encoded library **151**

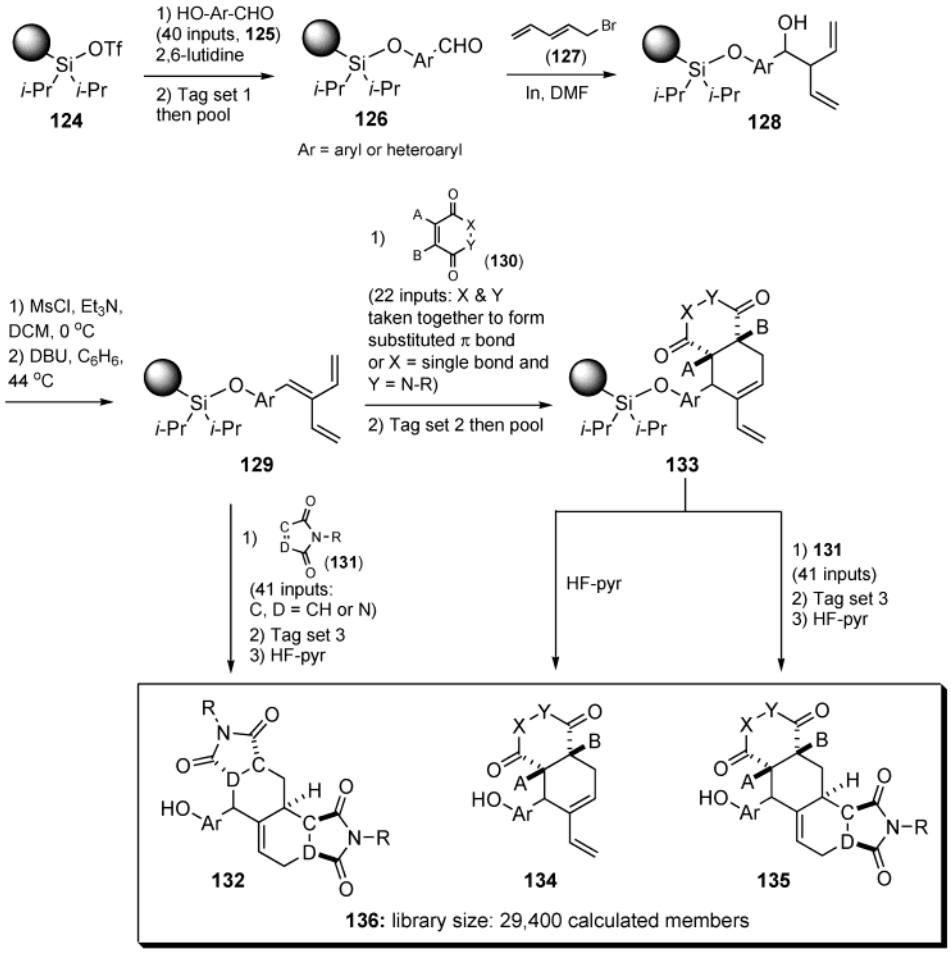


Figure 11. Diversity-oriented synthesis of polycyclic compounds (tags not shown for clarity).[218]

of tricyclics (Figure 12).[213] The efficient oxidation of resin-bound organocuprates was exploited in the atropdiastereoselective synthesis of biaryl-containing medium rings (9-, 10-, and 11-membered ring; library 4.20 (**163**−**165**; Figure 13).[336] Electrophoric tags were incompatible with its library chemistry (metalation of the polychlorinated tags occurred during biaryl bond formation), making encoded split-pool synthesis impossible. In this instance, care was taken to avoid building block constitutional isomers, (*S*)- and (*R*)-amino alcohols were processed in parallel libraries, and bead pooling was eliminated in the final synthetic step to ensure that compound identification could be secured by electrospray mass spectrometry. Biological evaluation of DOS-type libraries has yielded numerous novel small molecules having specific and potent protein-binding and cellular activities, representing potential probes for chemical genetic studies.[416]

Resin-bound 2*H*-pyran-3(6*H*)-one intermediates **171** were conceived as a multireactive core molecule from which a variety of pharmacophoric frameworks could be created (Figure 14).[100] In the work described by Couladouros and Strongilos, a series of α-hydroxyfurans **166**−**169** with an oxidation-sensitive (DDQ) linker was synthesized in solution and then immobilized to give resin **170**. The derivatized resin was then treated with NBS, THF/H_2O (4:1) at 0 → 25 °C for 1 h. Pyranones **171** so obtained were subjected to a host of chemistries, leading to both skeletal rearrangements and function group interconversions (**171** → **172** → **182**). Structurally diverse mono, di-, and tricyclic heterocycles were all obtained from **171**.

Solid-phase synthesis directed toward creating diverse collections of heterocycles has been reported. Strategies deployed to date require synthetic sequences to converge to a common intermediate or set of intermediates, which then diverge into different heterocyclic products. Purandare (Bristol-Myers Squibb) converted *o*-fluoronitrobenzoic acid into resin-bound aniline **187** and proceeded to construct six heterocyclic ring systems (**188**−**193**; Figure 15).[304] Huang (Shanghai Institute) converted Merrifield resin to a polymer-bound variant of Meldrum's acid **199** (Figure 16).[173] Condensation of **199** with triethylorthoformate generated the corresponding aminomethylene cyclic malonic acid esters **200**. Reaction of **200** with either an aniline, urea, or thiourea then intracyclative cleavage (thermolysis: 220−240 °C, 20 min) furnished quinolones **201**, pyrimidobenzothiazolones **202**, thiazolopyrimidinones **203**, uracils **204**, and thiouracils **205**, respectively.

Solid-Phase Synthesis Using Katritsky's Benzotriazole Chemistry. Nearly two decades ago, Katritzky began an odyssey exploring the utility of benzotriazole (Bt) in carbo- and heterocyclic synthesis and has published extensively in

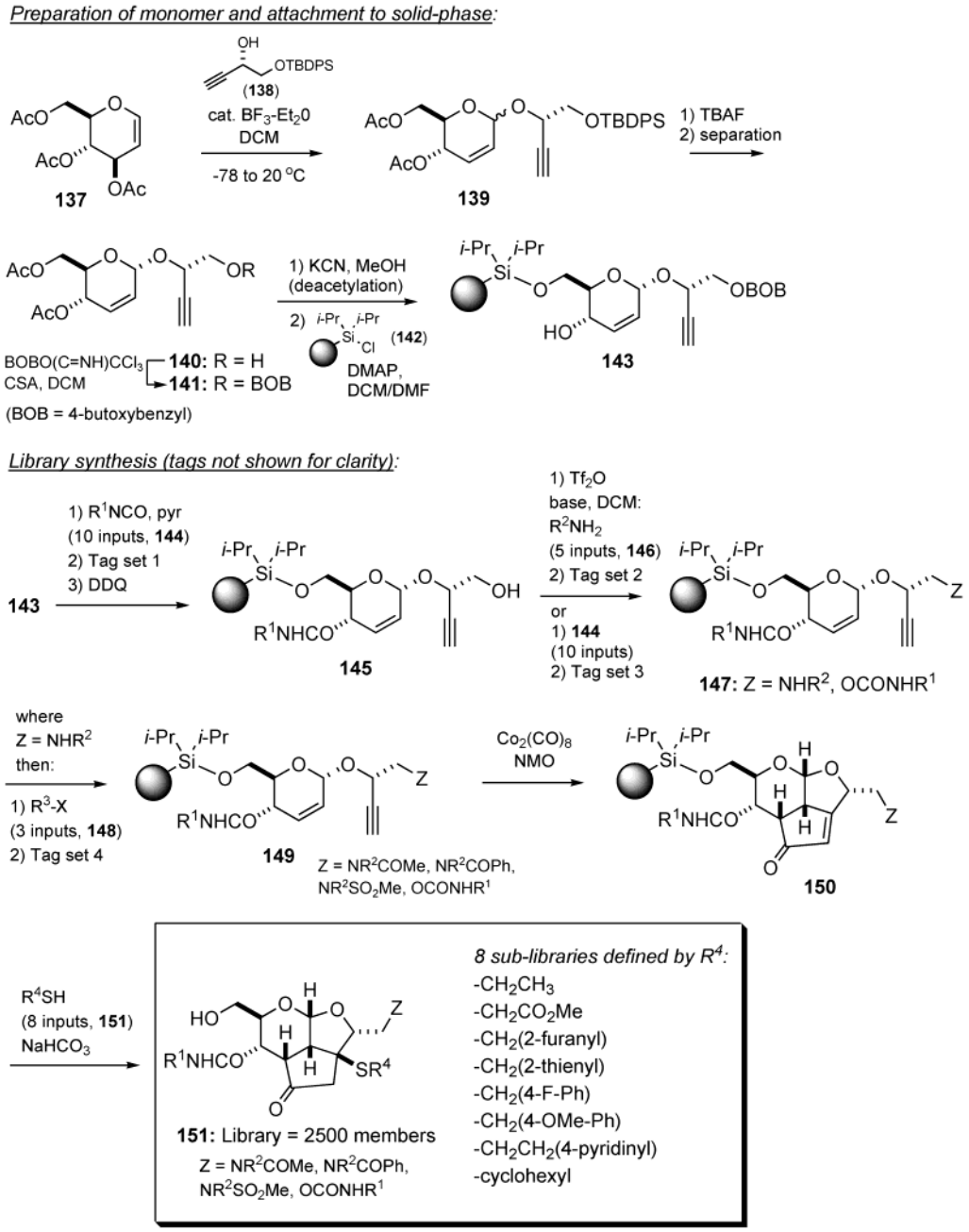


Figure 12. Diversity-oriented synthesis of tricyclic compounds.[213]

this area. Bt-based chemistry is finding its way into solid-phase synthesis. There were eight Bt-related publications appearing from four independent research groups in 2002.

Katritzky disclosed the solid-phase synthesis of 4,6-diaryl substituted and 3,4,6-trisubstituted pyrid-2-ones **213** by reaction of resin-bound chalcones **211** with 2-(benzotriazol-1-yl)- and 2-alkyl-2-(bentriazol-1-yl)acetamides **212** (Figure 17A).[193] Resin-bound chalcones **211** were prepared by linking 4-hydroxyacetophenone **208** to Wang resin **207** by a modified Mitsunobu protocol (DIAD, PPh_3, NMM, 25 °C, 48 h) followed by condensation with aryl aldehydes (MeONa, THF, 25 °C, 24 h). Pyridones **213** were obtained in excellent yield and purity upon reaction of **211** with 2-(benzotriazol-1-yl)acetamides (20 equiv) in the presence of NaOH (40 equiv) in EtOH/THF (1:5) at 70 °C for 24 h, after standard TFA cleavage conditions.

Katritzky reported the condensation of amine resins **215** with di(benzotriazol-1-yl)methanimine **216** (25 °C, 7 h) to give Bt-containing intermediates **217** (Figure 17B).[194] Treatment of **217** with thiols or secondary amine activated with EtMgBr lead to *S*-arylisothioureas **218** and guanidines **219**, respectively.

Finally, Katritzky demonstrated that *N*-acylbenzotriazoles **220** can be employed in the solid-phase preparation of amides (Figure 17C).[194] Wide structural variation in the R2 group was geneated by reaction of *N*-methansulfonylbenzotriazoles with a carboxylic acid in the presence of base. Resin-bound amines **215** were acylated under neutral conditions upon

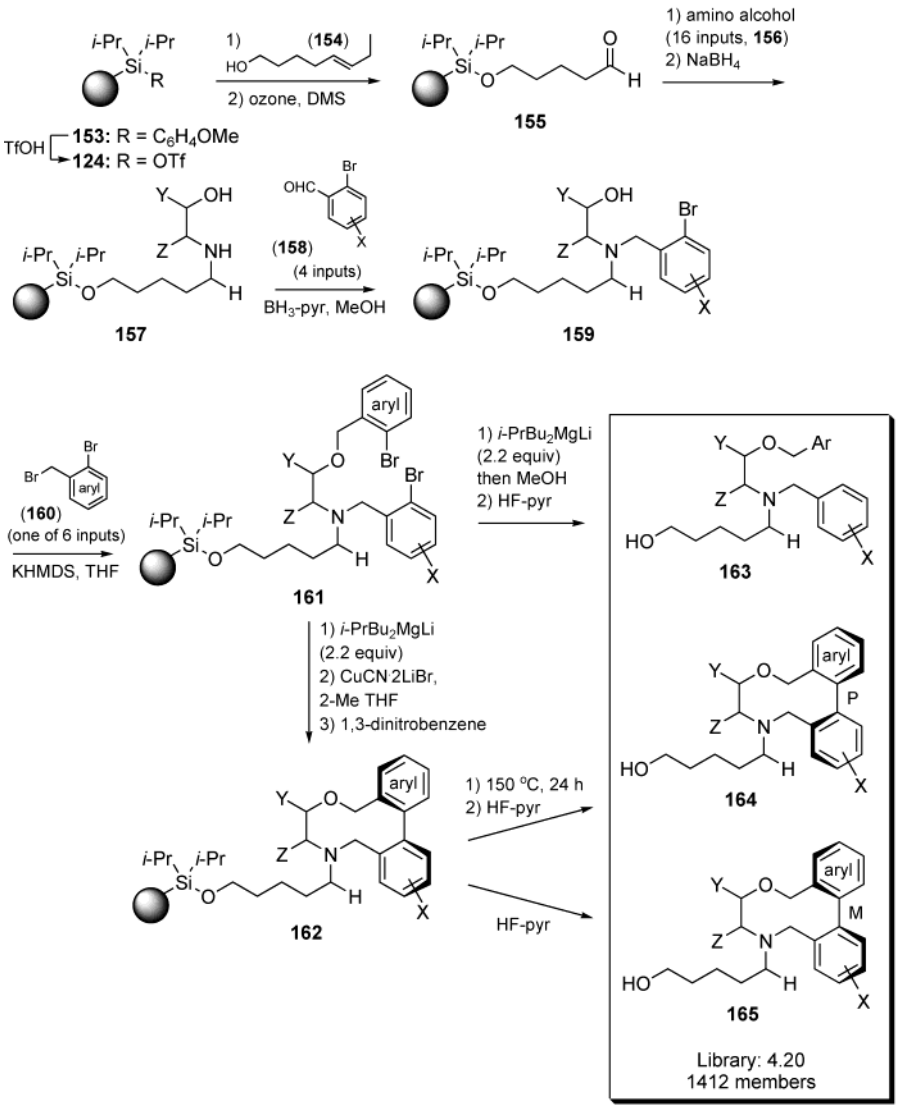


Figure 13. Diversity-oriented synthesis of biaryl-containing medium rings.[336]

treatment with **220** in refluxing THF for 48 h. Resin cleavage provided the correspoding amides **221**.

The versatility of benzotriazole-1-carboximidamide-type intermediates **222** was further demonstrated by Makara and co-workers in a regiocontrolled synthesis of 3-alkylamino-1,2,4-triazoles **224** and 1,2,4-oxadiazoles **225** (Figure 18).[248,249] Inspired by Katritzky's original solution synthesis, acylation of **222** with alkyl and aryl acid chlorides generated immobilized *N*-acyl-Bt-1-carboximidamides **223**. Reaction of **223** with N-substituted hydrazine or hydroxylamine with DBU as the optimal base in THF proceeded at 50 °C to give the respective heterocycles. DBU was essential to ensure efficient cyclization and minimal byproduct formation.

A facile route to 1,2,5-trisubstituted 4-imidazolidinones was reported by Houghten (Figure 19).[319] MBHA resin-bound amino acids **226** were prepared via classical amino acid coupling/Fmoc deprotection/reductive amination methodology. When resin **226** was refluxed with an aromatic, aliphatic, or heterocyclic aldehyde (10 equiv) and benzotriazole (10 equiv) in benzene for 16 h, the reactive *N*-[1-benzotriazol-1-yl)alkyl] species **227** was produced, which suffered spontaneous intramolecular cyclization via nucelophilic substituion of the Bt group with the amidic nitrogen (**226** → **227** → **228**). Treatment of resin **228** with HF released compounds **229**. The reaction is nonstereospecific and produces diastereomers in ratios that vary depending on the ring substitutents. The high-yielding reaction conditions and range of building blocks lends itself to the production of large, diverse collections of imidazolidinones as single compounds or in mixture-based synthesis. This group also reported the application of this chemsitry to the synthesis of peptidomimetic-based 4-imidazolidinones.[316]

Researchers from the Univeristy of Amsterdam were interested in creating libraries of 2-substituted piperidines **232** as potentially bioactive compounds (Figure 20).[366] An efficient solid-phase synthesis was developed starting from carbamate-tethered *δ*-amino acetals **230**. The key reaction was an intramolcular cyclization to form a transient *N*-acyliminium ion **231** that could be trapped with suitable C-nucleophiles. Lewis acidic conditions previously successful

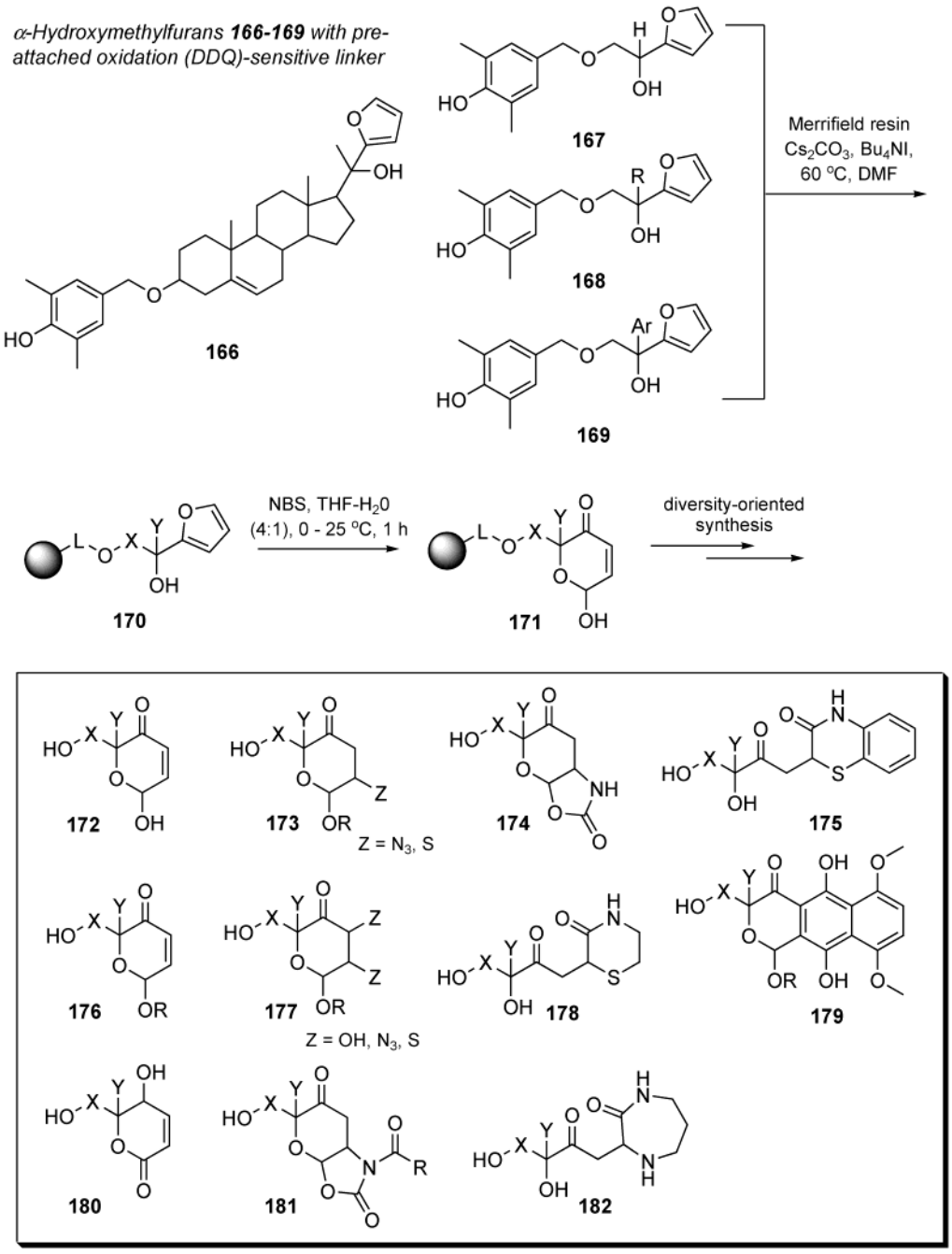


Figure 14. Diverse pharmacophores from resin-bound 2*H*-pyran-3(6*H*)-ones.[100]

in a high-yielding solid-phase preparation of 2-substituted pyrrolidines from γ-amino acetals failed with the homologous piperidine analogues. For example, although the reaction with **233** and allylsilane gave the expected 2-piperidine, it was contaminated with a linear side product resulting from competing intermolecular attack of the allylsilane onto the oxycarbenium ion instead of the intramolecular attack by the carbamate nitrogen atom. This side reaction was not observed in the pyrrolidine case. Several attempts were made to suppress the reaction, but to no avail. Model system **233** was then studied in solution. Treatment of **233** with $BF_3 \cdot Et_2O$ led to a mixture of **235** and the corresponding linear product **236**. Exposure of **233** to catalytic *p*-TSA in DCM or DCM/EtOH produced rather unstable intermediates **237** and **238**. However, the reaction of **233** with catalytic *p*-TSA in DCM for 15 min at room temperature followed by the addition of BtH **206** led to quantitative conversion to the 2-Bt-substituted piperidine **239**. Bt derivative **239** was stable to silica gel column chromatography and could be fully characterized. Treatment of **239** with a Lewis acid and allylTMS furnished **235** in 93% isolated yield. These reaction conditions were then applied to resin-bound acetal **230**. Complete conversion to the putative ring-closed intermediate **240** was established by IR (disappearance of the NH signal). Subsequent treatment of **240** with a range of C-nucelophiles and cleavage with 1 M NaOMe in THF/MeOH (2:1) gave

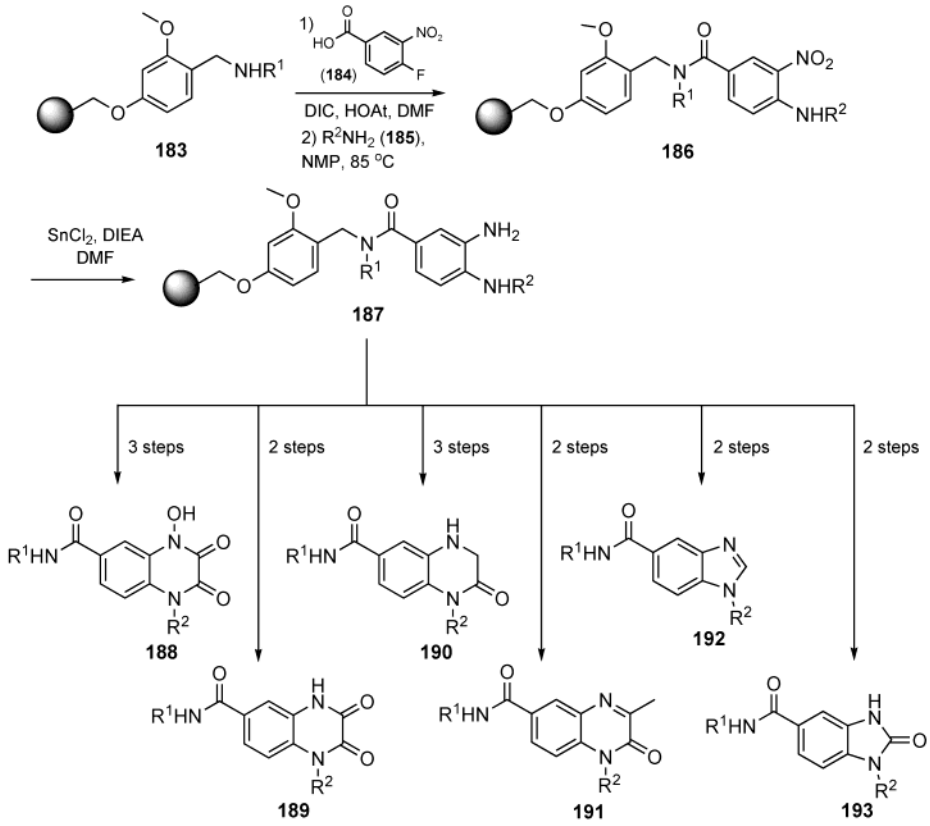


Figure 15. Divergent heterocyclic synthesis from a common resin-bound intermediate.[304]

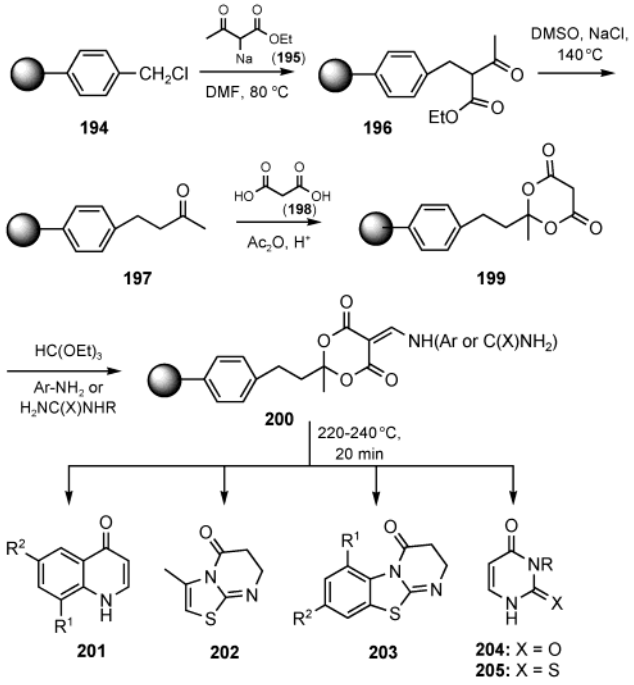


Figure 16. Diverse heterocycles from resin-bound Meldrum's acid.[173]

2-substituted piperidines **232** in good yield and purity and in high diastereoselectivity.

Amine Synthesis. Amines and derivatives thereof are ubiquitous in drug substances, and combinatorial methods are continually sought to generate this salient functional group. Examples of new protocols for the preparation of secondary and tertiary amines and the N-arylation of primary and secondary amines were reported in 2002.

Pelletier and co-workers at Wyeth described a novel, tandem three-phase reductive amination procedure for the preparation of secondary amines from primary amines with minimal side product formation (Figure 21).[291] Typical side products obtained from classical solution or solid-phase reductive amination conditions include (a) alcohol from reduction of the carbonyl group, (b) starting amine from incomplete reaction, and (c) products of over alkylation, all of which may diminish yield and compromise product purity. In Pelletier's multiphase reaction, resin-bound aldehyde **242** in its resin-bound imine form **244** undergoes a transimination/cleavage equilibrium with a primary amine **245** (0.5 equiv) to produce a solution-phase imine **246**. In the presence of polymer-bound borohydride (2 equiv), the solution imine **246** is reduced to the corresponding secondary amine. After filtration, excess starting resin **243**, resin-bound imine **244**, and reducing reagent are removed, leaving essentially pure product. Because there is no excess aldehyde present and the product (secondary amine) does not participate in the initial phase switch, over alkylation does not occur; neither is any alcohol from RCHO reduction observed. The methodology was applied to a library of β-adrenergic receptor ligands; compounds **249**−**251** are representative members. It will be of interest to see whether other research groups

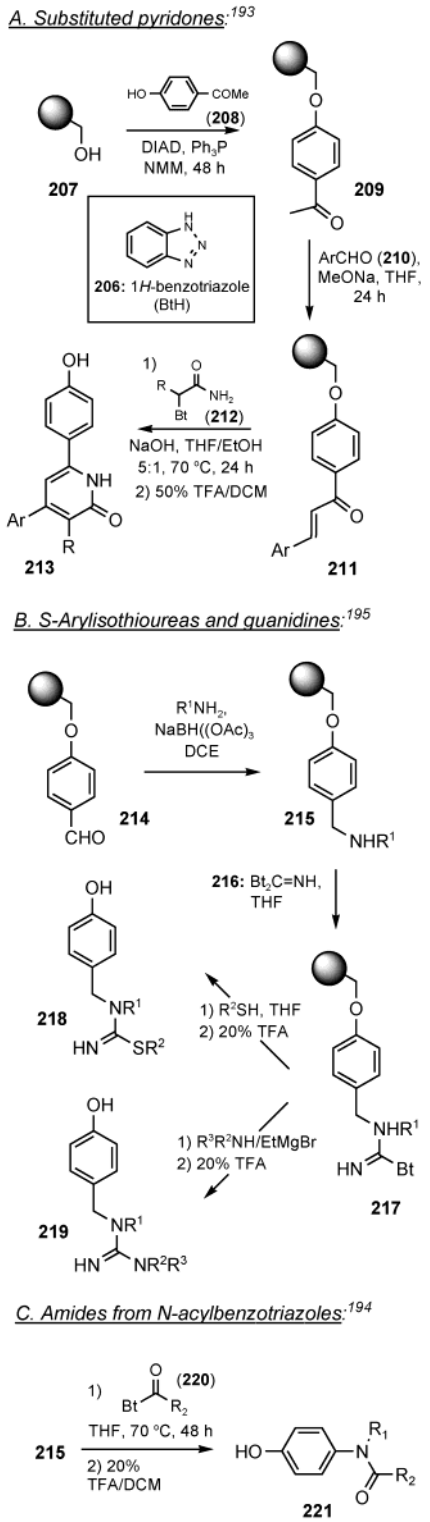


Figure 17. Application of Katritzky's benzotriazole to solid-phase synthesis.[193−195]

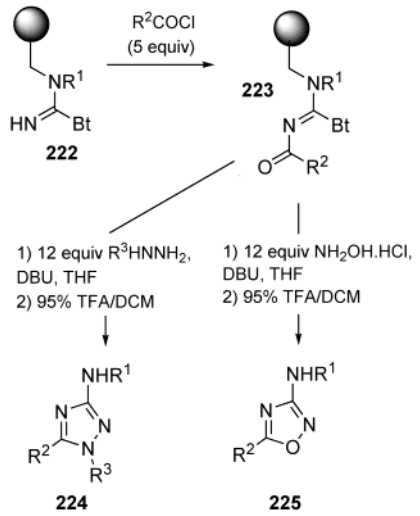


Figure 18. Benzotriazole-mediated triazole and oxadiazole synthesis.[248,249]

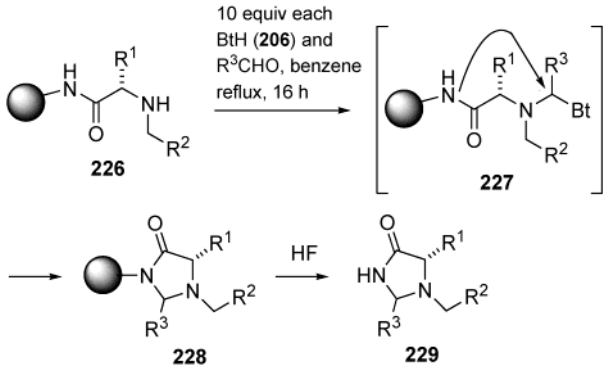


Figure 19. Benzotriazole-mediated 4-imidazolidinone synthesis.[319]

who attempt this simple, yet elegant, chemistry will find equally satisfying results.

A novel and versatile safety catch linkage strategy was developed by Schultz to generate libraries of functionalized *N*,*N*-dimethyltryptamines and β-carbolines (Figure 22).[386] Tryptamine scaffolds **252** (prepared in three steps from commercially available indoles) were immobilized through the Michael addition to vinyl sulfone resin **253**, furnishing tryptamine-bound resin **254**. In model studies, activation of the safety catch linker by exhaustive methylation (MeI, 15 equiv) and Hoffman elimination mediated by DIEA proceeded smoothly to furnish *N*,*N*-dimethyltryptamines (**254** → **255** → **256**). Alternatively, clean monomethylation to resin **257** was achieved upon brief exposure to a slight excess of MeI (2 equiv, 15 min). This resin **257** was sufficiently stable toward acylating reagents, Cu-catalyzed N-arylation and Suzuki coupling conditions permitting further scaffold diversity (**257** → **258**/**259**). Last, resin **254** was subjected to a Pictet−Spengler cyclization (**257** → **260**). Premature cleavage of material from the solid support was not observed. Quaternary ammonium formation and Hoffman elimination then generated the *N*-methyl-β-carbolines **261**. Excellent purity and yields were obtained for all transformations.

Combs at DuPont Pharmaceuticals, now Bristol-Myers Squibb, reported additional details on an operationally simple and mild method for the N-arylation of resin-bound primary and secondary amines (Figure 23).[94] *N*-arylamines are widely found in biologically active agents and, hence, are attractive pharmacophores for library exploitation. Copper acetate-promoted C/N cross-coupling of arylboronic acids with

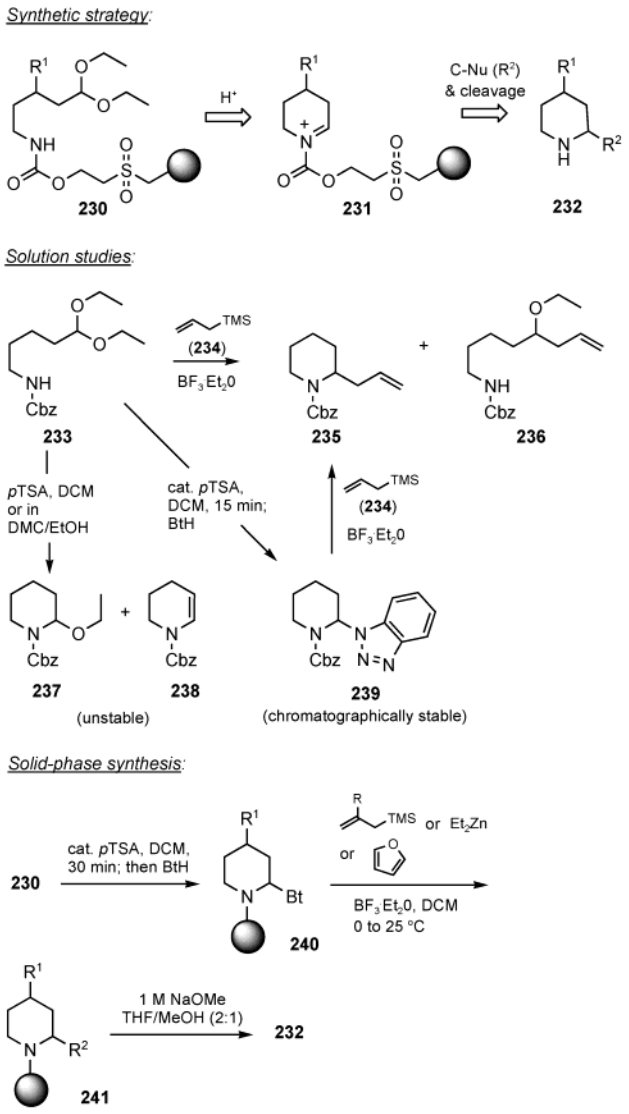


Figure 20. Benzotriazole-mediated piperidine synthesis.[366]

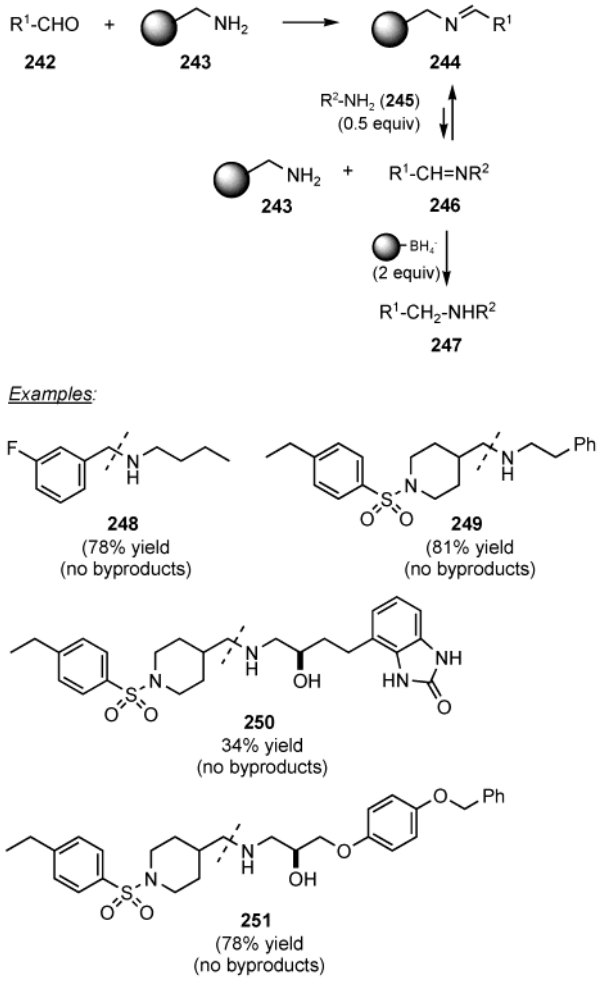


Figure 21. Tandem three-phase reaction for secondary amine synthesis.[291]

amines takes place via sequential addition of phenylboronic acid (4 equiv), anhydrous copper acetate (2 equiv), 4Å powdered molecular sieves (50 wt % of resin), and triethylamine (4 equiv) to the resin-bound amines (e.g., **262**) in THF. The cross-coupling reaction proceeds for ~3 h, after which time the resin is drained and washed. This is repeated for a total of three cycles to maximize formation of product **263**. Conversion to N-arylated products was on the order of 70−90% for para-substituted boronic acids, whereas lower conversions (35−50%) were observed for other substitution patterns. Overall yields were moderate to good after HPLC purification of the products (20−75%). One of the interesting features of this cross-coupling chemistry is that primary amines that lack an α-substituent are efficiently converted to the *N*,*N*-diaryl products (**264** → **265**) in high yield with <10% mono-*N*-aryl product fromation. Introduction of α-substitution, a small methyl group, for example, completely changes the product profile, and only mono-*N*-arylamines (**266** → **267**) are formed without any trace of the corresponding diarylamine. Sulfonamides and many heterocycles containing free N−H bonds afford good to excellent yields and purities of N-arylated products. In contrast, amides, carbamates, and ureas give no reaction.

Fluorous-Based Reagents and Scavengers. Fluorous chemistry was pioneered by Curran[417] and has formed the basis of a relatively new startup company, Fluorous Technology, Inc. (FTI). The basic tenet underlying the technology is that molecules tagged in some fashion with a perfluoroalkyl group can be rapidly, selectively, and quantitatively separated from molecules without such tags. The unique physiochemical properties of the perflouroalkyl group override other functionality present in the molecule. Liquid−liquid extraction (fluorohydrocarbon solvent) and chromatography on fluorous sorbants are employed to separate fluorous tagged/untagged compounds. The nascent technology is finding application in high-throughput synthesis, particularly in the parallel synthesis of discrete compounds. Combinatorial mixture synthesis is also possible using perfluoroalkyl groups of varying chain lengths.[409] Fluorous tags are inert to most chemical reaction conditions and offer a convenient handle for rapid separation, and chemistries can

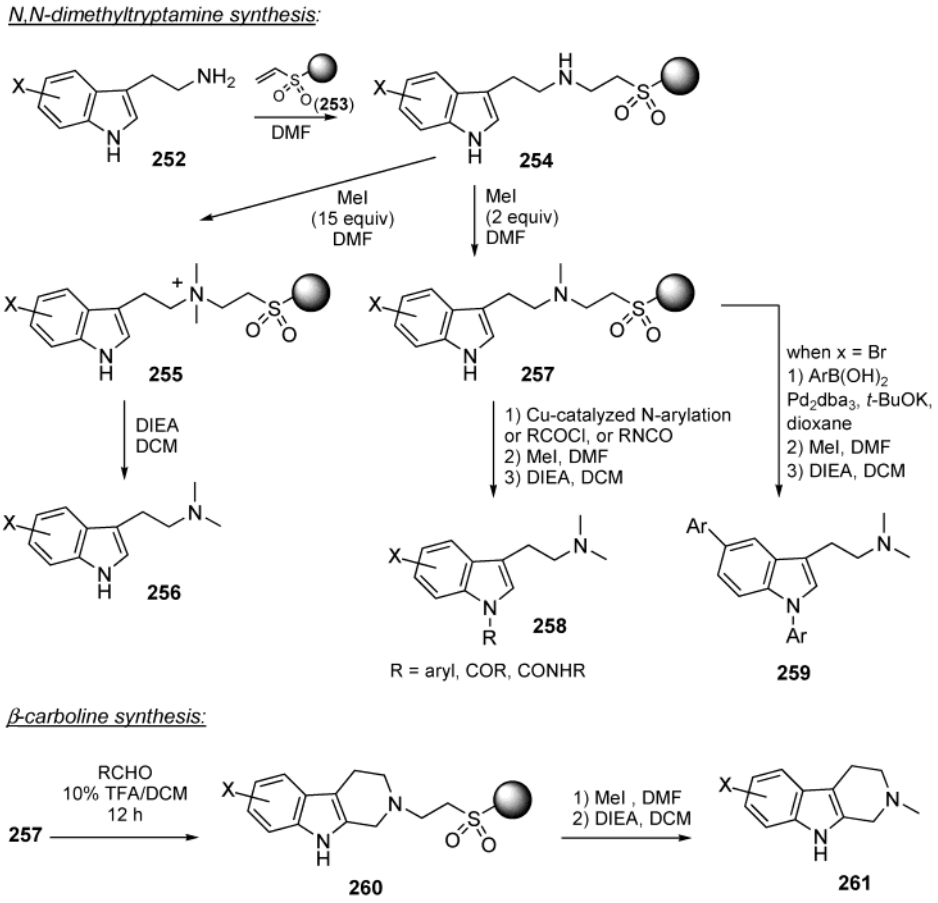


Figure 22. Safety-catch linkage strategy for the synthesis of *N,N*-dimethyltryptamines and β-carbolines.[386]

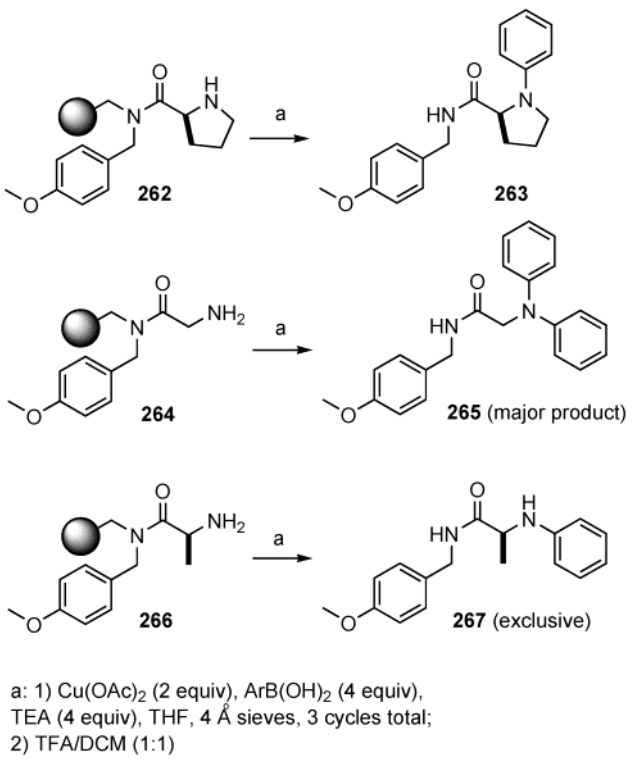
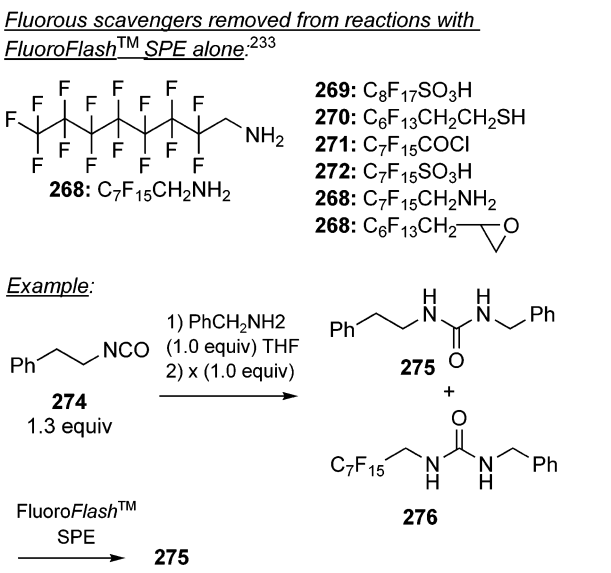


Figure 23. N-Arylation of primary and secondary amines on solid support.[94]

be performed in solution and are easily scaleable. A growing collection of fluorous reagents, protecting groups, miscellaneous tags, and assorted fluorous sorbants, for example, fluorous SPE cartridges (Fluoro*Flash* SPE), for purification are commercially available.

The Technology Enabled Synthesis Group at Merck has been actively developing fluorous-tethered reagents and scavengers to facilitate parallel solution synthesis. A novel fluorous variant of triphenylphosphine in combination with Fluoro*Flash* SPE was used in a Staudinger protocol for azide to amine reduction.[235] The reduction reaction was monitored by ^{31}P NMR, and reaction times of only 4 h were necessary, in contrast to >72 h required for resin-bound triphenylphosphine. A series of fluorous-tethered quenching reagents **268**−**273** were prepared and successfully utilized in several reaction classes to scavenge excess amine, aniline, alkoxide, and epoxide functionality from solution. For example, in the ureidation of benzylamine with excess phenethylisocyanate, Lindsley[233] demonstrated that excess phenethylisocyanate was efficiently scavenged by C_7F_{15}-tagged amine **268**, affording urea **275** in 93% yield and >98% purity after Fluoro*Flash* SPE chromatography (Figure 24).

The commercially availability of fluorous-tagged acid chlorides and a great number of diamines led to the design and synthesis of scavengers **277**−**282** by the Merck group.[234] Simple acylation chemistry offered a convenient source of



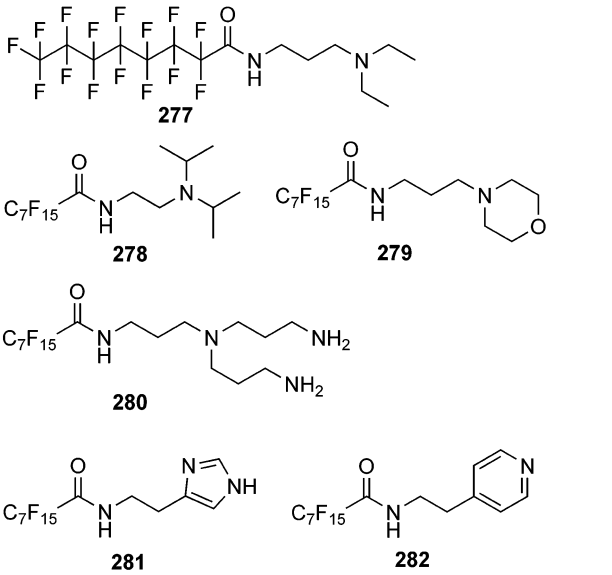


Figure 24. Fluorous-tethered scavengers for solution-phase parallel synthesis.[233,234]

these and potentially many other custom fluorous-tethered bases to complement existing resin-bound congeners and to capitalize on homogeneous solution-phase kinetics. However, during the initial evaluation of **280** in a sulfonylation reaction, ~15% of the fluorous base coeluted with sulfonamide product when the reaction was purified by Fluoro*Flash* SPE. It came as a great surprise to discover that none of the fluorous bases **277**−**282** were fully retained upon Fluoro*Flash* SPE. Even with a silica gel transfer precolumn in place, up to 60% of some for the fluorous amide scavengers passed though the fluorous SPE cartridge. This stands in contrast to current dogma that the chromatographic properties of the perflouroalkyl group dominate over other functionalities present in the molecule. Lindsley noted all previously

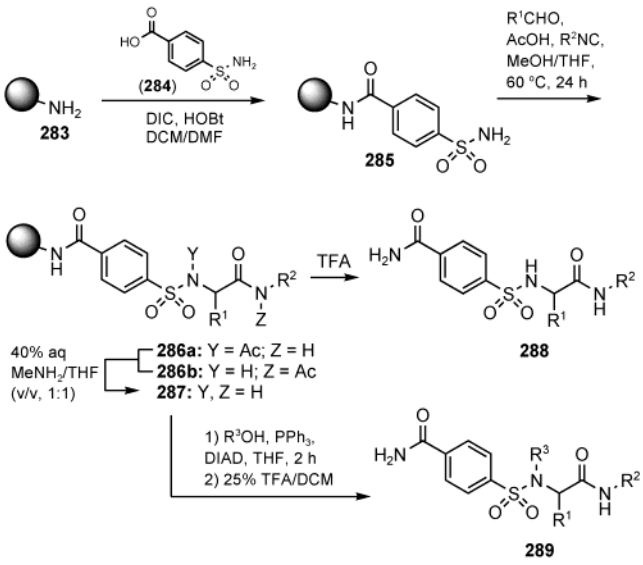


Figure 25. Ugi-type condensation using sulfonamide as amine input.[60]

reported fluorous-tagged reagents have the perfluoroalkyl group linked in close proximity to the scavenging functionality by a lipophilic tether, whereas scavengers **277**−**282** contain a polar amide bond and position a basic nitrogen several atoms away from the perfluoro tag. Ultimately, a "mixed sorbent" solved the problem: crude reaction mixtures were first passed through an ion exchange column followed by fluorous SPE. In this way, products were isolated in high yield and desired purity (>95%, free of fluorous tags). In addition, a set of guidelines based on LCMS retention time was developed to predict a fluorous-tethered reagent's chromatographic behavior on Fluoro*Flash* SPE.

Multicomponent Condensations. Multicomponent condensations give rise to products with several points of diversity by bringing together three or more different building blocks in a single reaction step. The Ugi reaction, popularized in recent years by combinatorial chemists, utilizes four components, a carboxylic acid, an amine, an aldehyde, and an isocyanide, generating acylamino amides, which may be further transformed into a wide variety of acyclic and heterocylic products. A research group at Advance SynTech explored sulfonamides as surrogates for the usual amine building block in this reaction, potentially yielding α-sulfonylamino amide derivatives (Figure 25).[60] The reaction was first examined in solution wherein a *p*-toluenesulfonamide was treated with 1 equiv each of acetic acid (HOAc), hydrocinnamaldehyde, and *tert*-butyl isocyanide in THF/MeOH (1:1). After 3 days, a complex mixture formed with only trace amounts of the desired four-component condensation product detected. Despite the poor reactivity of the sulfonamide, the fact that trace quantity of desired material was formed spurred further investigation on solid-phase. Resin-bound sulfonamide **285** (from **284** and Rink resin, DIC/HOBt coupling) was treated in exactly the same way as in the solution experiment, except that 10 equiv of each

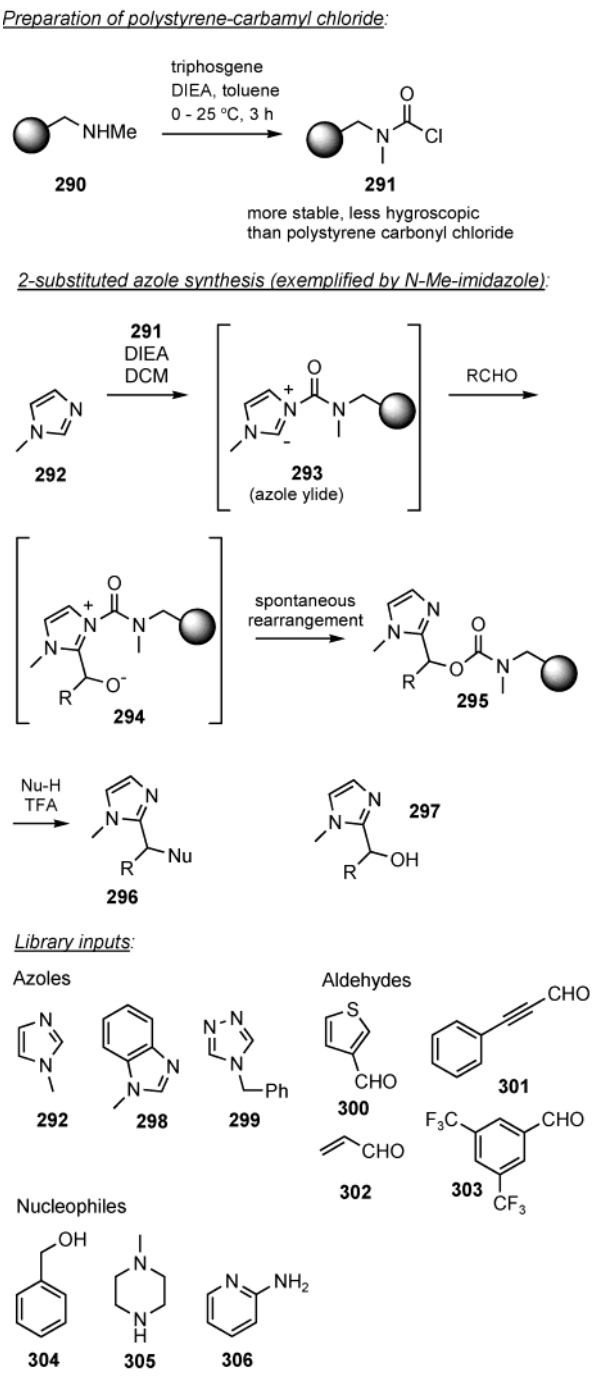


Figure 26. Hlasta's multicomponent 2-substituted azole synthesis on solid phase.[108]

component was used. After 3 d, the resin was exposed to 20% TFA in DCM. Products so cleaved were examined by LC/MS, and the results again confirmed trace product **288**, but largely unreacted sulfonamide. The reaction was repeated, but this time at elevated temperature (60 °C, 24 h). Cleavage gave the desired Ugi product **288** contaminated with acylated materials **286a**/**b**. Decetylation occurred easily upon exposure to 40% aq $MeNH_2$/THF (1:1), affording complete conversion to α-sulfonamino amide **288** after resin cleavage. The reaction conditions were successfully applied to a broad range

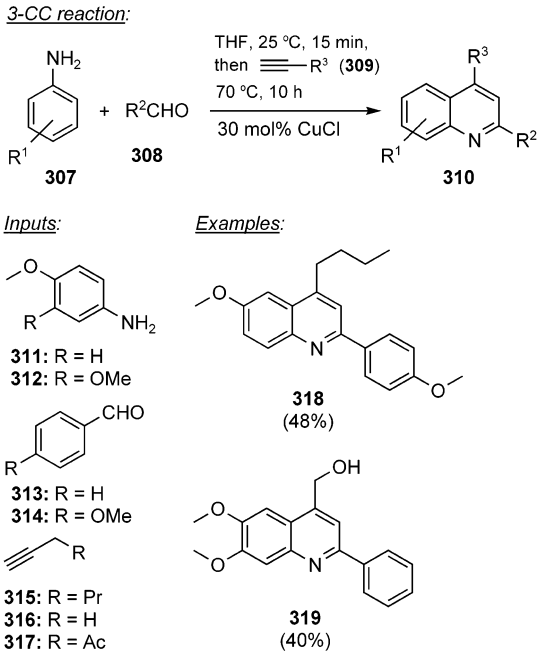


Figure 27. Three-component condensation yielding substituted quinolines.[176]

of aldehydes and isocyanides. The diversity of products could be further expanded by N-alkylation of **287** with alcohols under Mitsunobu conditions. Product yields for **289** were on the order of 40−93%, with purity ranging from 60 to 95% for 18 representative products.

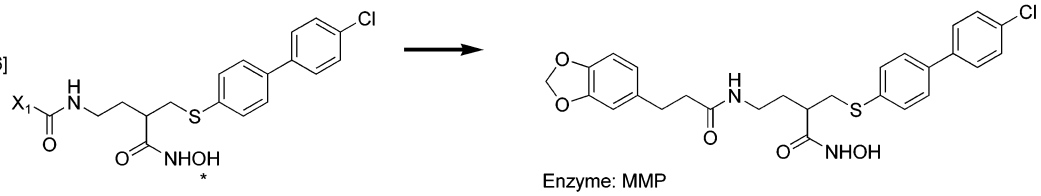
Hlasta described a traceless solid-phase synthesis of 2-substituted azoles (Figure 26).[108] The three-component synthesis employs an azole (imidazole exemplified), aldehyde, and an amine. Imidazole **292** (3 equiv) is captured on solid phase by reaction with resin-bound carbamoyl chloride **291**. This generates an azolium ylide **293** which undergoes immediate condensation with an aldehyde (5 equiv, 24 h) present in the reaction medium. Intramolecular acyl transfer occurs, forming resin-bound 2-substituted imidazole (**293** → **294** → **295**). Cleavage from resin using TFA in THF at reflux for 24 h in the presence of an amine, thiol, or alcohol nucleophile affords **296** via formation and trapping of an intermediate carbonium ion. In the absence of a nucleophile, alcohol **297** is produced. A 3 (heterocycle) × 4 (aldehyde) × 3 (nucelophile) library demonstrating the fidelity of the chemistry gave 34 out of 36 theoretical compounds, with 80% of the compounds possessing >80% purity.

A novel three-component condensation protocol for the synthesis of quinoline derivatives was reported (Figure 27).[176] In a one-pot reaction, anilines, aromatic aldehydes, and a catalytic amount of CuCl in THF were stirred together for 15 min, followed by the addition of a terminal alkyne in THF (reflux, 10 h). Quinolines **310** were obtained in good yield after chromatography to remove benzylamine byproducts. Noteworthy is the mild reaction conditions and the use of propargyl alcohol and its acetate as an alkyne input. These inputs make provision for further derivatization chemistry.

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

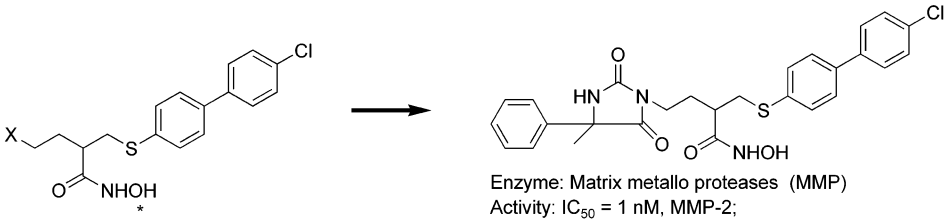
Metallo-proteases

Library: 1.1
Name: Hydroxamate
Size: 24 members
Affiliation: Chollet, A.-M.; *et al.* [86]



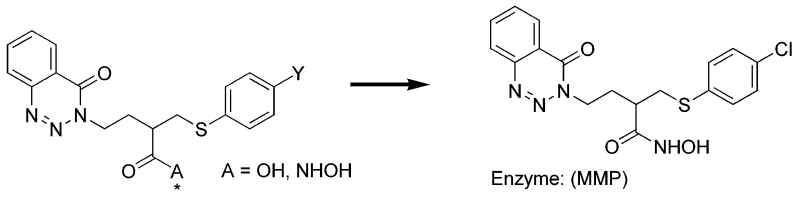
Enzyme: MMP
Activity: IC_{50} = 3 nM, MMP-2;
>5x selectivity versus MMP-1, 3, 9 and 13

Library: 1.2
Name: Hydroxamate
Size: 12 members
Affiliation: Chollet, A.-M.; *et al.* [86]
Note: Follow-up to library 1.1.



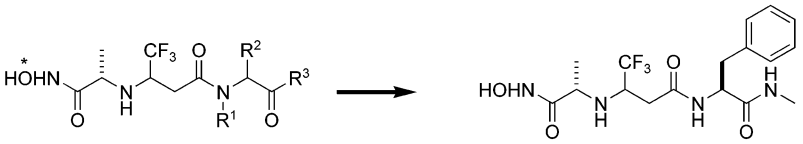
Enzyme: Matrix metallo proteases (MMP)
Activity: IC_{50} = 1 nM, MMP-2;
IC_{50} = 2 nM, MMP-9;

Library: 1.3
Name: Hydroxamate
Size: 12 members
Affiliation: Cholett, A.-M.; *et al.* [86]



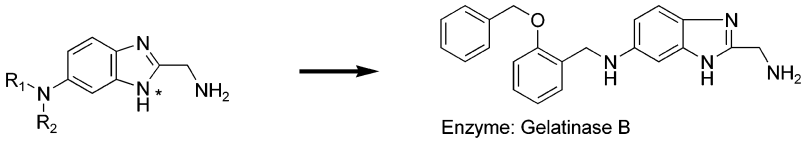
Enzyme: (MMP)
Activity: IC_{50} = 0.06 nM, MMP-2;
10 nM, MMP-3; 0.5 nM, MMP-9;
1.2 nM, MMP-13; >10^4 nM, MMP-1

Library: 1.4
Name: Hydroxamate
Size: *ca.* 18 members
Affiliation: Volonterio, A.; *et al.* [369]



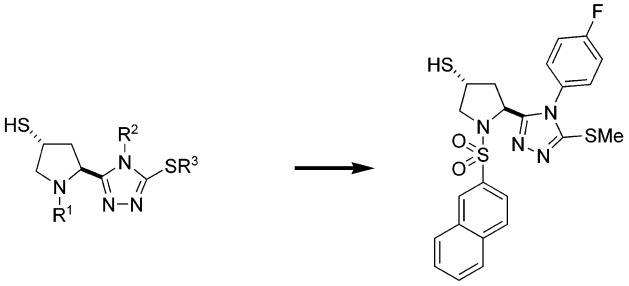
Enzyme: MMP-9
Activity: Dose-dependent
inhibition of MMP-9 gelatinolytic capacity

Library: 1.5
Name: Aminomethyl benzimidazole
Size: 176 members
Affiliation: Wang, X.; *et al.* [373]
Note: Benzimidazole attached to resin via DHP linker.



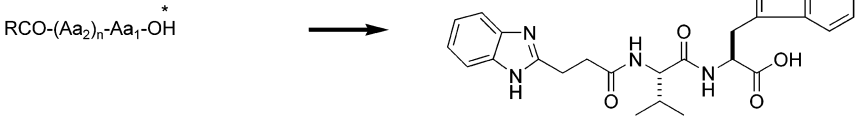
Enzyme: Gelatinase B
Activity: IC_{50} = 13 μM

Library: 1.6
Name: Triazole pyrrolidine
Size: *ca.* 20 members
Affiliation: Hoffmann-La Roche [206]



Enzyme: Endothelin converting enzyme (ECE)
Activity: IC_{50} = 150 nM

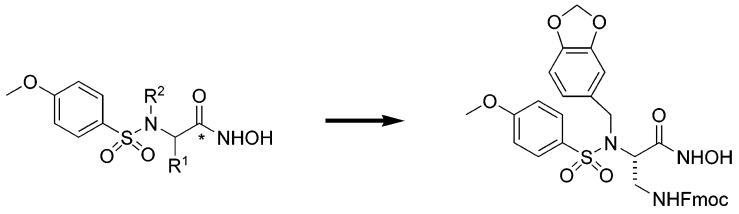
Library: 1.7
Name: Dipeptide
Size: *ca.* 40 members
Affiliation: Bala, M.; *et al.* [19]



Enzyme: Angiotensin converting enzyme (ACE)
Activity: IC_{50} = 6.2 μM

Table 1. (Continued)

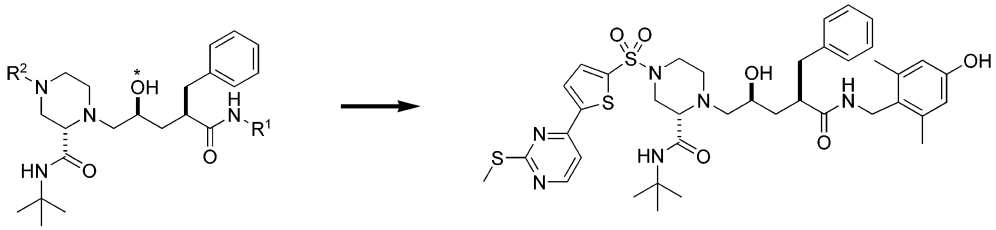
Library: 1.8
Name: Sulfonamide hydroxymate
Size: ~250 members
Affiliation: Roche Bioscience [104]
Note: Multiple libraries prepared optimizing R^1 and R^2.



Enzyme: Procollagen C-protinease
Activity: K_i = 0.024 nM

Aspartyl proteases

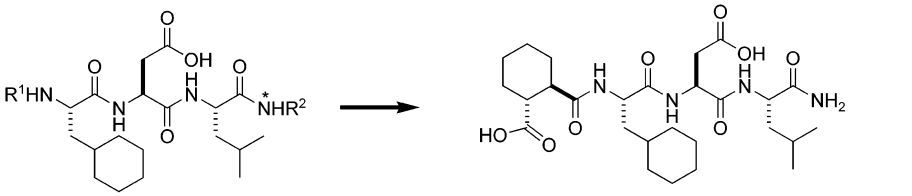
Library: 1.9
Name: Indinavir analog
Size 902 members
Affiliation: Merck [306]



Enzyme: HIV protease
Activity: IC_{50} = < 0.2 nM

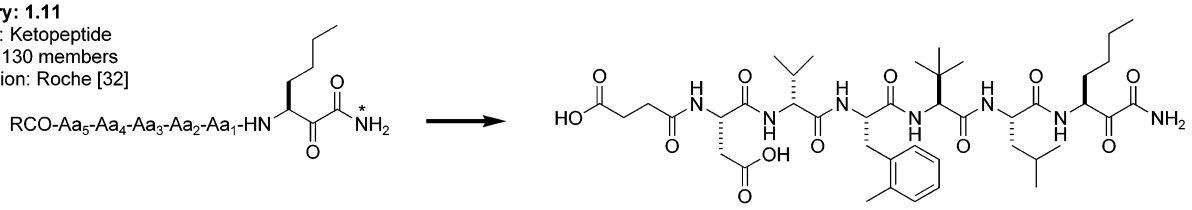
Serine proteases

Library: 1.10
Name: Tripeptide
Size: 26 members
Affiliation: Ingallinella, P.; *et al.* [179]



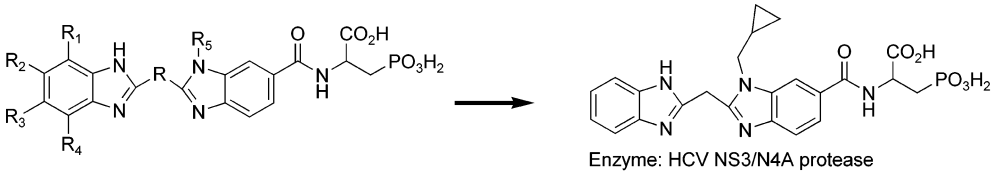
Enzyme: Hepatitis C virus (HCV) NS3/4A protease
Activity: IC_{50} = 15 μM

Library: 1.11
Name: Ketopeptide
Size: 130 members
Affiliation: Roche [32]



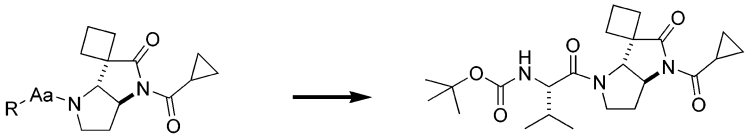
Enzyme: HCV NS3/4A protease
Activity: IC_{50} = 20 nM

Library: 1.12
Name: Bis-benzimidazole
Size: *ca.* 30 members
Affiliation: Celera [335]



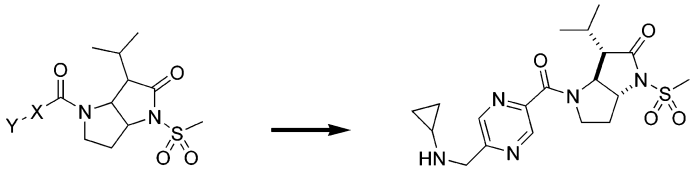
Enzyme: HCV NS3/N4A protease
Activity: K_i = 140 nM

Library: 1.13
Name: Pyrrolidine-5,5-*trans*-lactam
Size: Not defined
Affiliation: GSK [10]
Note: Sequential optimization of Aa then R substitutents.



Enzyme: HCV NS3/4A protease
Activity: k_{obs}/I = 400 $M^{-1}s^{-1}$

Library: 1.14
Name: Pyrrolidine *trans*-lactam
Size: >100 members
Affiliation: GSK [246]

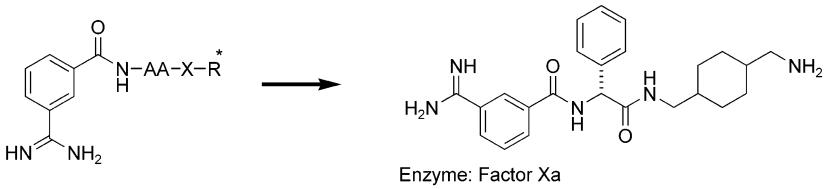


X = aryl, heteroaryl
Y = amine

Enzyme: Human neutrophil elastase (HLE)
Activity: $k_{obs}/[I]$ = 28,735 $M^{-1}s^{-1}$

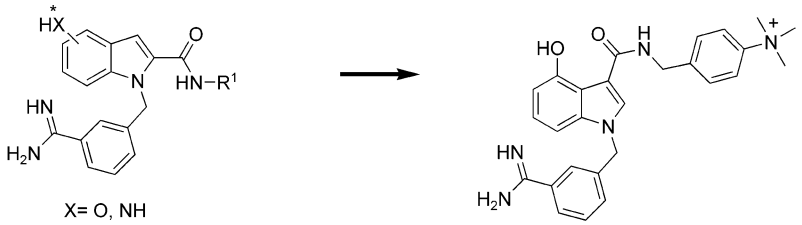
Table 1. (Continued)

Library: 1.15
Name: Amino acid amide
Size: >100 members
Affiliation: Protherics [231]
Note: *In silico* virtual library screening identified seed template which was elaborated using three iterations of library design.



Enzyme: Factor Xa
Activity: K_i = 16 nM

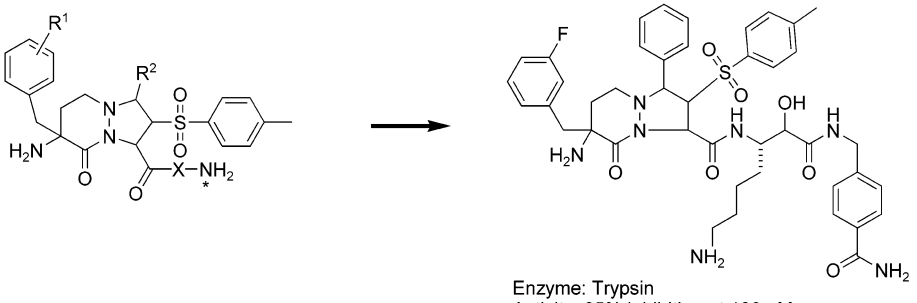
Library: 1.16
Name: Indole carboxamide
Size: *ca.* 50 members
Affiliation: Aventis [254]
Note: Part of a 138 compound library.



X= O, NH

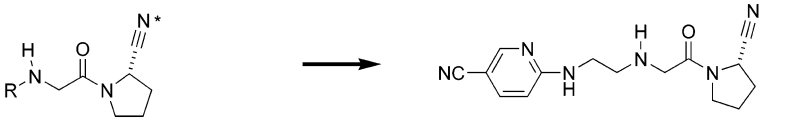
Enzyme: Factor Xa (human)
Activity: K_i = 9 nM

Library: 1.17
Name: β-strand mimetics
Size: 48 members
Affiliation: Fuchi, N.; *et al.* [131]
Note: Constructed via 1,3-dipolar cycloaddition using resin-bound vinylsulfones.



Enzyme: Trypsin
Activity: 65% inhibition at 100 nM

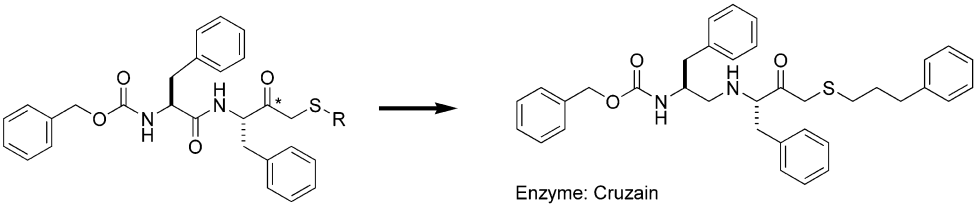
Library: 1.18
Name: Pyrrolidine carbonitrile
Size: *ca.* 200 members
Affiliation: Novartis [367]
Note: Corresponding primary amides (via Rink resin) were dehydrated to nitriles using trifluoroacetic acid anhydride.



Enzyme: Dipeptidyl peptidase IV (human)
Activity: IC_{50} = 22 nM

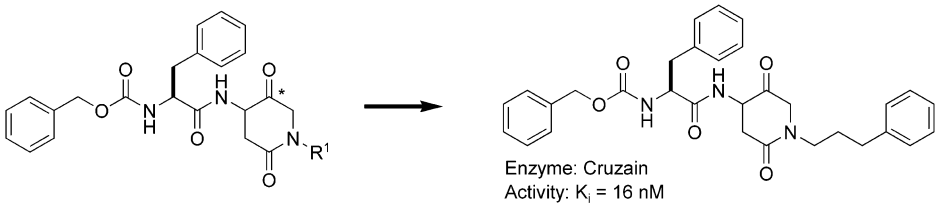
Cysteine proteases

Library: 1.19
Name: Mercaptomethyl ketone
Size: 20 members
Affiliation: Huang, L.; *et al.* [172]



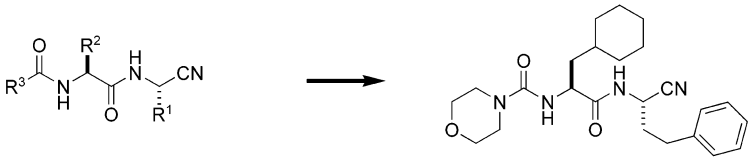
Enzyme: Cruzain
Activity: K_i = 2.0 nM

Library: 1.20
Name: Cyclic ketone
Size: *ca.* 7 members
Affiliation: Huang, L.; *et al.* [171]



Enzyme: Cruzain
Activity: K_i = 16 nM

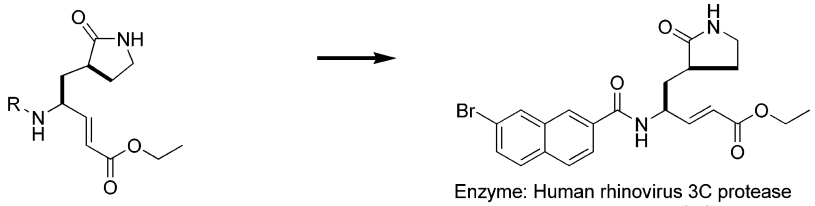
Library: 1.21
Name: Dipeptide nitrile
Size: Not defined
Affiliation: Boehringer Ingelheim [374]
Note: Multiple solution- and solid-phase libraries prepared to optimize R^1-R^3.



Enzyme: Cathepsin S
Activity: IC_{50} = 5 nM

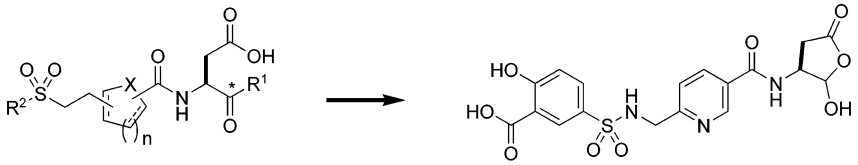
Table 1. (Continued)

Library: 1.22
Name: Pentenoic acid ester
Size: Not defined.
Affiliation: Pfizer [188]



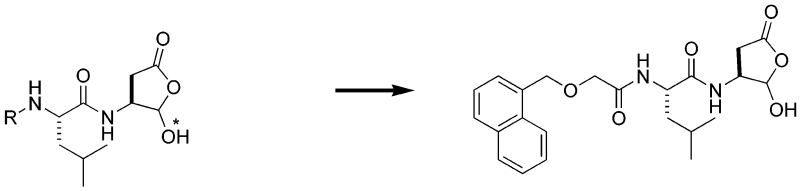
Enzyme: Human rhinovirus 3C protease
Activity: $k_{obs}/[I]$ = 31,400 $M^{-1}s^{-1}$

Library: 1.23
Name: Aspartic acid derivative
Size: Not defined
Affiliation: Sunesis Pharm. [88]
Note: Multiple libraries prepared optimizing R^1, heterocycle and R^2SO_2-.



Enzyme: Caspase 3
Activity: K_i = 50 nM

Library: 1.24
Name: Aspartic acid aldehyde
Size: *ca.* 45 members
Affiliation: Idun Pharm. [236, 237]

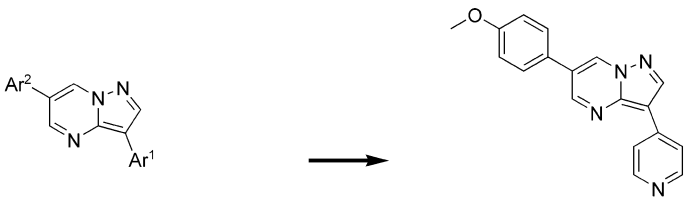


Enzyme: Caspase-1
Activity: IC_{50} = 140 nM

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

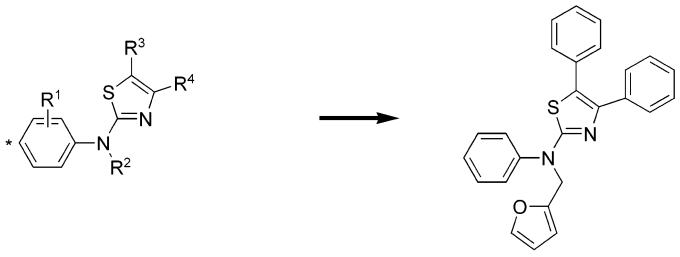
Kinases

Library: 2.1
Name: Diarylpyrazolo-[1,5-*a*]pyrimidine
Size: Not defined
Affiliation: Merck [130]



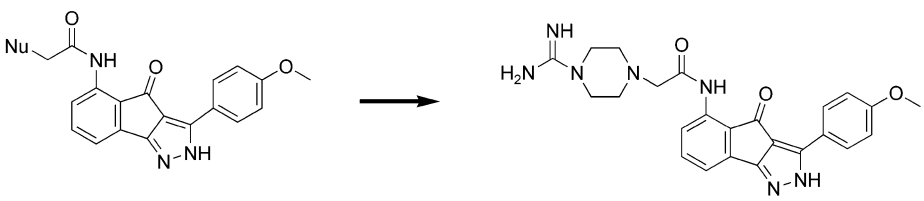
Enzyme: KDR kinase
Activity: IC_{50} = 37 nM

Library: 2.2
Name: 2-Aminothiazole
Size: 23 members
Affiliation: Stieber, F.; *et al.* [338]
Note: Traceless synthesis via oxidative cleavage of hydrazide linker.



Enzyme: Receptor tyrosine kinases
Activity: IC_{50} = 7.4 μM, KDR kinase;
IC_{50} = 9.8 μM,Tie-2 (dual activity).

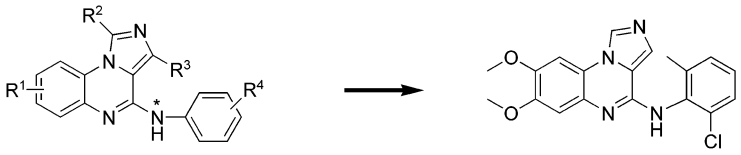
Library: 2.3
Name: Indenopyrazole
Size: Not defined
Affiliation: BMS [279]



Enzyme: CDK4
Activity: IC_{50} = 260 nM, CDK4;
IC_{50}= 7 nM, CDK2

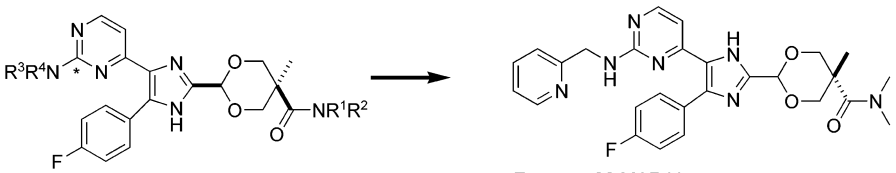
Table 2. (Continued)

Library: 2.4
Name: Imidazoquinoxaline
Size: *ca.* 175 members
Affiliation: BMS [74]
Note: Library prepared using solution- and solid-phase synthesis.



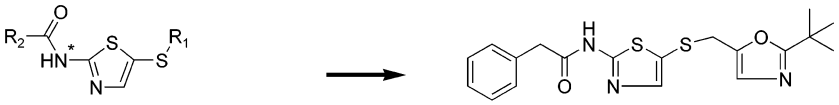
Enzyme: p56Lck
Activity: IC_{50} = 2 nM

Library: 2.5
Name: Pyrimidinylimidazole
Size: 570 members
Affiliation: Aventis [255]
Note: Substrates linked to resin via Wang thiol linkage; S-oxidation then traceless cleavage with R^3R^4NH.



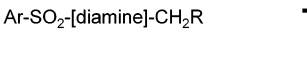
Enyme: p38 MAP kinase
Activity: IC_{50} = 4 nM

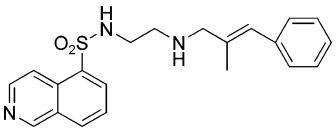
Library: 2.6
Name: Thiazole
Size: Not defined
Affiliation: BMS [203]
Note: Multiple solution- and solid-phase libraries.



Enzyme: Cyclin-dependent kinase 2
Activity: IC_{50} = 3 nM

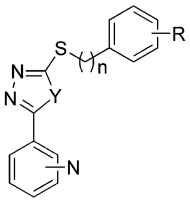
Library: 2.7
Name: Arylsulfonamide
Size: *ca.* 500 members
Affiliation: Reuveni, H.; *et al.* [312]
Note: Multiple libraries optimizing $ArSO_2$-, diamine, and $-CH_2R$.

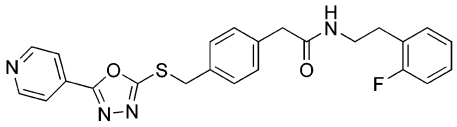




Enzyme: Protein kinase B/Akt
Activity: IC_{50} = 2 μM

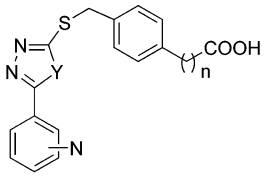
Library: 2.8
Name: Heterobiaryl
Size: 324 members
Affiliation: Novo Nordisk [267]
Note: Two solution phase libraries.

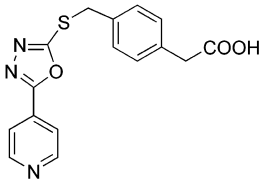




Enzyme: Glycogen synthase kinase-3 kinase-3 (GSK-3)
Activity: IC_{50} = 1.2 μM

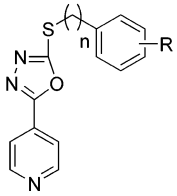
Library: 2.9
Name: Heterobiaryl
Size: >100 members
Affiliation: Novo Nordisk [267]
Note: Solution-phase follow-up library to library 2.8.

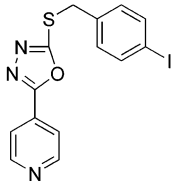




Enzyme: GSK-3
Activity: IC_{50} = 8.0 μM

Library: 2.10
Name: Heterobiaryl
Size: 96 members
Affiliation: Novo Nordisk [267]
Note: Solution-phase follow-up library to library 2.9.

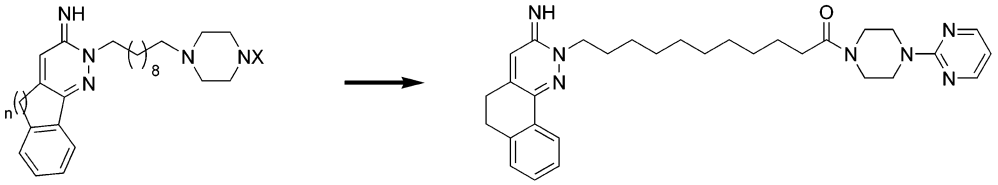




Enzyme: GSK-3
Activity: IC_{50} = 0.4 μM

Table 2. (Continued)

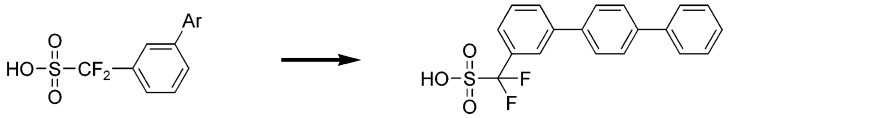
Library: 2.11
Name: 3-Aminopyridazine
Size: Not defined.
Affiliation: Mirzoeva, S.; *et al.* [259]
Note: Solution-phase parallel synthesis.



Enzyme: Calmodulin-dependent kinase II
Activity: IC_{50} = 9 μM

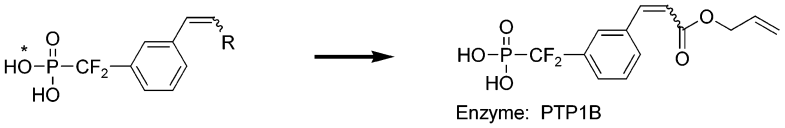
Phosphatases

Library: 2.12
Name: Difluoromethylene sulfonate
Size: 24 members
Affiliation: Leung, C.; *et al.* [226]



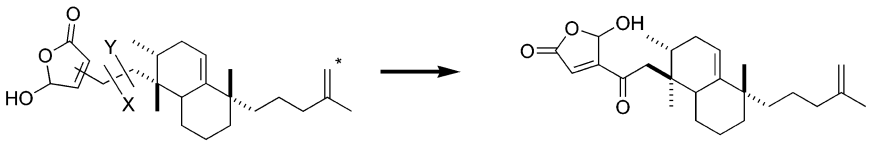
Enzyme: Protein tyrosine phosphatase-1B (PTP1B)
Activity: IC_{50} = 25 μM

Library: 2.13
Name: Difluoromethylene phosphonate
Size: 20 members
Affiliation: Hum, G.; *et al.* [175]



Enzyme: PTP1B
Activity: K_i = 8 μM

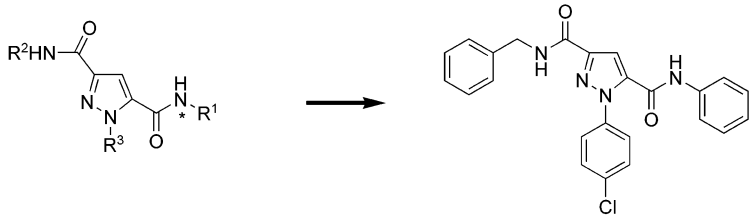
Library: 2.14
Name: Dysidiolide analog
Size: 12 members
Affiliation: Brohm, D.; *et al.* [52, 53]
Note: Resin cleavage via olefin metathesis.



Enzyme: cdc25c phosphatase
Activity: IC_{50} = 0.8 μM

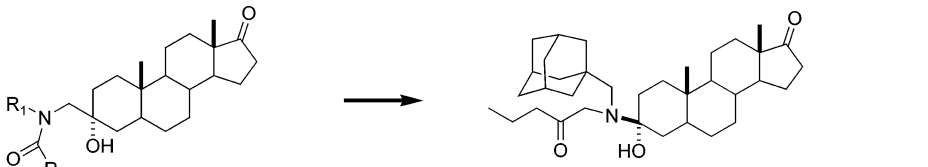
Dehydrogenases

Library: 2.15
Name: Pyrazole
Size: *ca.* 280 members
Affiliation: BMS [158]
Note: Three focused libraries prepared.



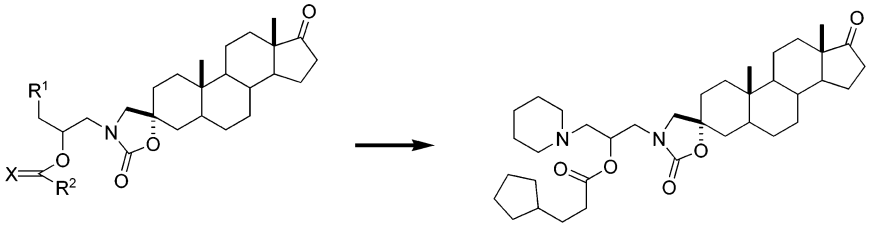
Enzyme: Dihydroorotate dehydrogenase (*H. pylori*)
Activity: K_i = 4 nM; >10,000x selective versus human enzyme.

Library: 2.16
Name: Substituted androsterone
Size: 273 members
Affiliation: Maltais, R.; *et al.* [251]
Note: One lead finding library (168 members) and 2 follow-up libraries (56 and 49 members respectively).



Enzyme: Type 3 17β-hydroxysteroid dehydrogenase
Activity: IC_{50} = 35 nM

Library: 2.17
Name: Substituted androsterone
Size: 25 members
Affiliation: Maltais, R.; *et al.* [251]
Note: Follow-up to library 2.16.

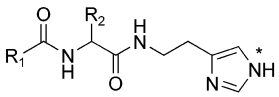


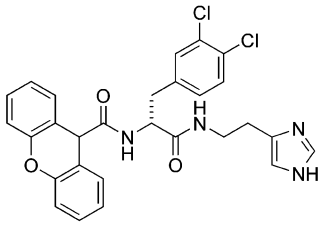
Enzyme: Type 3 17β-hydroxysteroid dehydrogenase
Activity: IC_{50} = 74 nM

Table 2. (Continued)

Transferases

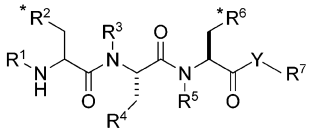
Library: 2.18
Name: Histamine peptide
Size: *ca.* 1200 members
Affiliation: Banyu [346]
Note: Initial lead was a dithiothreitol derivative. Sequential series of optimization libraries to arrive at potent inhibitor.

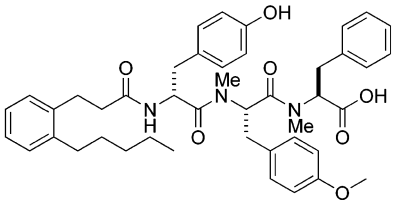




Enzyme: Geranylgeranyl transferase(GGTase; *C. albicans*)
Activity: IC_{50} = 10 nM

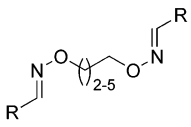
Library: 2.19
Name: Pepticinnamin E analog
Size: 50 members
Affiliation: Thutewohl, M.; *et al.* [356]
Note: Resin attachment through tyrosine phenolic OH at R^2 or R^6.

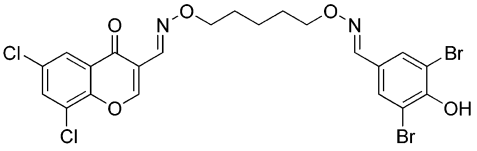




Enzyme: Protein farnesyltransferase
Activity: IC_{50} = 6.4 μM

Library: 2.20
Name: Oxime dimer
Size: 2565 members
Affiliation: Kehoe, J. W.; *et al.* [197]
Note: 171-well library with each well containing 2x RCHO and 5x O,O'-diaminoalkanediol linkers giving statistical mixture of 15 compounds per well.

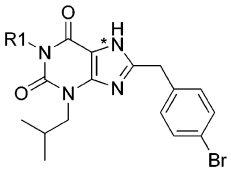


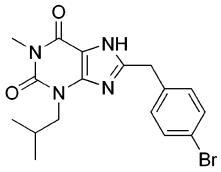


Enzyme: Tyrosylprotein sulfotransferase-2
Activity: IC_{50} = 30 μM

Miscellaneous

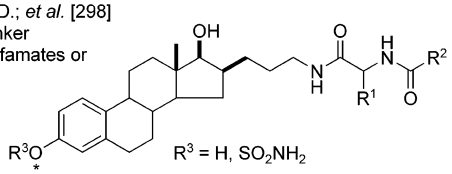
Library: 2.21
Name: Xanthine derivative
Size: *ca.* 18 members
Affiliation: Novartis [31]

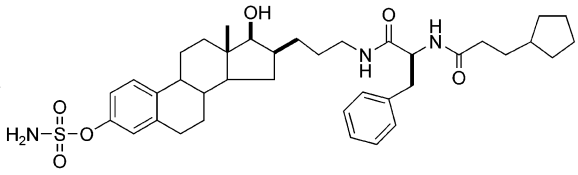




Enzyme: Phosphodiesterase 5 (PDE5)
Activity: 90% inhibition at 1 μM

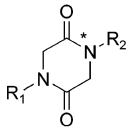
Library: 2.22
Name: Estradiol derivative
Size: 156 members
Affiliation: Poirier, D.; *et al.* [298]
Note: Sulfamate linker cleaved to give sulfamates or phenols.

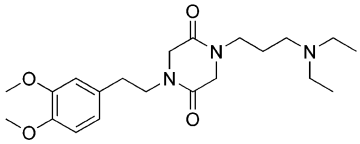




Enzyme: Steroid sulfatase
Activity: 98% inhibition at 1 μM

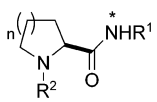
Library: 2.23
Name: 2.5 Diketopiperazinedione
Size: 104 members
Affiliation: Carbonell, T.; *et al.* [62]
Note: Synthesis of initial screening library then a follow-up library.

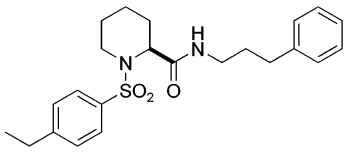




Enzyme: Acetylcholinesterase
Activity: IC_{50} = 2.2 μM;
selective versus butyrylcholinesterase

Library: 2.24
Name: Prolyl/pipecolyl amide
Size: 50 members
Affiliation: Guilford Pharm. [376]

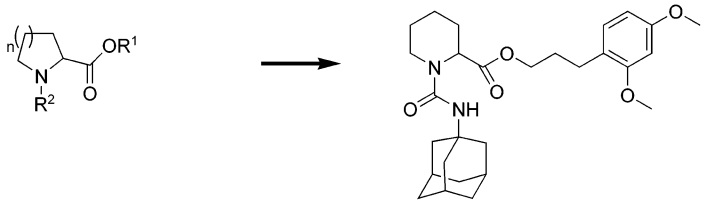




Enzyme: FKBP12
Activity: K_i = 640 nM

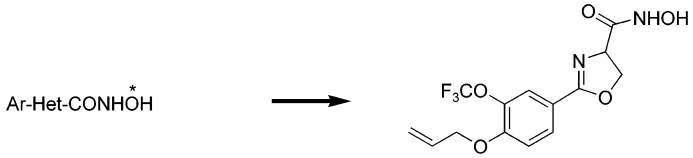
Table 2. (Continued)

Library: 2.25
Name: Prolyl/pipecolic esters
Size: Not defined
Affiliation: Guilford Pharm. [85]



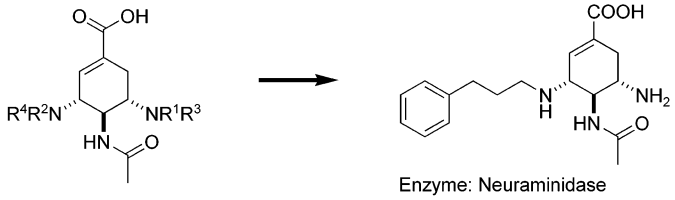
Enzyme: FKBP12
Activity: K_i = 12 nM

Library: 2.26
Name: Hydroxamic acid
Size: *ca.* 64 members
Affiliation: Chiron Corp. [209]
Note: Several libraries generated where Het = oxazoline, thiazoline and oxazine.



Enzyme: LpxC (*P. aeruginosa*)
Activity: IC_{50} = 120 nM

Library: 2.27
Name: Substituted cyclohexenoic acid
Size: Large
Affiliation: Therascope AG [164]
Note: Dynamic combinatorial library of diamines and aldehydes.

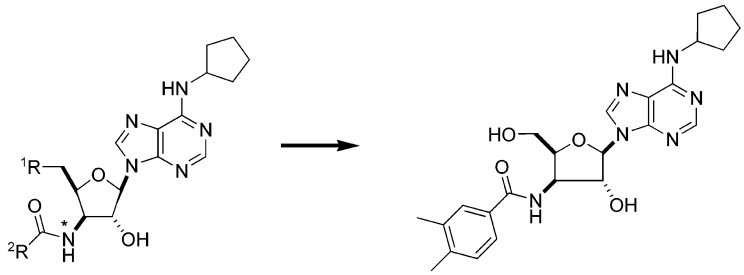


Enzyme: Neuraminidase
Activity: K_i = 1.6 μM

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

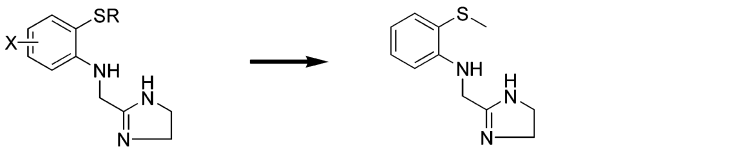
In aphabetical order:

Library: 3.1
Name: Cyclopentyladenine
Size: *ca.* 20 members
Affiliation: Van Calenbergh, S.; *et al.* [364]



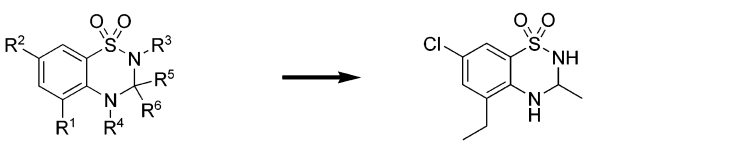
Receptor: Adenosine A_1 (human)
Activity: K_i = 137 nM

Library: 3.2
Name: (Anilinomethyl)imidozolines
Size: Not defined
Affiliation: GSK [166]
Note: Optimization of non-selective lead obtained from library gave α_{1a} subtype selective agonists.



Receptor: α_{1a} Adrenergic
Activity: pK_i = 7.36 (non selective agonist)

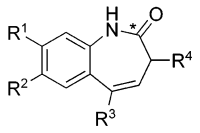
Library: 3.3
Name: Benzothiadiazide
Size: *ca.* 64 members
Affiliation: Phillips, D.; *et al.* [295]

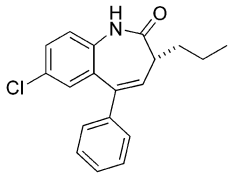


Receptor: AMPA (glutamate subgroup)
Activity: EC_{50} = 22 μM

Table 3. (Continued)

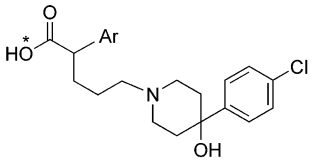
Library: 3.4
Name: 1,4-Benzodiazepine
Size: 168 members
Affiliation: Lattmann, E.; *et al.* [222]
Note: Constructed on syn-phase crowns.

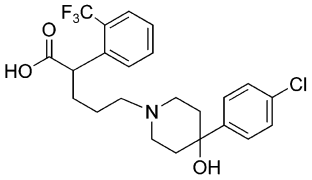




Receptor: Cholecystokinin-B (CCK-B)
Activity: IC_{50} = 180 nM

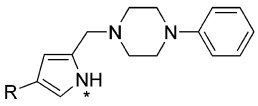
Library: 3.5
Name: Hydroxypiperidine
Size: > 100 members
Affiliation: Berlex Bioscience [55]

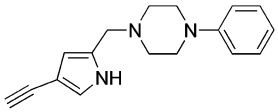




Receptor: CCR1
Activity: K_i = 214 nM; K_i = 74 nM of Me ester

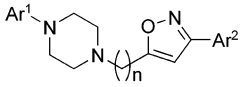
Library: 3.6
Name: 2,4-Disubstituted pyrrole
Size: 3 members
Affiliation: Bergauer, M.; *et al.* [36]

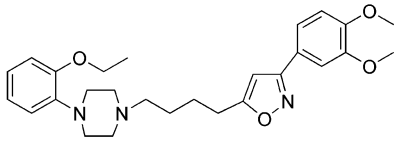




Receptor: Dopamine D4 (human)
Activity: K_i = 6 nM (agonist)

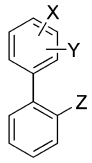
Library: 3.7
Name: Phenylpiperazinylalkylisoxazole
Size: 300 members
Affiliation: Cha, M. Y.; *et al.* [66]

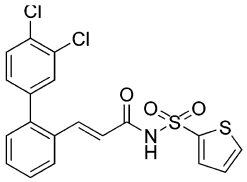




Receptor: Dopamine D-3
Activity: K_i = 2.6 nM, D-3;
>10x selective versus D-2, D-4

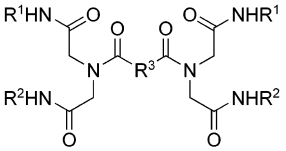
Library: 3.8
Name: Biaryl acylsulfonamide
Size: >25 members
Affiliation: Merck Frosst [133]

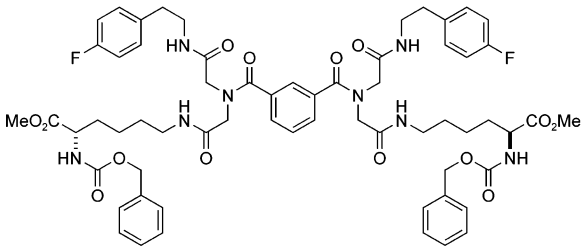




Receptor: EP_3 prostanoid receptor
Activity: K_i = 25 nM (antagonist);
K_i = > 1000 nM, EP_1 and EP_2

Library: 3.9
Name: Iminodiacetamide
Size: *ca.* 600 members
Affiliation: Goldberg, J.; *et al.* [139]
Note: Solution phase synthesis.

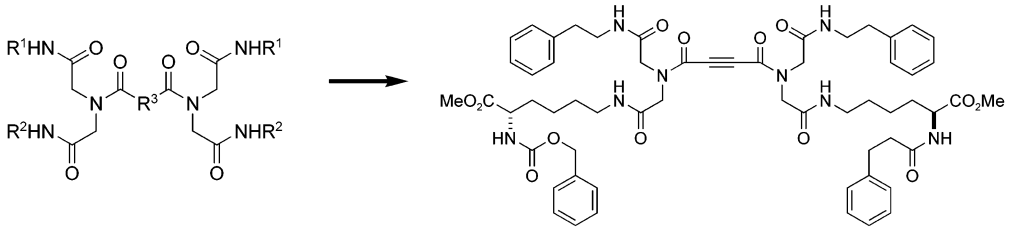




Receptor: Erythropoietin (EPOr)
Activity: 32% inhibition at 50 μM to displace ^{125} I-EPO from immobilized EPOr

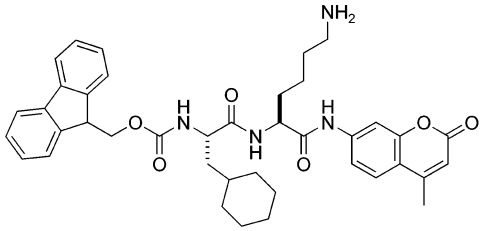
Table 3. (Continued)

Library: 3.10
Name: Iminodiacetamide
Size: Not defined
Affiliation: Goldberg, J.; *et al.* [139]
Note: Two follow-up libraries from lead identified in Library 3.9.



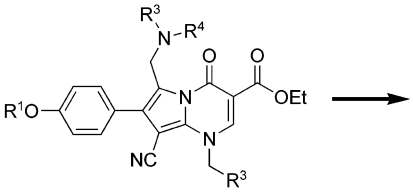
Receptor: Erythropoietin (EPOr)
Activity: Maximal mitogenic response (MMR) = 155% at 10 μM (weak partial agonist); MMR of EPO = 812% at 0.01 μM

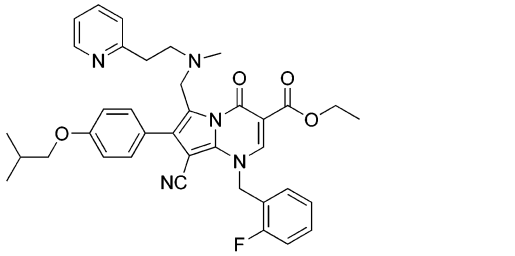
Library: 3.11
Name: Dipeptide
Size: *ca.* 256 members
Affiliation: Saar, K.; *et al.* [323]



Receptor: Galanin
Activity: K_i = 3 μM (agonist)

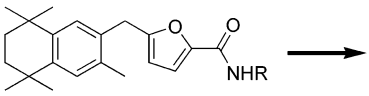
Library: 3.12
Name: Pyrrolpyrimidone
Size: 400 members
Affiliation: Neurocrine Biosci. [413]
Note: Solution-phase parallel synthesis.

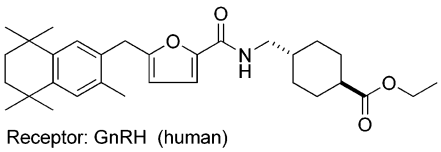




Receptor: Gonadotropin-releasing hormone (GnRH; human)
Activity: K_i = 100 nM (antagonist)

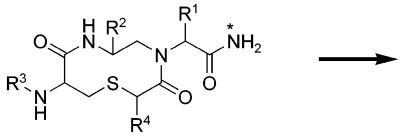
Library: 3.13
Name: Pentamethyltetra-hydronaphthalene
Size: *ca.* 33 members
Affiliation: Pfizer [243]

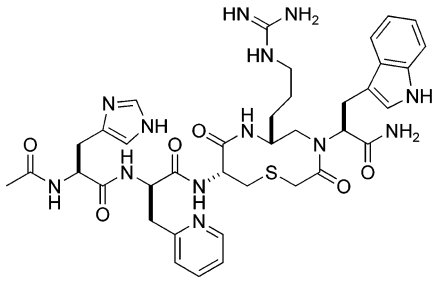




Receptor: GnRH (human)
Activity: K_i = 13 nM (antagonist)

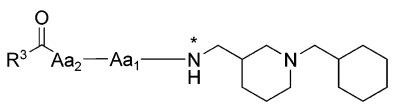
Library: 3.14
Name: Peptidomimetic
Size: 16 members
Affiliation: Bondebjerg, J.; *et al.* [45]

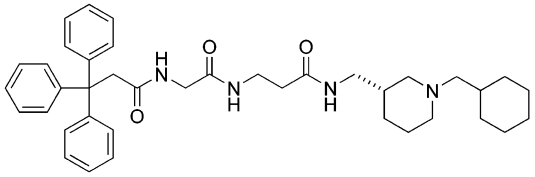




Receptor: Melanocortin-1 (MMCIR; mouse)
Activity: EC_{50} = 165 nM, MMC1R;
EC_{50} = 7600 nM, MMC3R;
EC_{50} = 335 nM, MMC4R

Library: 3.15
Name: 1-Cyclohexylmethyl-3-aminomethylpiperidine
Size: 1000 members
Affiliation: Banyu [324]

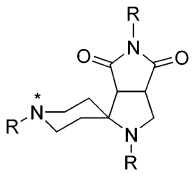


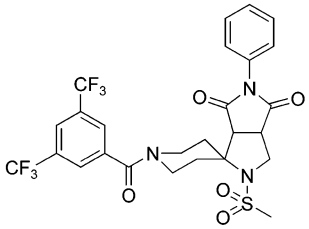


Receptor: Muscarinic M_3 (human)
Activity: K_i = 0.31 nM (antagonist); M_1/M_3 >200; M_2/M_3 = 100

Table 3. (Continued)

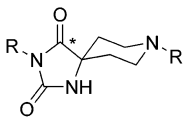
Library: 3.16
Name: Spiropyrrolopyrrole
Size: Not defined
Affiliation: Hoffmann-La Roche [41]
Note: Multiple solution and solid-phase libraries.

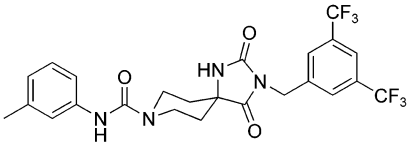




Receptor: Neurokinin-1 (human)
Activity: $pK_i = 8.29$ (antagonist)

Library: 3.17
Name: Spirohydantoin
Size: Not defined
Affiliation: Hoffmann-La Roche [42]
Note: All library members incorporated 3,5-bis(trifluoromethyl)phenyl, a known NK-1 receptor pharmacophore.

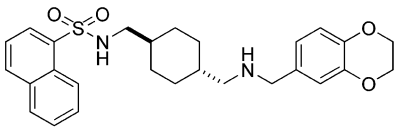




Receptor: Neurokinin-1 (NK-1, human)
Activity: $pK_i = 7.34$

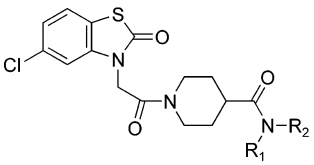
Library: 3.18
Name: Sulfonamide diamine
Size: *ca.* 240 members
Affiliation: Synaptic Pharm. [129, 180]

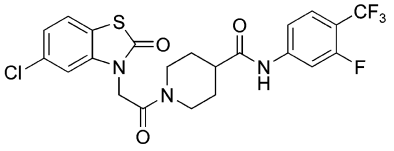
$ArSO_2HN\text{-}X\text{-}NH\text{-}Y\text{-}R$
X = cyclic, acyclic spacer;
Y = CO, CONH, CH_2



Receptor: Neuropeptide Y5
Activity: $K_i = 12$ nM (antagonist)

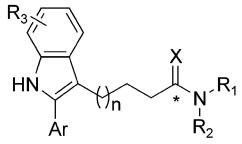
Library: 3.19
Name: Oxobenzothiazolin-3-acetic acid amide
Size: 300 members
Affiliation: Fugisawa [349]

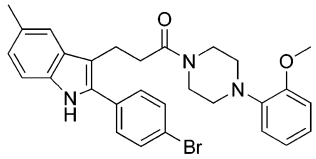




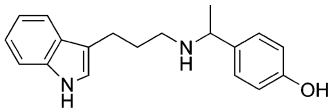
Receptor: Neuropeptide Y5
Activity: $IC_{50} = 0.70$ nM (antagonist)

Library: 3.20
Name: 2-Arylindole
Size: 128,000 members
Affiliation: Merck [380]
Note: Mixture library of 320 pools of 400 compounds each.

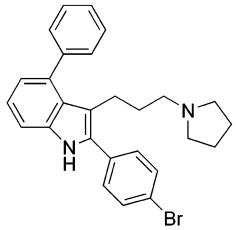




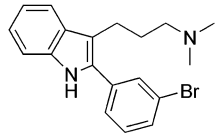
Receptor: Neurokinin-1
Activity: $K_i = 0.8$ nM (antagonist)



Receptor: Neuropepticle Y5
Activity: $K_i = 0.8$ nM



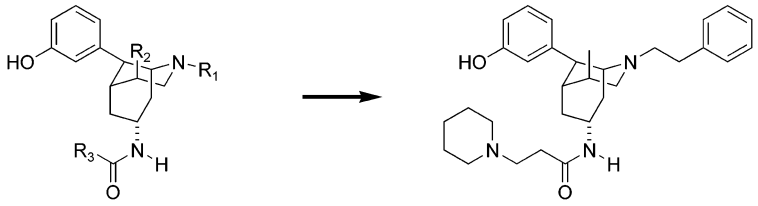
Receptor: $5\text{-}HT_{2a}$
Activity: $K_i = 10$ nM



Receptor: $5\text{-}HT_6$
Activity: $K_i = 0.7$ nM

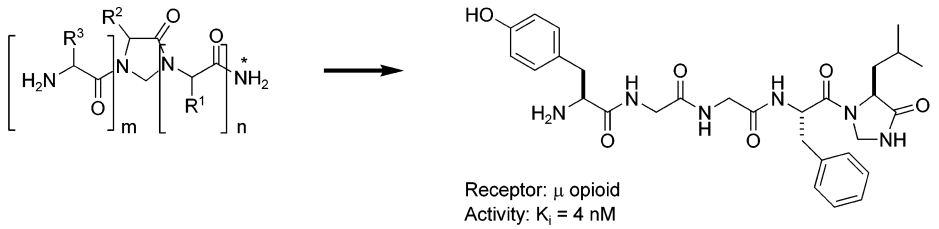
Table 3. (Continued)

Library: 3.21
Name: 5-Phenylmorphan
Size: Not defined
Affiliation: Thomas, J. B.; *et al.* [355]



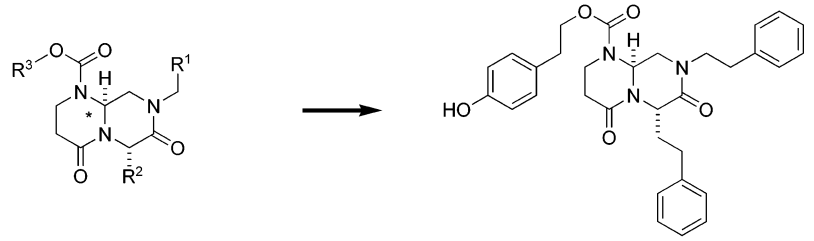
Receptor: κ opioid (human)
Activity: K_i = 4.3 nM (antagonist);
μ/κ = 34; δ/κ = 790.

Library: 3.22
Name: 4-Imidazolidinone
Size: Not defined
Affiliation: Rinnova, M.; *et al.* [318]



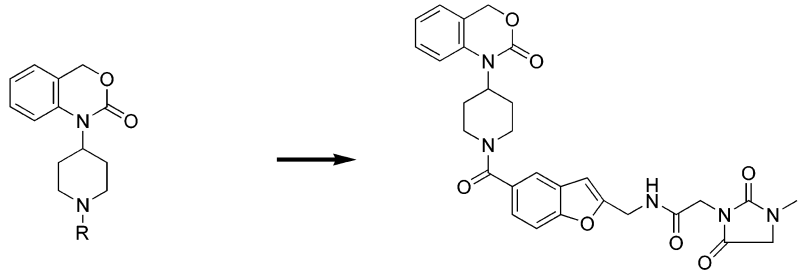
Receptor: μ opioid
Activity: K_i = 4 nM

Library: 3.23
Name: Bicyclic β-turn mimetic
Size: 30 members
Affiliation: Molecumetics [119]



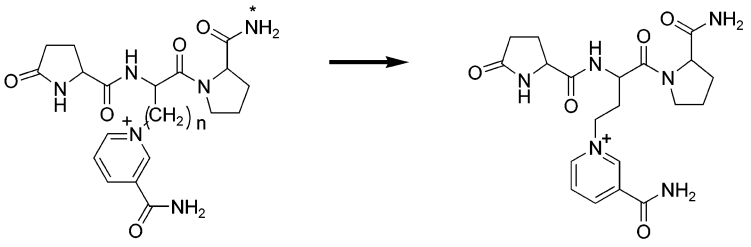
Receptor: μ opioid (human)
Activity: IC_{50} = 9 nM

Library: 3.24
Name: Piperidinyl dihydro-benzoxazinone
Size: > 500 members
Affiliation: GSK [387, 388]
Note: Multiple solution and solid-phase libraries built around core structure.



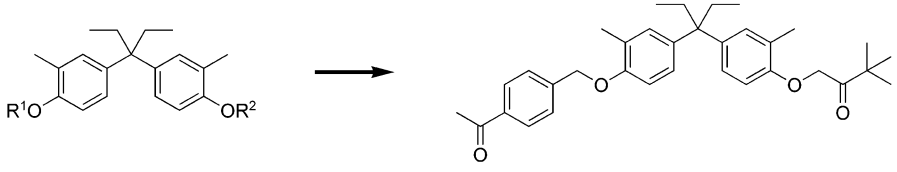
Receptor: Oxytocin (human)
Activity: pK_i = 8.5 (antagonist)

Library: 3.25
Name: Pyridinium amino acid amide
Size: 4 members
Affiliation: Prokai-Tatrai, K.; *et al.* [303]



Receptor: Thyrotropin-releasing hormone
Activity: Analeptic action *in vivo*

Library: 3.26
Name: Bisbenzyl ether
Size: *ca.* 20 members
Affiliation: Swann, S. L.; *et al.* [347]

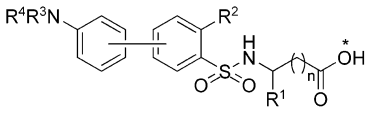


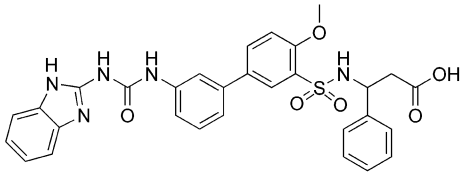
Receptor: Mutant vitamin D (VOR(R27-4L))
Activity: EC_{50} 3.3 nM (agonist)

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

Integrins

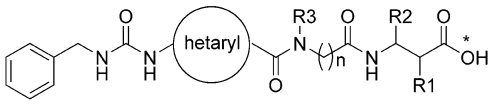
Library: 4.1
Name: Biphenyl
Size: *ca.* 30 members
Affiliation: Bayer AG [362]

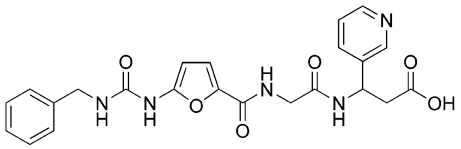




Receptor: Vitronectin $\alpha_v\beta_3$
Activity: K_i = 0.7 nM\ (antagonist)

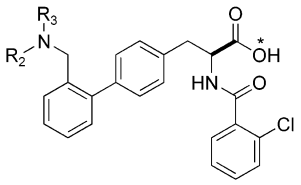
Library: 4.2
Name: Peptidomimetic
Size: 240 members
Affiliation: Abbott [221]

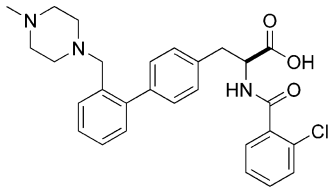




Target: $\alpha_v\beta_3$
Activity: IC_{50} = 0.1 nM (antagonist)

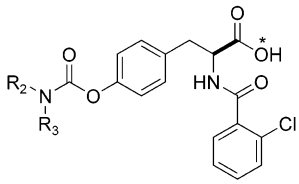
Library: 4.3
Name: Biphenylalanine
Size: >100 members
Affiliation: Genentech [64]

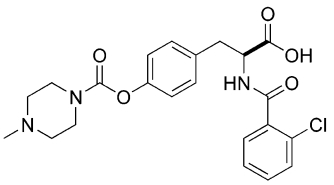




Target: $\alpha_4\beta_1$/VCAM and $\alpha_4\beta_7$/MAdCAM
Activity: IC_{50} = 10 nM, $\alpha_4\beta_1$;
IC_{50} = 2.5 nM, $\alpha_4\beta_7$ (antagonist)

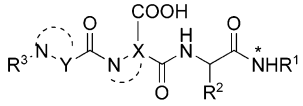
Library: 4.4
Name: Tyrosine carbamate
Size: 80 members
Affiliation: Genentech [64]

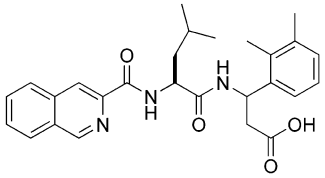




Target: $\alpha_4\beta_1$/VCAM and $\alpha_4\beta_7$/MAdCAM
Activity: IC_{50} = 12 nM, $\alpha_4\beta_1$;
IC_{50} = 1.1 nM, $\alpha_4\beta_7$ (antagonist)

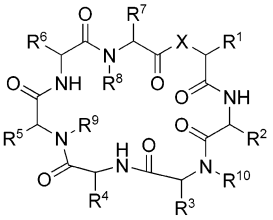
Library: 4.5
Name: Peptidomimetic
Size: Not defined
Affiliation: Gottschling, D.; *et al.* [143]

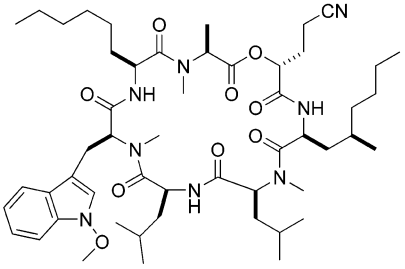




Target: Cell adhesion ($\alpha4\beta7$/VCAM-1)
Activity: Inhibition observed at 12%
of medium control.

Library: 4.6
Name: HUN-7293 analog
Size: *ca.* 40 members
Affiliation: Chen, Y.; *et al.* [75]

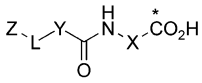


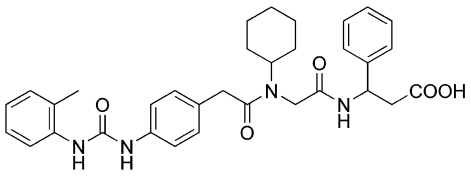


Target: VCAM-1
Activity: IC_{50} = 1.6 nM (antagonist);
18x selectivity versus ICAM-1

Table 4. (Continued)

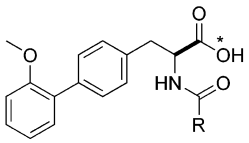
Library: 4.7
Name: Peptidomimetic
Size: *ca.* 4000 members
Affiliation: Merck [106]
Note: Combination of solution and solid-phase synthesis.

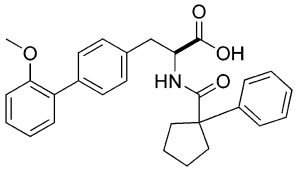




Receptor: VLA-4
Activity: IC_{50} = 3.2 nM (VCAM/VLA4 antagonist)

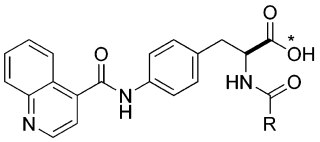
Library: 4.8
Name: *N*-(Arylacetyl)biphenylalanine
Size: 42 members
Affiliation: Merck [228]

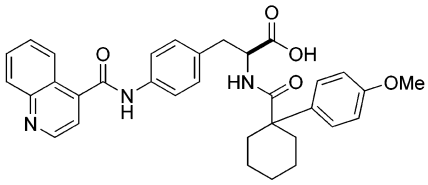




Target: VLA-4 ($\alpha_4\beta_1$)
Activity: IC_{50} = 9 nM (antagonist)

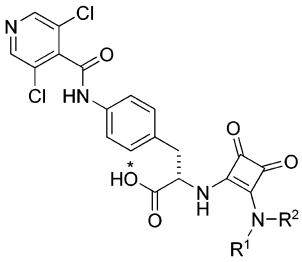
Library: 4.9
Name: *N*-Acylphenylalanine
Size: 42 members
Affiliation: Roche [73]

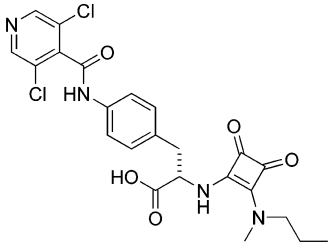




Target: VLA-4 ($\alpha_4\beta_1$)
Activity: IC_{50} = 1.2 nM (antagonist)

Library: 4.10
Name: Squaric acid derivative
Size: >50 members
Affiliation: Celltech [229]

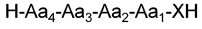




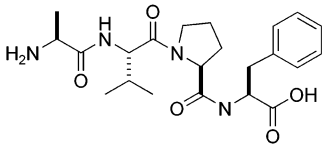
Target: VLA-4
Activity: IC_{50} = 200 nM (antagonist)

Miscellaneous

Library: 4.11
Name: Tetrapeptide
Size: *ca.* 50 members
Affiliation: Kipp, R. A.; *et al.* [205]
Note: Sequential Aa optimization of AVPI lead.

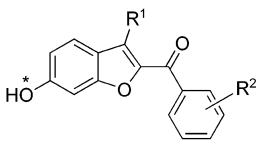


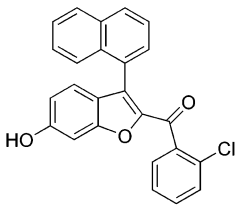
X = O, NH



Target: B1R3 (bacolovirus IAP repeat) domain of XIAP (X-linked inhibitor of apoptosis protein)
Activity: K_D = 40 nM

Library: 4.12
Name: Benzofuran
Size: 320 members
Affiliation: Bayer [332]

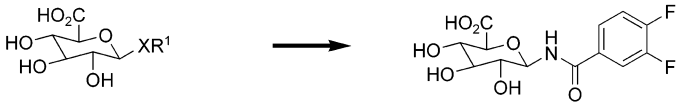




Receptor: Estrogen ER-α
Activity: IC_{50} = 30 nM

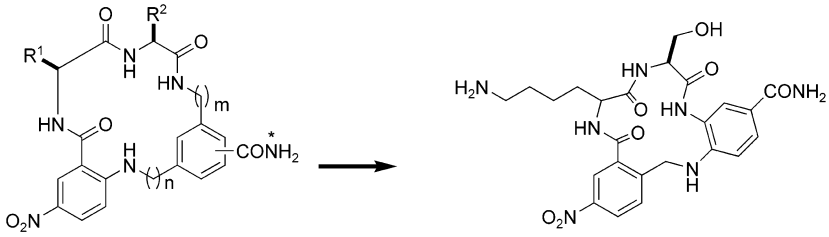
Table 4. (Continued)

Library: 4.13
Name: Glucuronic acid
Size: 16 members
Affiliation: Murphy, P. V.; *et al.* [265]



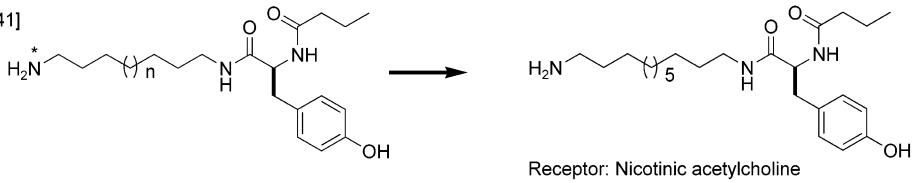
Target: Fibroblast growth factor (FGF-2)
Activity: 39% inhibition of FGF binding to heparin-albumin conjugate at 340 μM.

Library: 4.14
Name: Peptidomimetic
Size: 11 members
Affiliation: Pattarawarapan, M.; *et al.* [290]



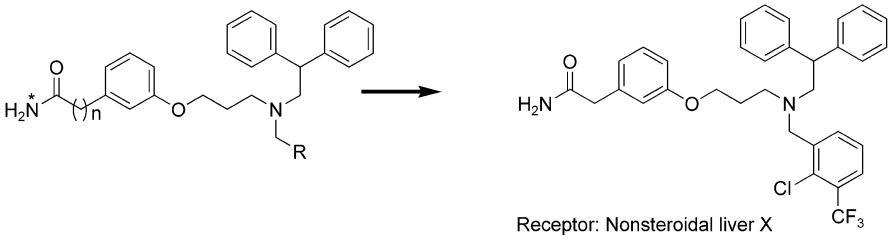
Receptor: Neurotrophin-3
Activity: Partial NT-3-like survival activity in synergy with suboptimal (100 pm) NT-3 concentrations.

Library: 4.15
Name: Philanthotoxin-12 analog
Size: 5 members
Affiliation: Stromgaard, K.; *et al.* [341]



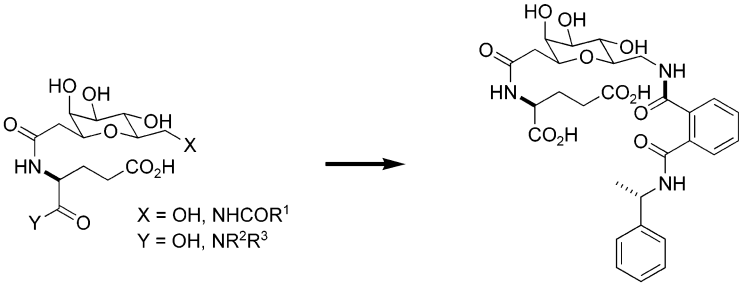
Receptor: Nicotinic acetylcholine
Activity: IC_{50} = 0.46 μM (antagonist)

Library: 4.16
Name: Aminoalkylether
Size: 1500 members
Affiliation: GSK [93]
Note: Two libraries of tertiary amines: 120 and 1280 members.



Receptor: Nonsteroidal liver X
Activity: EC_{50} = 45 nM (agonist)

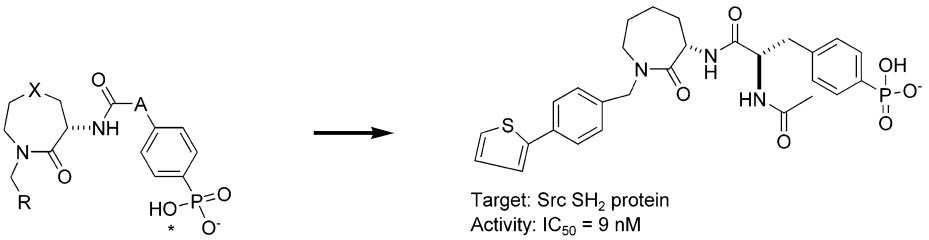
Library: 4.17
Name: Mannoside
Size: *ca.* 107
Affiliation: Wyeth [190]
Note: Three libraries via solution-phase synthesis.



X = OH, $NHCOR^1$
Y = OH, NR^2R^3

Target: P-selectin
Activity: IC_{50} = 2.5 mM

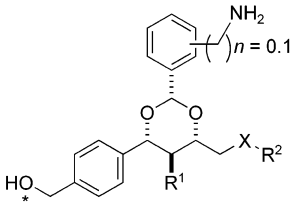
Library: 4.18
Name: Peptidomimetic
Size: Not defined
Affiliation: Aventis [110, 111]
Note: Combination of solution- and solid-phase synthesis.

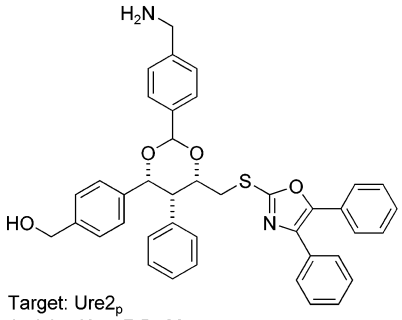


Target: Src SH_2 protein
Activity: IC_{50} = 9 nM

Table 4. (Continued)

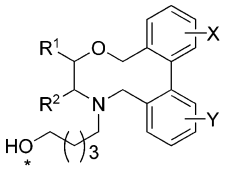
Library: 4.19
Name: 1,3-Dioxane
Size: 3780 members
Affiliation: Kuruvilla, F. G.; *et al.* [217]

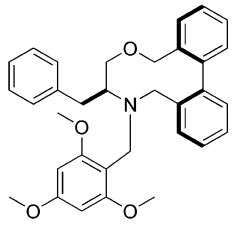




Target: $Ure2_p$
Activity: K_D = 7.5 μM

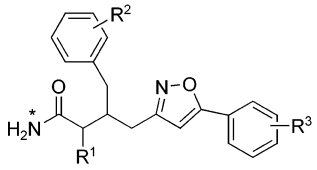
Library: 4.20
Name: Cyclic biaryl
Size: 1412 members
Affiliation: Spring, D. R.; *et al.* [336]
Note: Split pool synthesis.

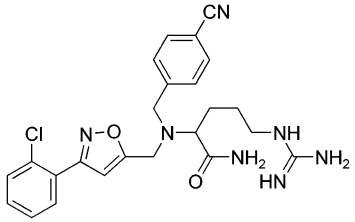




Target: *A. thaliana*
Activity: Phenotype modulation

Library: 4.21
Name: Phenylisoxazole
Size: 141 members
Affiliation: Batra, S.; *et al.* [23]
Note: Three isoxazole-based libraries of 32, 96 and 45 compounds.



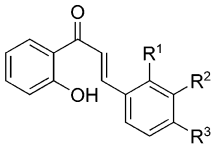


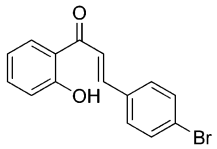
Target: *In vitro* antithrombin
Activity: 90% protection upon thrombolytic challenge at 30 μM.

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

Cytotoxics

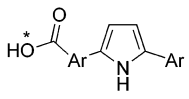
Library: 5.1
Name: 2-Hydroxychalcone
Size: 8 members
Affiliations: Stoyanov, E. V.; *et al.* [339]

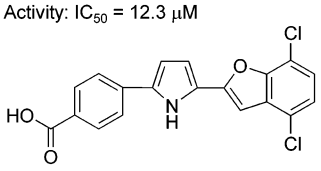




Target: MCF-7 (human breast cancer cell line)
Activity: IC_{50} = 12.3 μM

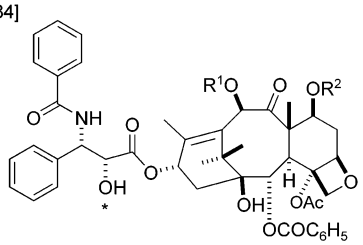
Library: 5.2
Name: Pyrrole
Size: *ca.* 275 members
Affiliation: Eisai Co. [210]
Note: Stetter reaction on solid-phase.

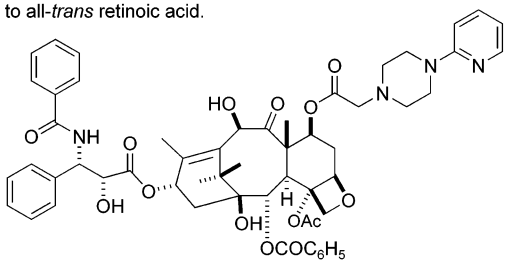




Target: LPS-induced mouse B-cell proliferation inhibition
Activity: Relative IC_{50} comparable to all-*trans* retinoic acid.

Library: 5.3
Name: Paclitaxel analog
Size: ~36 members
Affiliation: Jagtap, P. G.; et al. [184]
Note: Two dozen diacyl ester analogs prepared on solid-phase using silyl ether linkage. Mono-ester analogs prepared via solution-phase synthesis.

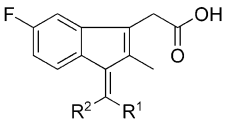


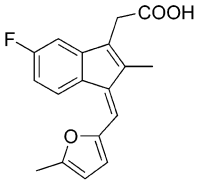


Target: A2780 ovarian cancer cells
Activity: IC_{50} = 0.14 μg/mL
(10x more active than paclitaxel)

Table 5. (Continued)

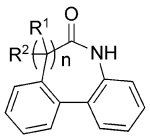
Library: 5.4
Name: Indene derivative
Size: *ca.* 8 members
Affiliation: Karaguni, I. - M.; *et al.* [192]

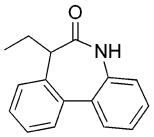




Cell line: NIH3T3
Activity: IC_{50} = 20 μM (anti-proliferative)

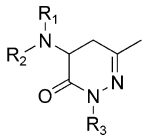
Library: 5.5
Name: Biaryl lactam
Size: 5 members
Affiliation: Baudoin, O.; *et al.* [24]

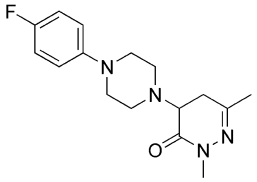




Cell line: KB
Activity: IC_{50} = 32 μM

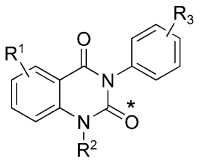
Library: 5.6
Name: Dihydropridazin one
Size: 6 members
Affiliation: Gouault, N.; *et al.* [144]

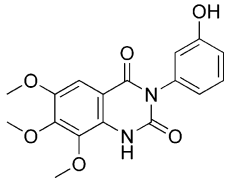




Cell line: L1210 cells
Activity: Cytotoxic concentration
(CC_{50}) = 39 μM

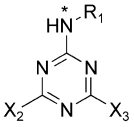
Library: 5.7
Name: 3-Aryl-2,4-quinazolindi-one
Size: *ca.* 42 members
Affiliation: Choo, H.-Y. P.; *et al.* [87]

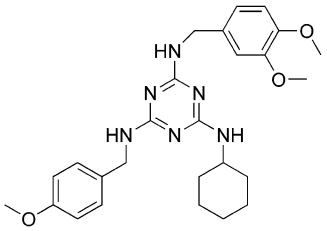




Cell line: Colon carcinoma (Col2)
Activity: Growth inhibition = 16.5 μg/mL

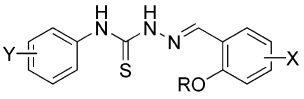
Library: 5.8
Name: Substituted triazene
Size: >100 members
Affiliation: Moon, H.-S.; *et al.* [260]

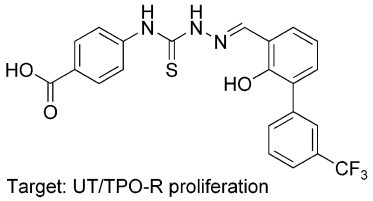




Target: Tubuline polymerization
(bovine brain)
Activity: MIC = 5 μM

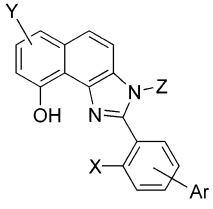
Library: 5.9
Name: Thiosemicarbazone
Size: >36 members
Affiliation: GSK [118]
Note: Solution-phase synthesis.

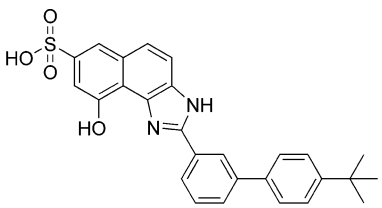




Target: UT/TPO-R proliferation
(thrombopoietin responsive cell line
Activity: EC_{50} = 20 nM

Library: 5.10
Name: Naphtho[1,2-*d*]imidazoles
Size: >300 members
Affiliation: GSK [117]

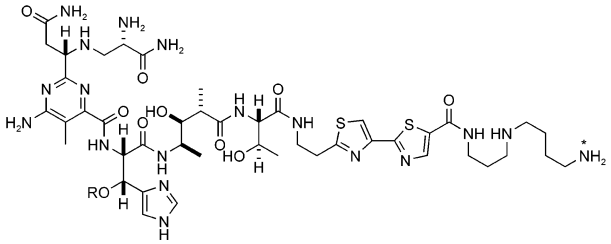


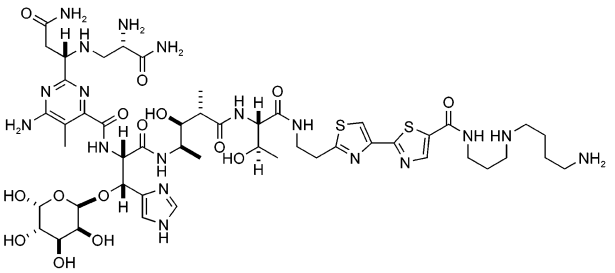


Target: UT7/TPO-R proliferation
(thrombopoietin responsive cell line)
Activity: EC_{50} = 80 nM

Table 5. (Continued)

Library: 5.11
Name: Bleomycin A_5 analog
Size: 3 members
Affiliation: Thomas, C. J.; *et al.* [354]

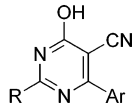


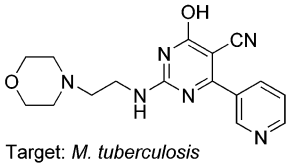


Target: DNA cleavage
Activity: Efficiency equal to bleomycin A_5

Antiinfectives

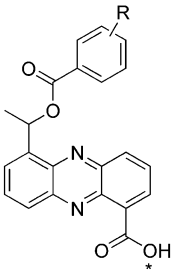
Library: 5.12
Name: Pyrimidine
Size: 80 members
Affiliation: Kumar, A.; *et al.* [215]

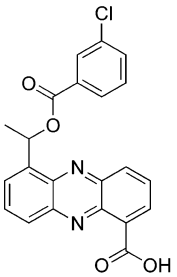




Target: *M. tuberculosis*
Activity: MIC = 25 μg/mL

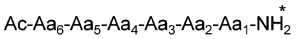
Library: 5.13
Name: Saphenamycin benzoate
Size: 12 members
Affiliation: Laursen, J. B.; *et al.* [224]





Target: *B. subtilis*
Activity: MIC = 0.07 μg/mL

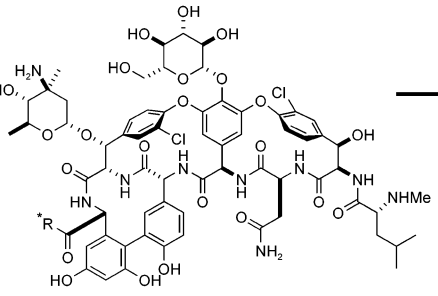
Library: 5.14
Name: Hexapeptide
Size: 19^5 members
Affiliation: Lopez-Garcia, B.; *et al.* [241]
Note: All D-amino acid positional scanning library.

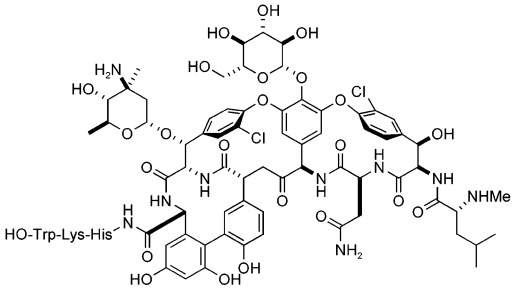


Ac-arg-lys-trp-his-phe-trp-NH_2

Microbe: *Penicillium digitatum*
Activity: IC_{50} = 7 μM

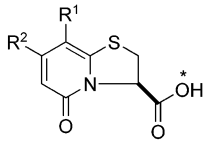
Library: 5.15
Name: Chloroorienticin B carboxamide
Size: >80 members
Affiliation: Shionogi [400]

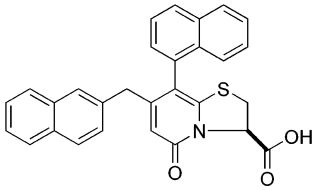




Microbe: *S. aureus* 5R3637 (MRSA)
Activity: MIC = <0.125 μg/mL

Library: 5.16
Name: Bicyclic lactam
Size: 20 members
Affiliation: Emtenas, H.; *et al.* [121]

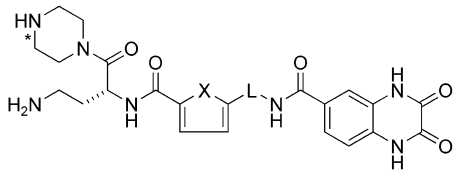


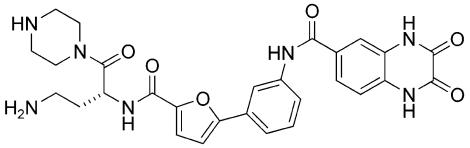


Target: Bacterial periplasmic chaperone PapD (*E. coli*)
Activity: Pilicide activity demonstrated by surface plasmon resonance

Table 5. (Continued)

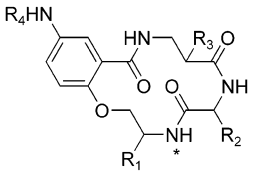
Library: 5.17
Name: Quinoxalin-2,3-dione amide
Size: *ca.* 5 members
Affiliation: Ibis Therapeutics [348]
Note: SAR by NMR identified heterocyclic fragments that were coupled together through linker L via solid-phase synthesis.

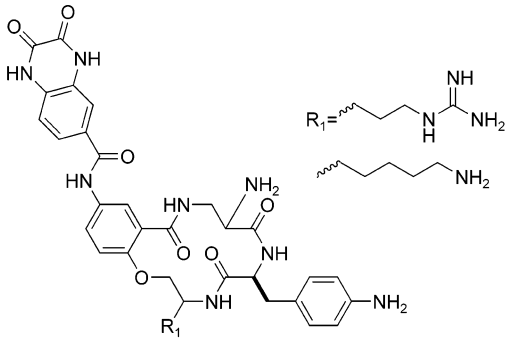




Target: Bacterial transcription/translation
Activity: IC_{50} = 14 μM

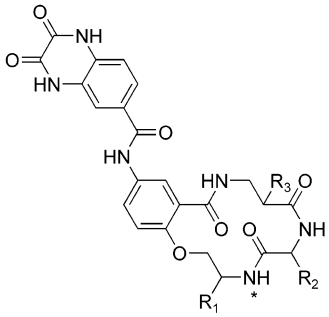
Library: 5.18
Name: Peptidomimetic
Size: 12,000 members
Affiliation: Ibis Therapeutics [186]
Note: Solid-phase synthesis carried out using IRORI technology.

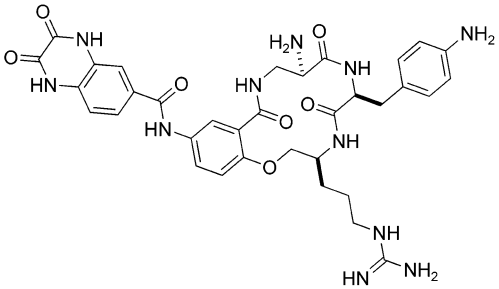




Target: In vitro transcription/translation (*E.* coli)
Activity: IC_{50} = 25-50 μM (mixture of R^1 substituents)

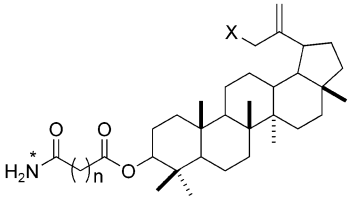
Library: 5.19
Name: Peptidomimetic
Size: 64 members
Affiliation: Ibis Therapeutics [186]
Note: Follow-up library to library 5.18.

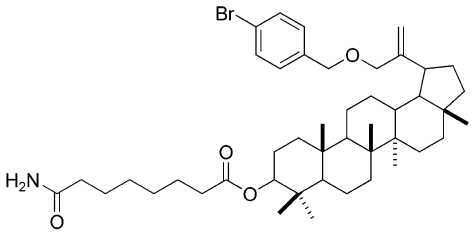




Target: In vitro transcription/translation (*E.* coli)
Activity: IC_{50} = 13 μM

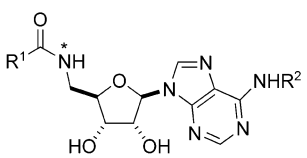
Library: 5.20
Name: Lupeol analog
Size: 96 members
Affiliation: Srinivasan, T.; *et al* [337]

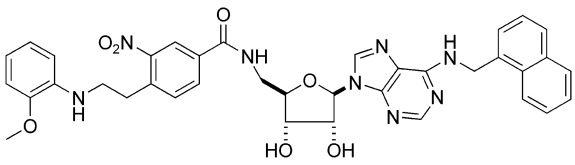




Target: *P. falciparum*
Activity: IC_{50} = 13 μM

Library: 5.21
Name: Adenosine derivative
Size: *ca.* 35 members
Affiliation: Herforth, C.; *et al.* [162]
Note: Acylation (R^1CO) of 5-amino nucleoside templates using carboxylic acids activated by Kenner safety-catch linker.

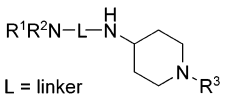


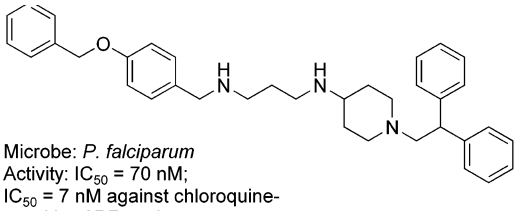


Target: *P. falciparum*
Activity: IC_{50} = 1.5 μM

Table 5. (Continued)

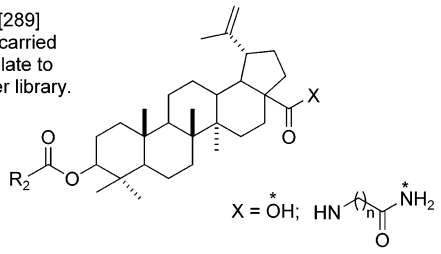
Library: 5.22
Name: Aminopiperidine
Size: *ca.* 50 members
Affiliation: Brinner, K. M.; *et al.* [51]
Note: Multiple libraries exploring R^1-R^3 in combination with discrete analog synthesis.

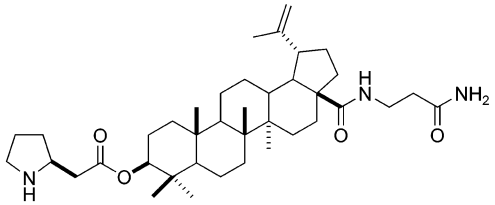




Microbe: *P. falciparum*
Activity: IC_{50} = 70 nM;
IC_{50} = 7 nM against chloroquine-sensitive 3D7 strain.

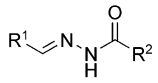
Library: 5.23
Name: Betulinic amide
Size: 18 members
Affiliation: Pathak, A.; *et al.* [289]
Note: Analogous chemistry carried using ursolic acid as a template to generate second 10 member library.

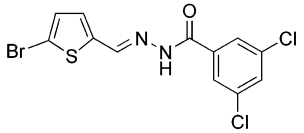




Microbe: *P. falciparum*
Activity: MIC = 10 μg/mL

Library: 5.24
Name: Acyl hydrazide
Size: Not defined
Affiliation: Caffrey, C. R.; *et al.* [58]



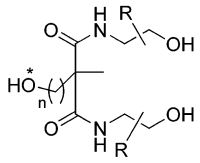


Microbe: *Trypanosoma brucei*
Activity: IC_{50} = 2 μM

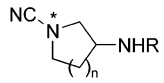
Table 6. Scaffold Derivatization (Asterisk (*), Point of Attachment to Resin)

Part A: Solid-Phase

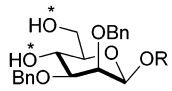
- Harned, A. M. [159]
- 8 ex; 58-97%
- Mitsunobu coupling of ROH to norbornenyl N-hydroxysuccinimide then capture-ROMP-release with H_2NNH_2



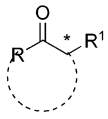
- Weissberg, A. [378]
- 11 ex; 33-100%
- conversion of esters to hydroxyalkylamides via transesterification then O to N-acyl migration



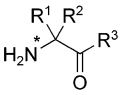
- Celltech [262]
- 8 ex; 45-55%
- cleavage of resin-bound amines with CNBr



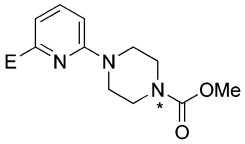
- Crich, D. [101]
- 6 ex; 73-88%
- from thiopyranoside attached to resin via borinate ester linkage



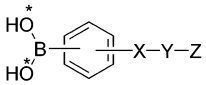
- Lazny, R. [225]
- 12 ex; 19-92%
- alkylation of resin-bound hydrazones



- Garcia, J. [135]
- 5 ex; 76-94%
- from carbamate-linked amino acid Weinreb amides

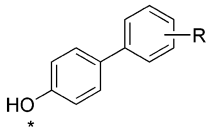


- Gros, P. [149]
- 8 ex; 69-93%
- lithiation of resin-bound 2-pyridylpiperazine then cleavage with $ClCO_2Me$

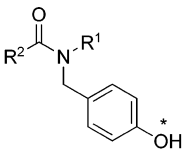


- Gravel, M. [145]
- >15 ex; good yield
- derivatization of immobilized aryl boronic acids

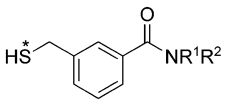
- BMS [94]
- *ca.* 14 ex; 21-65%
- $Cu(OAc)_2$-mediated arylation of aliphatic amines and $ArB(OH)_3$



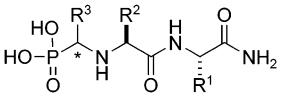
- Revell, J. D. [313]
- 10 ex; 42-73%
- ionic liquid accelerated Suzuki cross coupling of resin-bound ArI



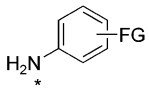
- Katritzky, A. R. [194]
- *ca.* 40 ex; 30-99%
- acylation of resin-bound amines with acylbenzo-triazoles



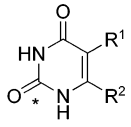
- Mourtas, S. [264]
- 3 ex; good yield
- from resin-bound mercapto acids



- Rinnova, M. [317]
- 14 ex; 53-92%
- condensation of resin-bound amino acid amides with R^3CHO and $(MeO)_2P(O)H$



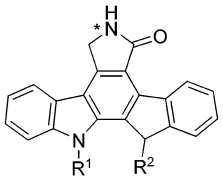
- Novartis [377]
- 12 ex; 32-96%
- Pd-catalyzed amination of aryl halides on Rink resins



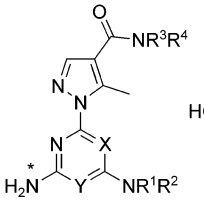
- Petricci, E. [294]
- 8 ex; 65-98%
- Oxone-facilitated cleavage of corresponding resin-bound thioester

Table 6. (Continued)

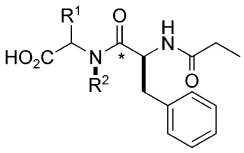
Part A: Solid-Phase (Continued)



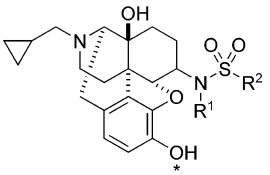
- Cephalon [360]
- 11 ex; good yield
- alkylation resin-bound dianion



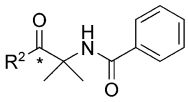
- Daiichi [160]
- 40 members
- X, Y = N or CH



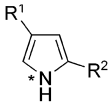
- Corbett, A. D. [98]
- 5 ex; 6-26%
- aqueous-phase peptide coupling with TFP resins



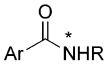
- Toray Ind. [281]
- 339 members
- from corresponding 6-ketomorphinan



- RHeo Gene [357]
- 3 ex; good yield
- addition of Grignard reagent to resin-bound Weinreb amides

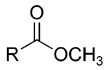


- Bergauer, M. [35]
- *ca.* 6 ex; good yield
- functionalization of pyrroles immobilized via dialkoxy-methyl linkage

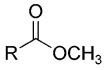


- Vago, I. [363]
- 20 ex; 15-100%
- acylation of resin-bound amines with *in situ* generated arylacyl chlorides

Part B: Solution-Phase

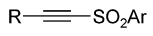


- Crosignani, S. [103]
- 9 ex; 93-100%
- esterification via resin-bound *O*-methylisourea

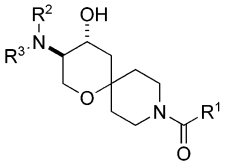


- Crosignai, S. [102]
- 8 ex; >98%
- esterification of RCOOH with resin-bound O-methyl-isourea

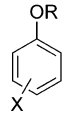
- Anilkumar, G. [11]
- 14 ex; 88-98%
- iodination of alcohols using polymer-supported Ph_3P/I_2/imidazole



- Qian, H. [305]
- 13 ex; 76-90%
- radical-mediated addition of resin-bound selenosulfonate to alkynes then elimination

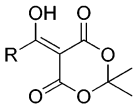


- Pfizer [371]
- 12 ex; 73-88%
- aminolysis of spirocyclic expoxide



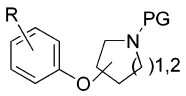
- Abbott [137]
- 48 members
- Mitsunobu reaction using polymeric reagents

- Ley, S. V. [227]
- *ca.* 6 ex; good purity
- conversion of thioiso-cyanates to isocyanates



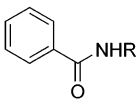
- Affymax [308]
- *ca.* 15 ex; good purity
- Meldrum's acid, RCOOH, DCC and DMAP

- Launay, D. [223]
- 6 ex; >95%
- dehydration of formamides with polymeric sulfonyl chloride and microwave

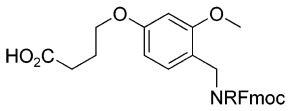


- Tularik [239]
- 12 ex; good yield
- optimized aryl ester formation using resin-bound Ph_3P

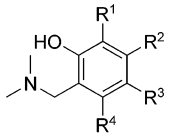
- Merck [234]
- 7 ex; 80-90%
- Staudinger protocol ($R\text{-}N_3$ to RNH_2) using fluorous Ph_3P



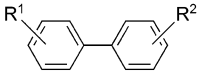
- ArQule [275]
- 15 ex; 0-100%
- benzoylation using polymer-bound imide



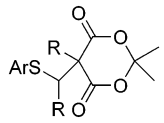
- Aventis [18]
- 6 ex; 60-80%
- reductive amination of 4-formyl-3-OMe-phenoxy-butyric acid then Fmoc-Suc



- Bream, R. N. [50]
- 8 ex; 82-97%
- treatment of phenols with Eschenmoser's salt and polymeric base

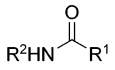


- Hebel, A. [161]
- *ca.* 8 ex; 84-91%
- polygylcerol boronic esters as soluble reagents for Suzuki cross-coupling reactions

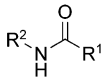


- Yadav, J. S. [392]
- 9 ex; 65-94%
- 3CC of Meldrum's acid with ArSH catalyzed by polymer-supported piperazine

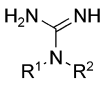
- Baxendale, I. R. [29]
- 14 ex; 43-100%
- RCHO to nitriles via solid-supported hydrazine



- Argonaut [142]
- 48 ex; 15-93%
- optimization of amide synthesis using resin-bound HOBt esters via statistical design of experiments (DoE)



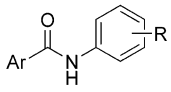
- Petricci, E. [293]
- 9 ex; 40-100%
- amine acylation via polymeric 4-acyloxy-pyrimidines



- J&J [152]
- 10 ex; 87-95%
- bis-Boc-thiourea, an amine and polymeric carbodiimide then TFA deprotection

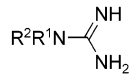
Table 6. (Continued)

Part B: Solution-Phase (Continued)

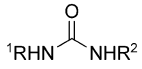


- Kim [204]
- 21 ex; 62-95%
- use of Girand's reagent T as an RCOCl scavenger

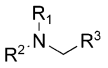
- Baxendale, I. R. [30]
- 13 ex; 75-100%
- oxidation of trifluoromethyl alcohols with Amberlyst A-27 permanganate



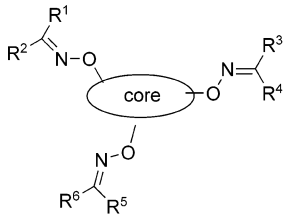
- Drager, G. [115]
- 11 ex;
- amidinations with pyrazole-based polymeric reagent



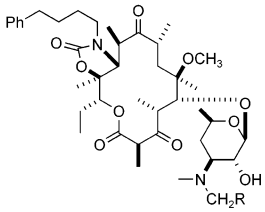
- Bosanac, T. [47]
- 10 ex; 88-100%
- R^1NCO and excess amine; latter scavenged by photo activated precipiton



- Fluorous Tech. [408]
- 12 ex; 75-95%
- alkylation of R^1R^2NH with R^3CH_2Br then fluorous thiol scavenging



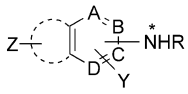
- Nazarpack-Kandlousy, N. [271]
- large mixture library
- from di- and triaminooxy-containing scaffolds



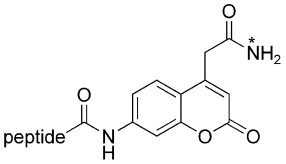
- Aventis [109]
- 20 ex; 70-99%
- reductive amination of a N-desmethylketolide

Table 7. Acyclic Synthesis (Asterisk (∗), Point of Attachment to Resin)

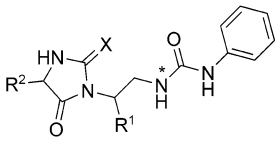
Part A: Solid-Phase



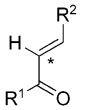
- Ding, S. [113]
- 45,140 members
- diverse set of polychloro-substituted heterocycles reacted with N-nucleophiles and subjected to Suzuki cross-coupling



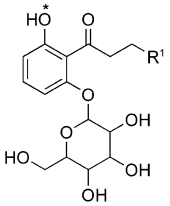
- Maly, D. J. [252]
- *ca.* 25 ex; 50-98%
- coupling of Fmoc-amino acids to resin bound coumarin



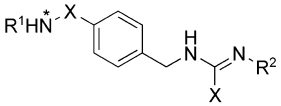
- Nefzi, A. [272]
- 12 ex; >90%
- from resin-bound diamines; X = O, S



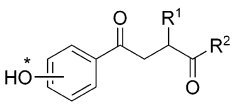
- Strohmeier, G. A. [340]
- 21 ex; good yield
- Knoevenagel condensation with resin-bound acetoacetates



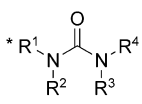
- Tanaka, H. [350]
- 132 members
- from resin-bound 2,6-di-OH-acetophenone



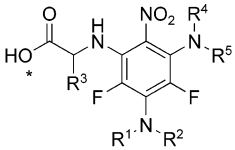
- Disc. Part. Int. [169]
- 14 ex; 71-99%
- preparation of resin-bound carbodiimides and reaction with amines



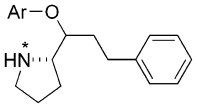
- Raghavan, S. [306]
- 12 ex; 55-75%
- thiazolium salt promoted Michael additions of RCHO to resin-bound chalcones



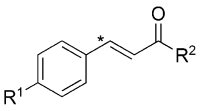
- BMS [412]
- *ca.* 20 ex; good yield
- resin-bound amines reacted with N-acyl imidazolium salts



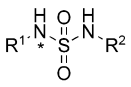
- Holland, R. J. [167]
- 36 members
- sequential addition of amine nucleophiles to pentafluoronitrobenzene



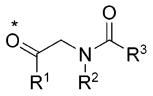
- Disc. Part. Int. [390]
- 4 ex; 0-85%
- Ullmann condensation of resin-bound alcohols and aryl iodides



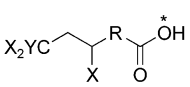
- Cheng, W. - C. [81]
- 4 ex; good yield
- alkylation of resin-bound sulfone with expoxides, then oxidation and β-sulfinate elimination



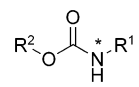
- Almirall [123]
- 15 ex; 38-61%
- alkylation resin-bound BOC-protected sulfamide then cleavage



- Millennium [90]
- 1400 members
- condensation of α-halo ketones to carbazate linker, amine displacement, acylation and cleavage



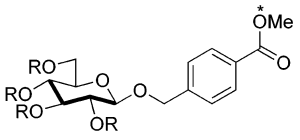
- Kumar, H. M. S. [216]
- 7 ex; 62-97%
- free radical addition of halo alkanes to resin-bound olefins



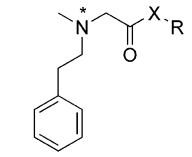
- Almirall [126]
- size not defined
- reductive amination on BAL resin, then reaction with succinimidyl carbonate and R^2OH

Table 7. (Continued)

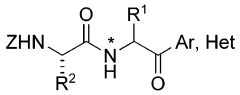
Part A: Solid-Phase (Continued)



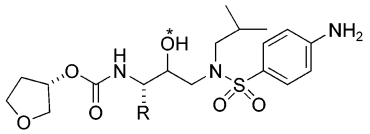
- Izumi, M. [182]
- *ca.* 5 ex; 14-21%
- use of propargyloxy-carbonyl linkage and cleavage with $Co_2(CO)_8$ and TFA



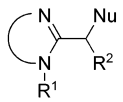
- Organon [263]
- 15 ex; good yield
- Hofmann elimination transesterification/ amidation on REM resin using perfluorous solvent



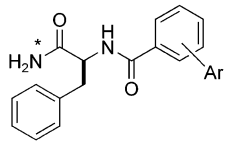
- Pfizer [343]
- 8 ex; 0-50%
- from resin-bound amino acid Weinreb amides



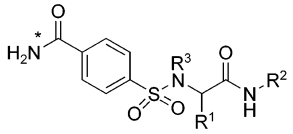
- Chino, M. [84]
- 2 ex; 66-70%
- from resin-bound bromo azide



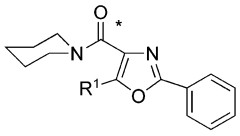
- J&J [108]
- *ca.* 36 members
- condensation of azoles and R^2CHO with carbamyl chloride resin then traceless release with Nu



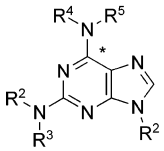
- Hoffmann-La Roche [244]
- 20 ex; good yield
- triflation of resin-bound phenols and Suzuki cross-coupling



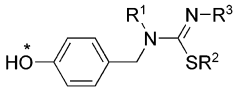
- Adv. Syntech [60]
- 13 ex; 40->95%
- Ugi 4CC with resin-bound arylsulfonamide as the amine component



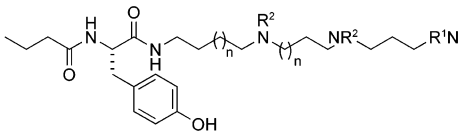
- Clapham, B. [89]
- *ca.* 24 ex; 0-50%
- from resin-bound α-diazo-β-keto esters



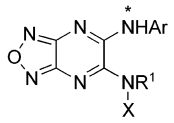
- Ding, S. [112]
- *ca.* 24 ex; good yield
- from resin-bound C-6 thio-linked 2-fluoro-purine



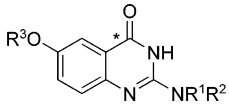
- Katritzky, A. R. [195,196]
- 30 ex; 92-100%
- reaction of resin-bound 1,1-disubstituted-2-aryl-isothioureas with aryliso-cyanates then cleavage



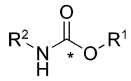
- Jonsson, D. [189]
- 2 members
- multistep sequence from propylenediamine



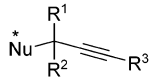
- GSK [125]
- 320 members
- resin-bound anilines reacted with 5,6-dichloro-furanopyrazine then addition of RNHX; X = H, NHR^2



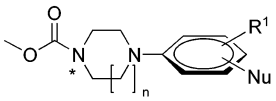
- Gedeon Richter [375]
- 9 ex; 0-75%
- derived from resin-bound 2,4-dichloro-6-hydroxyquinazolines



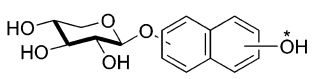
- Sumiyoshi, H. [344]
- *ca.* 22 ex; 70-95%
- reaction of amines with resin-bound N-hydroxy-succinimide



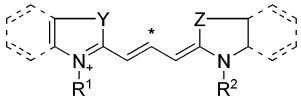
- Cassel, J. A. [63]
- 12 ex; 0-56%
- reaction of resin-bound alkynol cobalt complexes with Nu



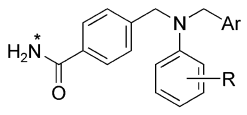
- Ruhland, T. [322]
- *ca.* 36 ex; good yield
- iron-assisted S_NAr reaction to introduce Nu



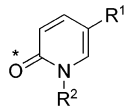
- Jacobson, M. [183]
- 14 ex; 6-28%
- xylosylation of resin-bound dihydroxynaphthalenes



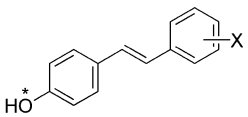
- Mason, S. J. [253]
- 9 ex; 0-79%
- capture and activation of a hemi-cyanine intermediate on sulfonyl chloride resin followed by reaction and concomitant cleavage by a heterocyclic carbon nucleophile



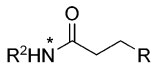
- Akamatsu, H. [8]
- 26 ex; 50-70%
- selective LAH-mediated reduction of resin-bound bis-amides



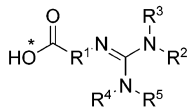
- Karo Bio [321]
- *ca.* 30 ex; 0-86%
- 2-halopyridines coupled to Wang resin, alkylation (R^2) then cleavage



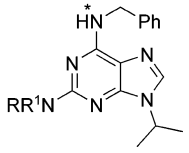
- Chang, S. [69]
- 8 ex; 54-72%
- cross metathesis of resin-bound styrenyl ether



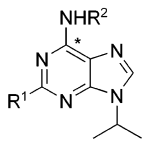
- Caddick, S. [57]
- *ca.* 12ex; 16-98%
- radical addition to TFP acrylate then aminolysis



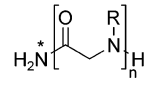
- Kilburn, J. P. [201]
- 6 ex; 35-66%
- desulfurisation of resin-bound thioureas in the presence of R^5R^4NH



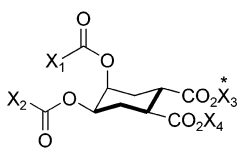
- Selectide [17]
- 2 ex; 45-59%
- microwave assisted solid-phase synthesis from resin-bound 2-amino-6-iodopurine



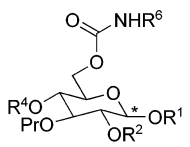
- Brun, V. [54]
- 2 ex; good yield
- Pd-catalyzed cross-coupling of resin-bound 6-thio-2-iodopurine



- Olivos, H. J. [282]
- 6 ex; good yield
- 1 min microwave irradiation of bromo-acetamides and amines



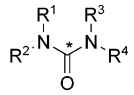
- Arosio, D. [13]
- >100 members
- from dihydroxy-cyclohexanedioic acid



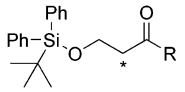
- Opatz, T. [283]
- 60 members
- functionalization of resin-bound thioglycoside

Table 7. (Continued)

Part A: Solid-Phase (Continued)



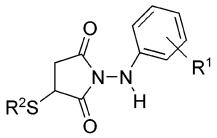
• Whitehead, D. M. [379]
• 4 ex; 63-73%
• aminolysis of resin-bound carbamate derived from a thiohydroxamine acid linker



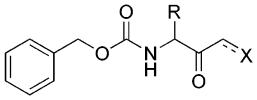
• McKerlie, F. [256]
• reduction of α-aryloxy carbonyl compounds with SmI_2

• Organon [59]
• DMSO is optimal solvent for quaternization of REM resin

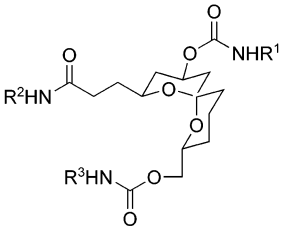
Part B: Solution-Phase



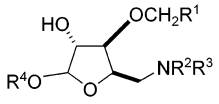
• BMS [79]
• 300 members
• alumina-catalyzed addition of thiols to N-anilinomaleimides



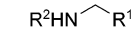
• Aventis [393]
• 10 ex; 58-92%
• diazoketones (X = N_2) and bromomethyl ketones (X = Br) from Cbz-protected amino acids



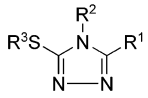
• Kulkarni, B. A. [214]
• *ca.* 17 ex; 77-98%
• derivatization of a trifunctional spiroketal



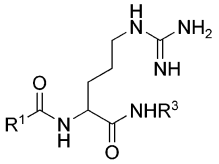
• Disc. Part. Int. [212]
• *ca.*15 ex; 41-71%
• reductive amination of furanose protected aldehyde



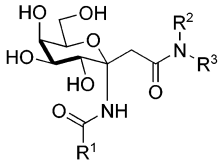
• Wyeth [291]
• 4 ex; good yield
• tandem three-phase reaction sequence for reductive amination without by-products



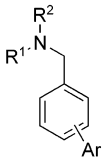
• GSK [146]
• 2500 members
• classical condensation of acylhydrazines with RNCS using resin-bound reagents



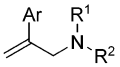
• Guery, S. [151]
• 4 ex; 31-95%
• Ugi 4CC using a guanidylated aldehyde



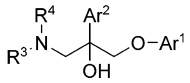
• Lohse, A. [240]
• 56 members
• formation of dihydro-oxazinones via modified Ritter reaction then ring opening with amines



• Organ, M. G. [284]
• 24 ex; good yield/purity
• from bromobenzylbromides



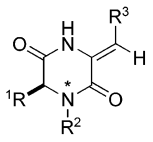
• Organ, M. G. [284]
• 1344 members
• from 2,3-dibromo-1-propene



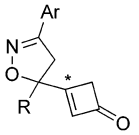
• Organ, M.G. [284]
• 20 members
• from 2,3-dibromo-1-propene

Table 8. Monocyclic Synthesis (Asterisk (∗), Point of Attachment to Resin)

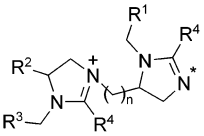
Part A: Solid-Phase



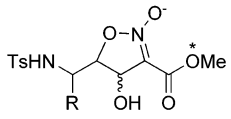
• Li, W. R. [229]
• 8 ex; 11-53%
• condensation of resin-bound oxazolones with RCHO then intracyclative cleavage



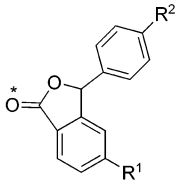
• Cheng, W.-C. [82]
• 6 ex; 27-38%
• multi-step sequence via a traceless solid-phase sulfone linker strategy



• Acharya, A. N. [3]
• 16 ex; 60-75%
• multi-step sequence from resin-bound diacylated dipeptide N^{σ} and N^{ε}



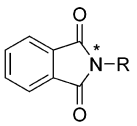
• Righi, P. [315]
• 3 ex; 72-100%
• tandem nitroaldol-intramolecular cyclization of N-tosyl-2,3-aziridine carboxaldehydes



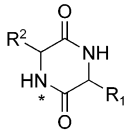
• Shimomura, O. [331]
• 9 ex; 66-100%
• synthesis performed on microgels

Table 8. (Continued)

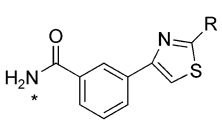
Part A: Solid-Phase (Continued)



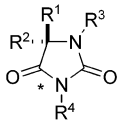
• Xiao, Z. [391]
• 6 ex; 43-98%
• derivatization of hydroxy polystyrene resin with phthalic anhydride, amide coupling and intracyclative release



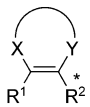
• Wang, D.-X. [372]
• 18 ex; 60-82%
• from resin-bound N-Boc protected amino acid phenacyl esters



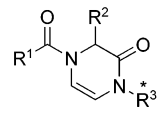
• Kazzouli, S. E. [120]
• 5 ex; 79-98%
• condensation of resin-bound bromomethyl ketones with thioamides



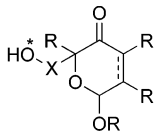
• Lamothe, M. [219]
• 24 ex; 10-58%
• from resin-bound Fmoc-amino acid amides



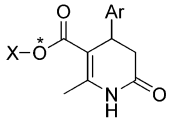
• Nicolaou, K. C. [276]
• *ca.* 20 ex; 20-90%
• heterocyclic systems from resin-bound α-tosyloxyketones



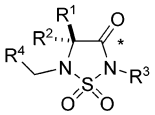
• Chugai Pharm. [77]
• 8 ex; 68-97%
• Ugi 4CC



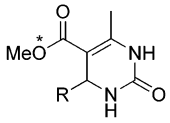
• Couladouros, E. A. [100]
• 25 ex; 65-95%
• oxidation of resin-bound furanyl alcohols



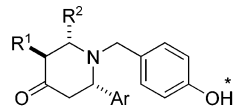
• Rodriguez, H. [320]
• 8 ex; 65-85%
• from resin-bound β-keto esters and Hantzsch type heterocyclization; X = H, Me



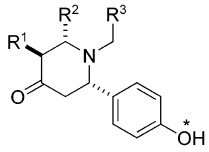
• Tremblay, M. [359]
• 29 ex; 21-89%
• sulfamoylation of resin-bound amino acid esters then intracyclative cleavage



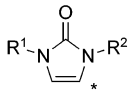
• Xia, M. [389]
• 6 ex; 74-86%
• from soluble-support bound acetate, urea, RCHO microwave, then NaOMe



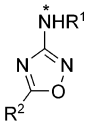
• Barluenga, J. [20]
• 11 ex; 67-93%
• imino-Diels-Alder cycloaddition



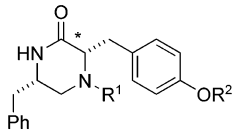
• Barluenga, J. [20]
• 4 ex; 42-66%
• imino-Diels-Alder cycloaddition



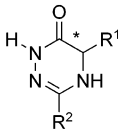
• Chugai Pharm [78]
• 11 ex; ~60%
• amination of resin-bound bromo acetaldehyde diethyl acetal, acylation with isocyanate, then intracyclative cleavage



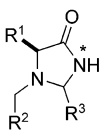
• Neo Genesis [249]
• 15 ex; 75-95%
• cyclization of resin-bound N-acyl-1H-benzotriazole-1-carboximidamides with NH_2OH



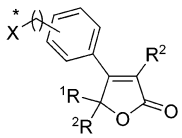
• Gonzalez-Gomez, J. C. [141]
• 10 ex; 50-80%
• reductive amination of resin-bound amino acids with amino acid aldehydes then intracyclative cleavage



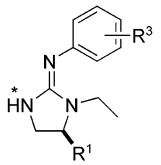
• P&G Pharm. [39]
• 15 ex; 23-75%
• from resin-bound amino acid thioamides and intracyclative cleavage with H_2NNH_2



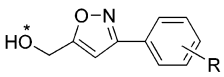
• Rinnova, M. [316, 319]
• 34 ex; 14-84%
• derivatization of resin-bound amino acid amides wtih R^3CHO, BtH, then intracyclative cleavage



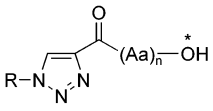
• Ma, S. [245]
• 25 ex; good yields
• Pd-mediated coupling-cyclization of resin-bound aryl aryliodides with 1,2-allenic carboxylic acids (X = OH, Br)



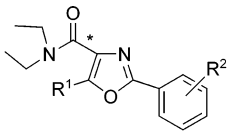
• Yu, Y. [404]
• 15 ex; 85-91%
• reduction of resin-bound N-acylated amino acid amides, then aryl isothiocyanation treatment with $HgCl_2$ and HF cleavage



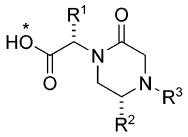
• Shang, Y.-J. [330]
• 8 ex; 48-91%
• 1,3-dipolar cycloaddition of soluble-polymer-bound propargyl ester and aryl nitrile oxides



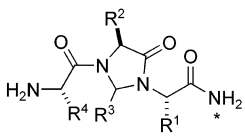
• Tornoe, C. W. [358]
• 24 ex; good purity
• Cu-catalyzed 1,3-dipolar cycloaddition of resin-bound peptide alkynes and RN_3



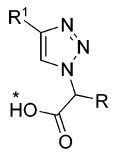
• Spanka, C. [334]
• 10 ex; 19-36%
• from α-diazo-β-ketoesters immobilized on microgel resin



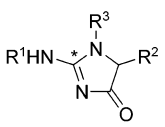
• Khan, N. M. [200]
• 8 ex; 20-34%
• from resin-bound chloromethyl amino acid amides



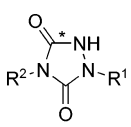
• Rinnova, M. [316]
• 7 ex; 81-97%
• BtH/RCHO N-terminal derivatization of dipeptide amides and intramolecular cyclization



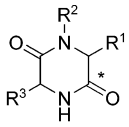
• P&G Pharm. [38]
• 9 ex; 4-27%
• [2+3] cycloaddition of resin bound azides with terminal alkynes



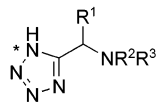
• Adv. Syntech [397]
• *ca.* 17 ex; 53-100%
• from resin-bound thioureas and Boc-protected amino acids; intracyclative cleavage



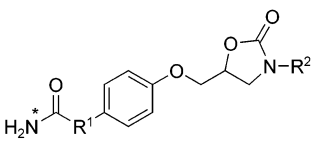
• BMS [288]
• 8 ex; 18-44%
• isocyanation of resin-bound carbazate then intracyclative cleavage



• P&G [72]
• 4 ex; 23-78%
• Ugi 3CC with resin-bound isonitrile



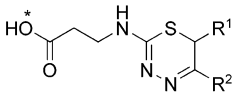
• P&G [72]
• 5 ex; 25-89%
• Ugi 3CC with resin-bound isonitrile



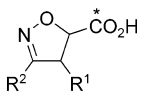
• Rastogi, S. K. [310]
• *ca.* 8 ex; 72-90%
• ring opening of resin-bound epoxide with N_3, carbonate formation, N_3 reduction and intramolecular ring closure

Table 8. (Continued)

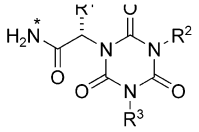
Part A: Solid-Phase (Continued)



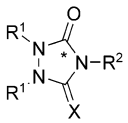
- Novo Nordisk [202]
- 6 ex; 12-47%
- ring formation via reaction of $RCOCH_2Br$ with resin-bound thiosemicarbazide



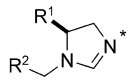
- Chandrasekhar,S. [67]
- 15 ex; 63-82%
- [3+2]-cycloaddition of nitrile oxide and resin-bound α,β-unsaturated esters



- Yu, Y. [402]
- 10 ex; 56-72%
- treatment of resin-bound urea with ClCONCO, alkylation then cleavage

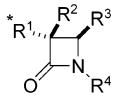


- Phoon, C. W. [296]
- 16 ex; 0-68%
- resin-bound carbazate treated with RNCO or RNCS and intracyclative cleavage; X = O, S

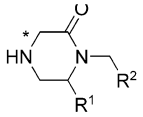


- Acharya, A. N. [6]
- 21 ex; 60-80%
- cyclization of resin-bound diamines with Vilsmeier reagent

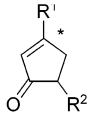
- Dasgupta, S. K. [105]
- 14 ex; 60-68%
- Staudinger reaction on Rink resin



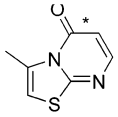
- Schunk, S. [328]
- *ca.* 25 ex; good yield
- triazene linked resin-bound ester-enolate condensed with imines then traceless cleavage



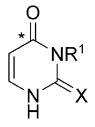
- Nefzi, A. [273]
- 18 ex; good yield
- acylation of resin-bound diamine with bromoacetic acid then cyclization (major isomer shown)



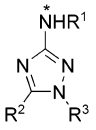
- Cheng, W.-C. [80]
- 11 ex; 18-40%
- oxidation/elimination of resin-bound sulfones



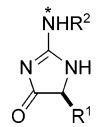
- Huang, X. [173]
- 1 ex; 80%
- condensation of resin-bound malonate with $HC(OEt)_3$, addition of amino thiazole then thermolysis



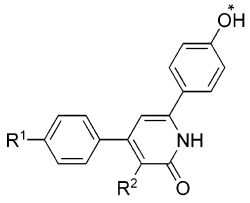
- Huang, X. [173]
- 10 ex; 65-82%
- condensation of resin-bound malonate with $HC(OEt)_3$, addition of aniline then thermolysis; X = O, S



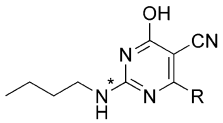
- Neo Genesis [248]
- 7 ex; 0-65%
- from resin-bound Bt-1-carboximidamides and hydrazine



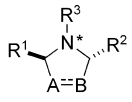
- Yu, Y. [403]
- 10 ex; 85-93%
- intramolecular cyclization of resin-bound thioureas with Mukaiyama's reagent



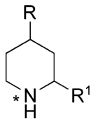
- Katritzky, A. R. [193]
- 9 ex; 79-87%
- reaction of resin-bound chalcones with 2-(benzotriazol-1-yl)-acetamides



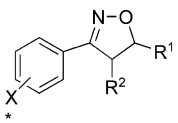
- Chauhan, P. M. S. [71]
- 12 ex; 85-93%
- reaction of resin-bound thiouronium salt with ethyl cyano acetate and RCHO then S-oxidation and cleavage with amine



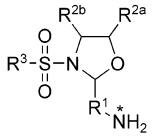
- Komatsu, M. [211]
- *ca.* 7 ex; good yield
- cycloaddition of polymer-supported azomethine ylide via a 1,2-silatropic shift of α-silylimines



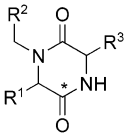
- Veerman, J. J. N. [366]
- 9 ex; 0-86%
- introduction of R^1 via N-acyliminium ion chemistry



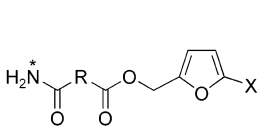
- Faita, G. [124]
- ca. 18 ex; 15-90%
- 1,3-dipolar cycloaddition of resin-bound nitrile oxides; X = OH, COOH



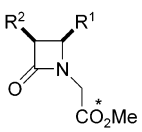
- Novo Nordisk [95]
- *ca.* 30 ex; good yield
- condensation of amino alcohols with resin-bound carbamate linked aldehydes



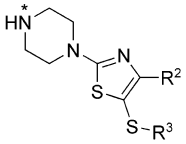
- Array Biopharm [198]
- 80 members
- Ugi 4CC using resin-bound isonitrile



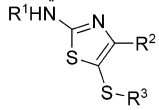
- Gupta, P. [156]
- 32 ex; good purity
- assorted heterocyclic furans from resin-bound furfural



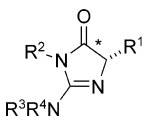
- Delpiccolo, C. M. L. [107]
- 21 ex; good yields
- Staudinger reaction via resin-bound glycine



- Novo Nordisk [148]
- 6 ex; good yield
- C-sulfanylation of resin-bound 2-aminothiazoles



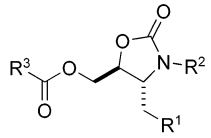
- Novo Nordisk [148]
- 6 ex; good yield
- C-sulfanylation of resin-bound 2-aminothiazoles



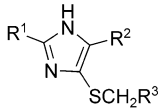
- BASF [220]
- 14 ex; 47-93%
- dehydration of resin-bound ureas with Burgess reagent then addition of R^4R^3NH and intracyclative cleavage

Table 8. (Continued)

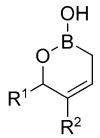
Part B: Solution-Phase



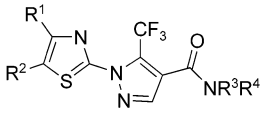
- Bergmeier, S. C. [37]
- 3 ex; *ca.* 50%
- multi-step sequence from bicyclic aziridine



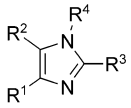
- Coleman, C. M. [92]
- 24 members
- three-component condensation of RCHO, 2-oxothioacetamides and NH_4OAc



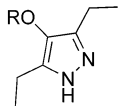
- Micalizio, G. C. [258]
- 7 ex; 66-92%
- allylboronic ester annulation via RCM



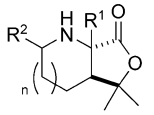
- Rohm Hass [114]
- 422 members
- condensation of 2-ethoxy methylene-3-oxo-trifluoro butanoate with thiosemicarbazide



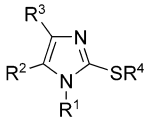
- Hoffmann-La Roche [40]
- 21 ex; 32-76%
- 4-step sequence from 1,2-amino-alcohols



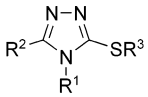
- Pfizer [300]
- 11 ex; 10-40%
- alkoxylation of 1,3-diones with $(PhIO)_n$ and ROH, then hydrazine



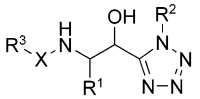
- Jia, Q. [187]
- 6 ex; 23-72%
- $Yb(OTf)_3$-catalyzed electrophilic cyclization of glyoxalate-derived unsaturated imines



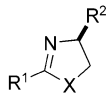
- BMS [351]
- 275 members
- from thioisocyanates and acylhydrazines then S-alkylation



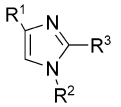
- BMS [351]
- 283 members
- from thioisocyanates and acylhydrazines then S-alkylation



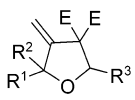
- AMGEN [277]
- 80 members
- $TMSN_3$-modified Passerini 3CC



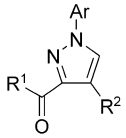
- Wipf, P. [382]
- 23 ex; 15-100%
- tandem condensation-cyclodehydration of RCOOH with amino alcohols and aminothiols



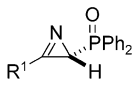
- Mellennium [90]
- 1400 members
- treatment of keto-amides with NH_4OAc in HOAc



- Cavicchioli, M. [65]
- 48 ex; 44-100%
- CuI-mediated cyclization of propargyl alcohols and activated olefins



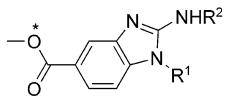
- Atlan, V. [16]
- 9 ex; 0-80%
- from Mannich type hydrazones



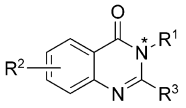
- Palacios, F. [286]
- 2 ex; 74-89%
- Neber reaction

Table 9. Bicyclic and Spirocyclic Synthesis (Asterisk (∗), Point of Attachment to Resin)

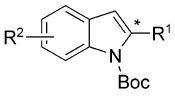
Part A: Solid-Phase



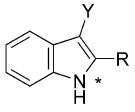
- Wu, C.-Y. [384]
- 12 ex; 80-99%
- from soluble polymer-supported 4-fluoro-3-nitrobenzoic acid



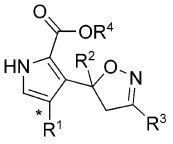
- SIDDCO [280]
- 7 ex; 11-20%
- from resin-bound amines and 2-nitrobenzoic acid; final cyclization performed after cleavage



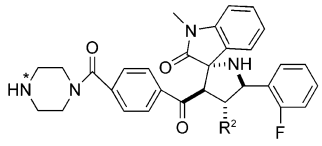
- Macleod, C. [247]
- 12 ex; 58-72%
- conversion of resin-bound esters to enol ethers via Ti(IV) benzylidenes bearing a masked nitrogen nucleophile



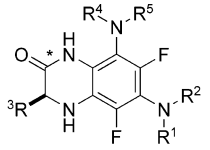
- BMS [370]
- 15 ex; 0-88%
- reductive amination of anilines onto Bal resin acylation, then intramolecular cyclization and cleavage



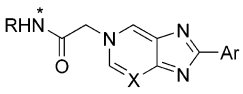
- Hwang, S. H. [178]
- 8 ex; 6-24% yield
- use of traceless sulfone linker



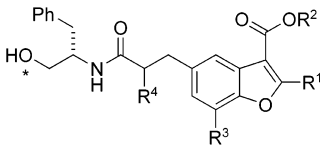
- ArQule [155]
- 5 ex; good yield
- from resin-bound chalcone N-methylisatin and fluorophenyl glycine



- Holland, R. J. [168]
- 11 ex; >80%
- reductive cyclization of 2,4,6-substituted-3,5-difluoro nitrobenzenes



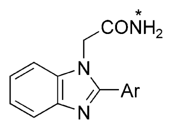
- Akamatsu, H. [7]
- 8 ex; 90%
- resin-bound bromomethyl amides alkylated with heterocyclic diamines the condensation with ArCHO



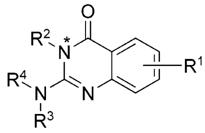
- Liao, Y. [230]
- 90 members
- carbonylative annulation of *o*-alkynylphenols

Table 9. (Continued)

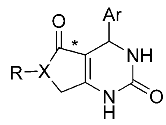
Part A: Solid-Phase (Continued)



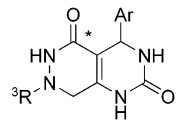
• Akamatsu, H. [7]
• 42 members
• resin-bound bromo-acetamide alkylated with phenylenediamines then condensation with ArCHO



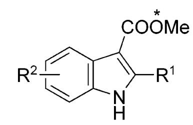
• Kesarwani, A. P. [199]
• 12 ex; 50-67%
• from resin-bound N-Fmoc-anthranilic acids



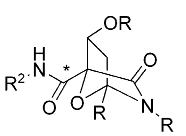
• Perez, R. [292]
• 18 ex; 33-75%
• condensation of resin-bound 5-Cl-acetoacetate with urea, and ArCHO then intracyclative cleavage



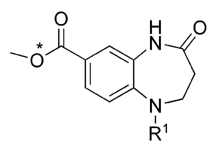
• Perez, R. [292]
• 8 ex; 26-82%
• condensation of resin-bound 5-Cl-acetoacetate with urea, and ArCHO then intracyclative cleavage with H_2NNHR^3



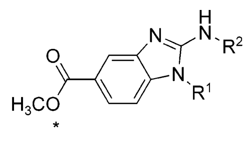
• Yamazaki, K. [395]
• 8 ex; 39-78%
• Pd-catalyzed cyclization of resin-bound β-(2-halo-phenyl)amino-substituted α,β-unsaturated esters



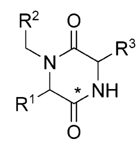
• Savinov, S. N. [327]
• *ca.* 18 ex; 49-65%
• 1,3-dipolar cycloaddition reaction of resin-bound isomunchnones and aminolytic cleavage



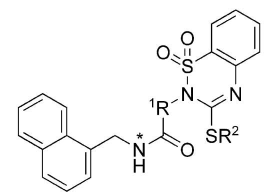
• Wu, C.-Y. [385]
• 12 ex; ~85%
• from soluble-polymer bound 4-fluoro-3-nitro-benzoic acid, 3-amino-propionic acid



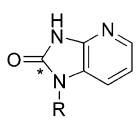
• Huang, K.-T. [170]
• 16 ex; ~85%
• from soluble-polymer bound 4-fluoro-3-nitro-benzoic acid, R^1NH_2, and isothiocyanates



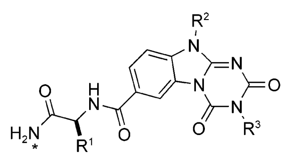
• Array Biopharm. [198]
• 80 members
• Ugi 4CC using resin-bound isonitrile



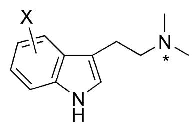
• Ajinomoto Co. [250]
• *ca.* 16 ex; 63-90%
• 2-nitrophenyl sulfonylation of resin-bound amine, NO_2 reduction, cyclization with thio-carbodiimidazole



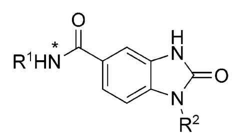
• Ermann, M. [122]
• 9 ex; good yield
• from resin-bound 2-amino-3-nitropyrimides, NO_2 reduction, optional reductive amination, then intracyclative cleavage



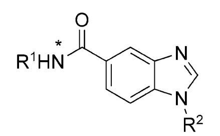
• Klein, G. [208]
• 17 ex; good purity
• multi-step sequence from resin-bound amino acid amide and 4-fluoro-3-nitrobenzoic acid



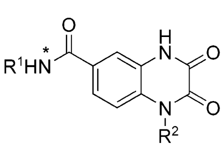
• Wu, T. Y. H. [386]
• 11 ex; 10-20%
• from tryptamines immobilized via vinyl-sulfonylmethyl poly-styrene resin



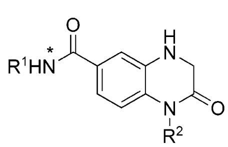
• BMS [304]
• 3 ex; good yield
• derived from resin-bound 4-fluoro-3-nitro-benzoic acid amides



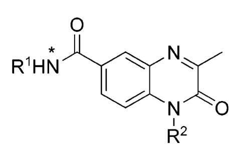
• BMS [304]
• 3 ex; good yield
• derived from resin-bound 4-fluoro-3-nitro-benzoic acid amides



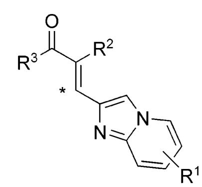
• BMS [304]
• 3 ex; good yield
• derived from resin-bound 4-fluoro-3-nitro-benzoic acid amides



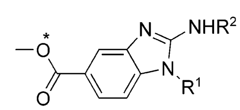
• BMS [304]
• 3 ex; good yield
• derived from resin-bound 4-fluoro-3-nitro-benzoic acid amides



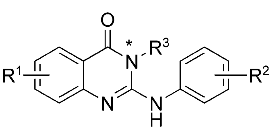
• BMS [304]
• 3 ex; good yield
• derived from resin-bound 4-fluoro-3-nitro-benzoic acid amides



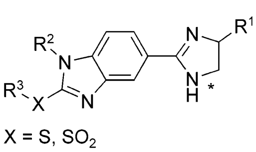
• Chen, Y. [76]
• 12 ex; 10-26%
• multi-step sequence using resin-bound Na benzenesulfinate as a traceless linker



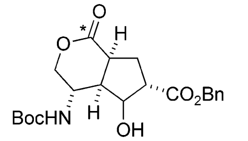
• Bendale, P. M. [34]
• 23 ex; >85%
• microwave-accelerated liquid-phase synthesis from 4-fluoro-3-nitro-benzoic acid



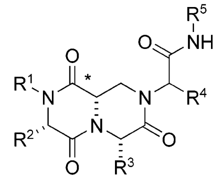
• Yu, Y. [401]
• 11 ex; 83-91%
• from resin-bound *o*-nitrobenzoic acid



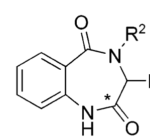
• Acharya, A. N. [2]
• 22 ex; good purity
• acylation of resin-bound diamine with 4-fluoro-3-nitrobenzioc acid, then multi-step elaboration to dihydroimidazoles



• Hanessian, S. [157]
• 1 ex; 40%
• chiral nitrone addition to resin-bound acrylate; solution-phase example also given



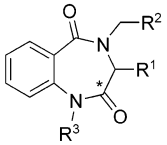
• P&G Pharm. [140]
• *ca.* 23 members
• Ugi 4CC



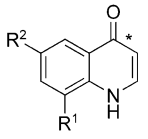
• P&G Pharm. [72]
• 6 ex; 29-91%
• Ugi 3CC with resin-bound isonitrile

Table 9. (Continued)

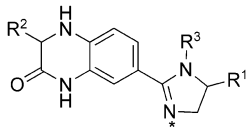
Part A: Solid-Phase (Continued)



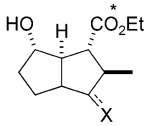
- Array Biopharm. [198]
- 80 members
- Ugi 4CC using resin-bound isonitrile



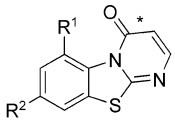
- Huang, X. [173]
- 9 ex; 49-62%
- condensation of resin-bound malonate with $HC(OEt)_3$, addition of aniline then thermolysis



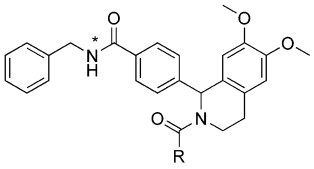
- Acharya, A. N. [4]
- 80 members



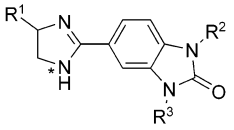
- Pisaneschi, F. [297]
- 2 ex; good yield
- from resin-bound maleate or 4-hydroxycrotonate and chiral 3-alkoxypyrroline N-oxide; ---X= H_2, O



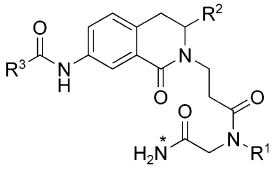
- Huang, X. [173]
- 6 ex; 72-86%
- condensation of resin-bound malonate with $HC(OEt)_3$, addition of 2-aminobenzothiazole then thermolysis



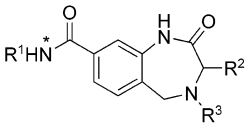
- Sun, Q. [345]
- 10 ex; 42-100%
- Pictet-Spengler reaction



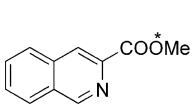
- Acharya, A. N. [5]
- 22 ex; 60-72%
- from 4-fluoro-3-nitro-benzoic acid



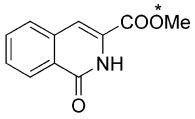
- Trega Biosc. [153]
- 38,400 members
- multi-step sequence from resin-bound bromo-acetamide



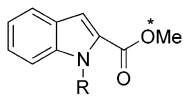
- Adv. Syntech [407]
- 14 ex; 73-97%
- from resin-bound 4-(bromomethyl)-3-nitro-benzoic acid



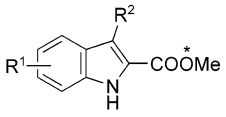
- Yamazaki, K. [396]
- 1 ex; 56%
- Pd-catalyzed tandem C,N-arylation reaction



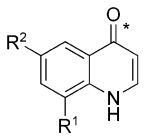
- Yamazaki, K. [396]
- 1 ex; 60%
- Pd-catalyzed tandem C,N-arylation reaction



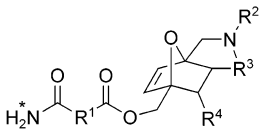
- Yamazaki, K. [394]
- 3 ex; good yield
- Pd-catalyzed tandem C,N-arylation reaction



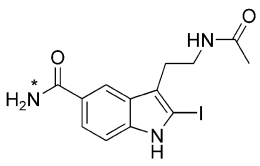
- Yamazaki, K. [396]
- 4 ex; 31-62%
- Pd-catalyzed cyclization of resin-bound haloarylen-amino esters



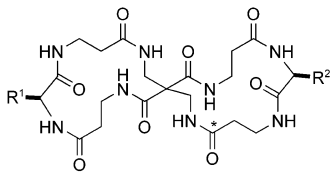
- Liu, Z. X. [238]
- 5 ex; 47-62%
- thermal intramolecular cyclization of resin-bound arylamine methylene cyclic malonic esters



- Gupta, P. [156]
- 4 ex; 40-45%
- [4+2] cycloaddition resin-bound furans with maleic anhydride

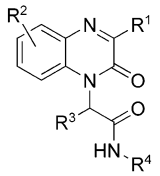


- Finaru, A. [128]
- 2 ex; good yield
- from resin-bound 4-amino-3-iodo benzamide and alkyne with microwave

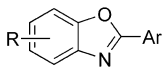


- Virta, P. [368]
- 5 ex; good yield
- from orthogonally protected bis(aminomethyl)malonic acid

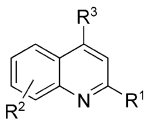
Part B: Solution-Phase



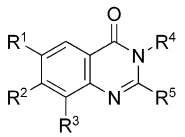
- AMGEN [278]
- 80 members
- Ugi/de-BOC/cyclize strategy



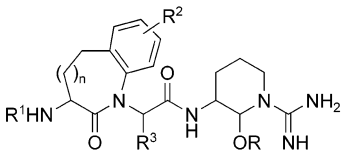
- Chang, J. [68]
- 11 ex; 74-96%
- DDQ-promoted oxidation of phenolic Schiff bases



- Huma, H. Z. S. [176]
- *ca.* 7 ex; 34-48%
- Cu-catalyzed 3CC



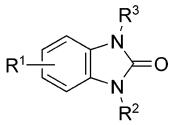
- Barthelemy, S. [21]
- 10 ex; 56-94%
- cyclization *o*-azido arylimides with perfluoro tagged Ph_3P or resin-bound triarylphosphine



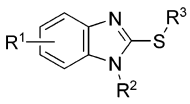
- Organ, M. G. [285]
- 2 ex
- multi-step sequence using RCM chemistry

Table 9. (Continued)

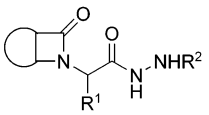
Part B: Solution-Phase (Continued)



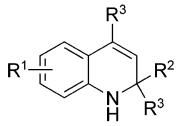
- Raju, B. [309]
- 30 members
- from 4-fluoro-3-nitro benzens



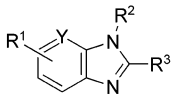
- Raju, B. [309]
- 30 members
- from 4-fluoro-3-nitro benzens



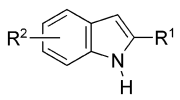
- Gedey, S. [136]
- *ca.* 15 ex; 23-81%
- Ugi 3CC



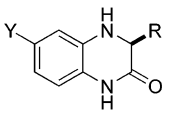
- BMS [352]
- *ca.* 45 ex; 30-98%
- aniline, ketone and $Sc(OTf)_3$ (Skraup reaction)



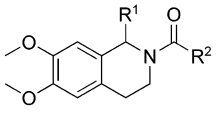
- Argonaut [405]
- *ca.* 19 ex; 61-97%
- polymer-assisted synthesis



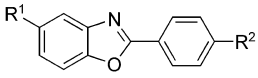
- Yasuhara, A. [399]
- 8 ex; good yield
- cyclization of ethynylanilines with polymeric TBAF



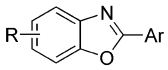
- GSK [185]
- 5 ex; 81-96%
- from 2,4-difluoronitrobenzene and polymeric reagents



- Sun, Q. [345]
- 21 ex; good purity
- Pictet-Spengler reaction



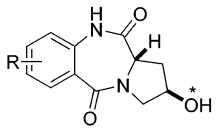
- Zhang, J.-Z. [406]
- 12 ex; 60-83%
- polymer-bound iodosodiacetate-mediated intramolecular cyclization of phenolic Schiff's base



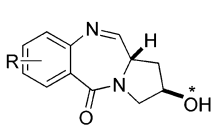
- Novartis [68]
- 11 ex; 74-96%
- DDQ-promoted oxidation of phenolic Schiff bases

Table 10. Polycyclic and Macrocyclic Synthesis (Asterisk (∗), Point of Attachment to Resin)

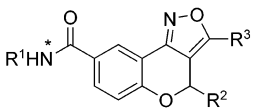
Part A: Solid-Phase



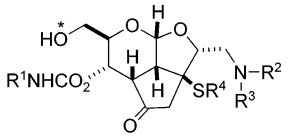
- Kamal, A. [191]
- 4 ex; 60-82%
- intramolecular acylation of aza-Wittig derived from arylazide and Ph_3P



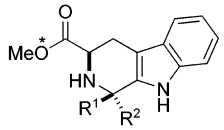
- Kamal, A. [191]
- 4 ex; 56-68%
- ring formation via intramolecular aza-Wittig



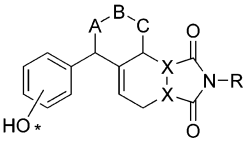
- GSK [70]
- 9 ex; 31-55%
- intramolecular nitrile oxide synthesis and 1,3-dipolar cycloaddition to alkynyl ether



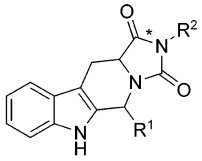
- Kubota, H. [213]
- 2500 members
- Pauson-Khand reaction on glycol template



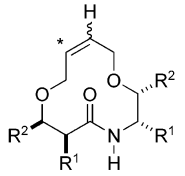
- Wu, C.-Y. [383]
- 15 ex; 88-99%
- microwave assisted Pictet-Spengler cyclization using novel soluble polymer support



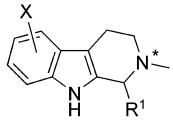
- Kwon, O. [218]
- 29,400 members
- X = CH, N



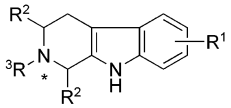
- Bonnet, D. [46]
- 12 ex; 15-44%
- N-acyliminium Pictet-Spengler reaction and cyclative cleavage



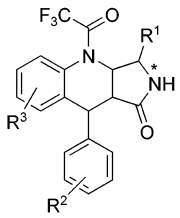
- Sasmal, S. [326]
- 2 ex
- RCM-based cyclo release; solution-phase ex given



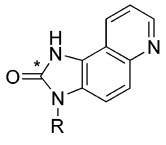
- Wu, T. Y. H. [386]
- *ca.* 10 ex; 10-20%
- from tryptamines immobilized via vinyl-sulfonylmethyl polystrene resin



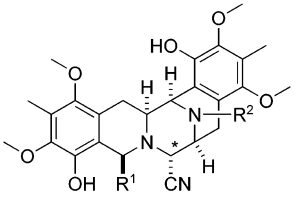
- Tularik [97]
- 800 members
- Pictet-Spengler synthesis using vinylsulfonylmethyl resin



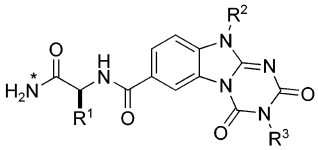
- Spaller, M. R. [333]
- 15 ex; 17-68%
- intramolecular aza-Diels-Alder reaction



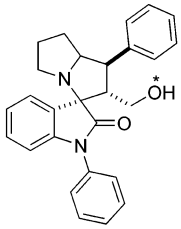
- Ermann, M. [122]
- 17 ex; 0-57%
- from resin-bound 5-amino-6-nitroquinoline, NO_2 reduction, optional reductive amination then intracyclative cleavage



- Myers, A. G. [266]
- 23 members
- 10-step sequence



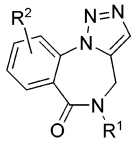
- Klein, G. [207]
- 17 ex; good purity
- from resin-bound 5-fluoro-3-nitrobenzamide



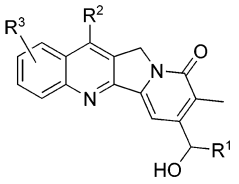
- Ganguly, A. K. [134]
- 1 ex; good purity
- 3 component condensation

Table 10. (Continued)

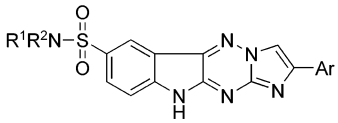
Part B: Solution-Phase



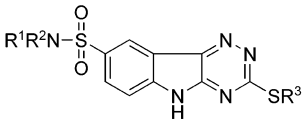
- Hoffmann-La Roche [353]
- 66 members
- intramolecular alkyne-azide 1,3-dipolar cycloaddition reaction



- Fluorous Tech. [409]
- 560 members
- fluorous mixture synthesis

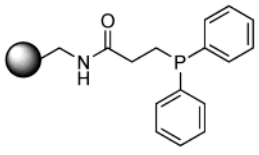


- Chem. Diversity [181]
- 12 ex; 26-64%
- condensation of 5-sulfamoyl isatin with 1,2-diamine

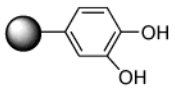


- Chem. Diversity [181]
- 11 ex; 16-72%
- condensation of 5-sulfamoyl isatin with thiosemicarbazide then NaOH and S-alkylation

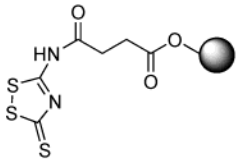
Table 11. Polymer-Supported Reagents and Scavengers



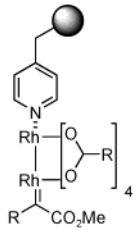
- Barthelemy, S. [21]
- intramolecular aza-wittig reaction



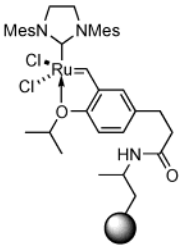
- Yang, W. [398]
- immobilization of boronic acids



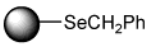
- Hybridon [410]
- sulfur transfer reagent



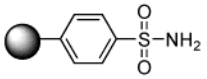
- Nagashima, T. [268]
- catalytic asymmetric cyclopropanation



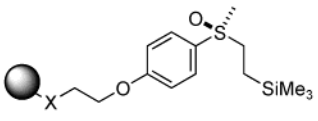
- Connon, S. J. [96]
- olefin metathesis in methanol and water



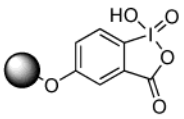
- Huang, X. [174]
- stereocontrolled synthesis of olefins and allyl



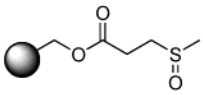
- Hinklin, R. N. [163]
- cleavage of *p*-methoxy benzyl ethers in presence of 0.1 equiv TfOH



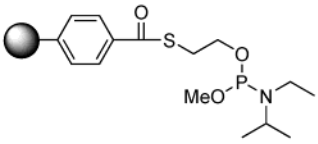
- Nakamura, S. [269]
- asymmetric conjugate addition then elimination to yield β-substituted α,δ-unsaturated esters



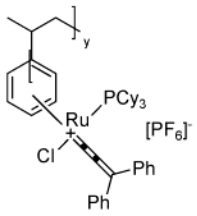
- Reed, N. N. [311]
- resin-bound IBX for oxidations



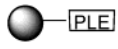
- Wyeth [91]
- recyclable resin-bound sulfoxide for Swern oxidation



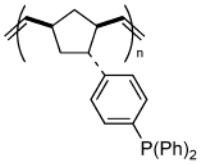
- Parang, K. [287]
- phosphorylation of alcohols



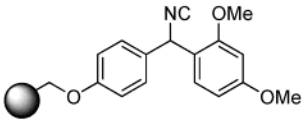
- Akiyama, R. [9]
- ring closing metathesis



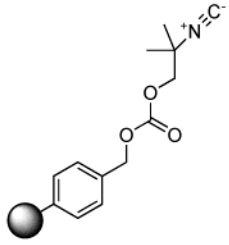
- Baxendale, I. R. [25]
- polymer-supported pig liver esterase



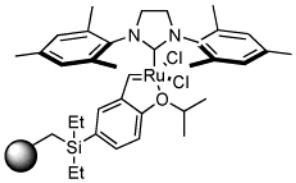
- Arstad, E. [15]
- high loading (2.5 mmol/g ROMP-gel supported triphenylphosphine



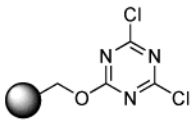
- P&G Pharm. [72]
- universal Rink-isonitrile for Ugi reactions



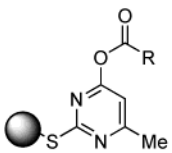
- Array Biopharm. [198]
- universal isonitrile for Ugi reactions



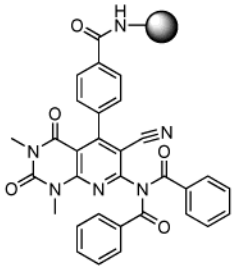
- Grela, K. [147]
- recyclable RCM catalyst



- BMS [242]
- acid chloride synthesis

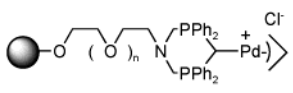


- Petricci, E. [293]
- amine acylation

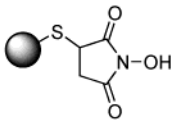


- ArQule [275]
- recyclable acylating reagent

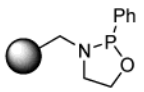
Table 11. (Continued)



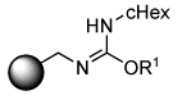
• Uozumi, Y. [361]
• Suzuki coupling in water



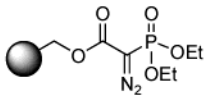
• Sumiyoshi, H. [344]
• carbamate synthesis



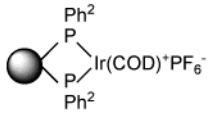
• Ley, S. V. [227]
• conversion of isothiocyanates to isocyanates for use in Ugi chemistry



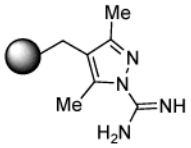
• Crosignani [102, 103]
• esterification of carboxylic acids



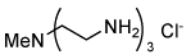
• Yamazaki, K. [394]
• resin-bound precursor for indole synthesis



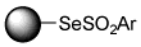
• Baxendale, I. R. [26, 27]
• isomerization of olefins (e.g., allylarylethers)



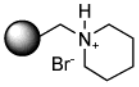
• Drager, G. [115]
• amidation of amines (guanidine synthesis)



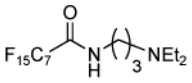
• Ghanem, N. [138]
• water soluble scavenger for anhydrides, acid chlorides, isocyanates



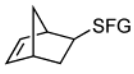
• Qian, H. [305]
• synthesis of acetylenic sulfones



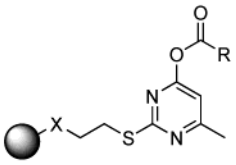
• Yadav-Bhatnagar, N. [393]
• monobromindation of diazoketones



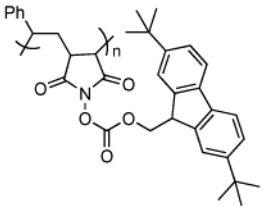
• Merck [233]
• one example of a set of fluorous-tethered amine bases



• Moore, J. D. [261]
• scavenger-ROMP-filter as homogeneous electrophilic scavenging (SFG = scavenging functional group)

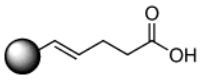


• Botta, M. [48]
• amine acylation

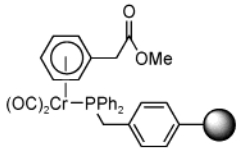


• Chinchilla, R. [83]
• Fmoc transfer reagent

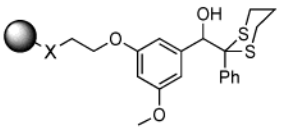
Table 12. Polymer-Supported Linkers



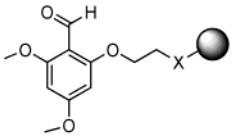
• ArQule [154]
• immobilization of amines via amide bond formation; release of amines with I_2 in THF/water (4:1)



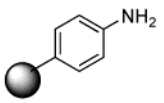
• Rigby, J. H. [314]
• π-arene chromium linker for C-C and C-O bond forming reactions



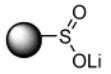
• Balasubramanian, S. [61]
• photolabile safety-catch linker for carboxylic acid attachment



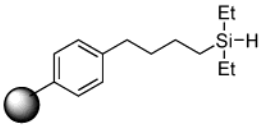
• Boas, U. [43]
• acid-sensitive linker for amide synthesis



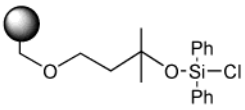
• Arseniyadis, S. [14]
• amine synthesis



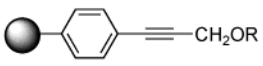
• Hwang, S. H. [178]
• traceless synthesis of pyrrole-2-carboxylates



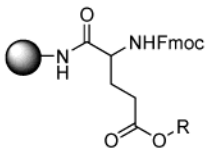
• Gu, W. [150]
• immobilizati of Ar-I via Pd-catalysis



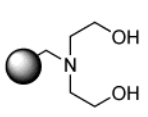
• Meloni, M. M. [257]
• immobilization of alcohols and phenols



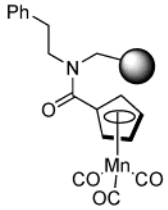
• Furst, M. [132]
• safety-catch linker for amines and carboxylic acids; activation release via CO_2 $(CO)_8$ and TFA; R = H, COCl



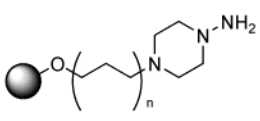
• Subra, G. [342]
• immobilization of alcohols as esters; cyclization-release upon Fmoc deprotection



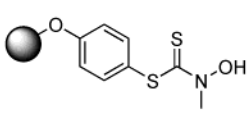
• Gravel, M. [145]
• immobilization of boronic acids



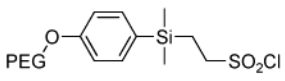
• Zhang, Z. [414]
• immobilization of olefins



• Lazny, R. [225]
• immobilization of ketones for alkylation

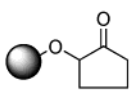


• Whitehead, D. M. [379]
• linker for urea synthesis

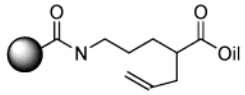


• Varray, S. [365]
• polymer-supported SES group for amine protection

Table 12. (Continued)

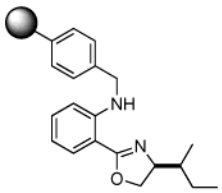


• McKerlie, F. [256]
• addition of organometallics the SmI_2 reduction to yield ketones

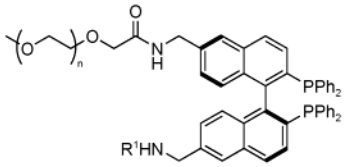


• ArQule [155]
• amides released as amines upon treatment with iodine in THF/water

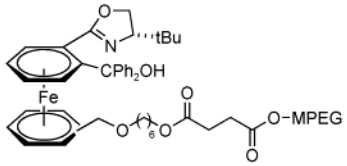
Table 13. Polymer-Supported Chiral Ligands



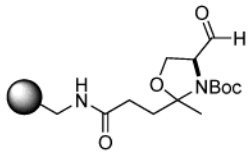
• Shaikh, N. S. [329]
• enantioselective addition of Et_2Zn to RCHO



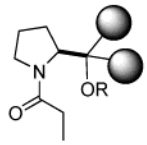
• Saluzzo, C. [325]
• eantioselective hydrogenation



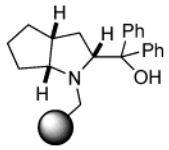
• Bolm, C. [44]
• eantioselective transfer of phenyl to RCHO



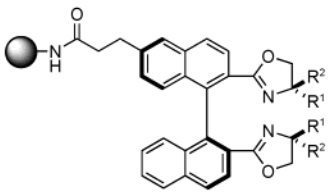
• Wills, A. J. [381]
• Garner aldehyde equivalent fo asymmetric synthesis



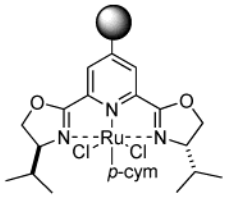
• Price, M. D. [301]
• chiral auxiliary for γ-butyrolactone synthesis



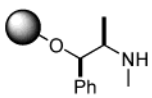
• Burguete, M. I. [56]
• catalyst for enantio-selective addition of Et_2Zn to RCHO



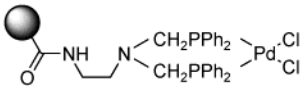
• Hocke, H. [165]
• asymmetric Wacker-type cyclization



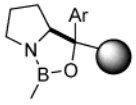
• Cornejo, A. [99]
• corresponding Ru complexes are catalysts for enantio-selective cyclopropanation



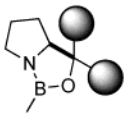
• Hutchison, P. C. [177]
• peudoephedrine linker for asymmetric alkylations



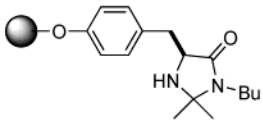
• Antebi, S. [12]
• dendrimer Pd catalyst for carbonylationof Ar-I



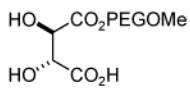
• Price, M. D. [302]
• enantioselective ketone reduction



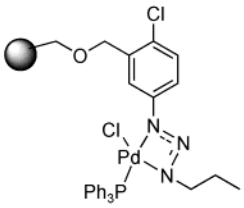
• Price, M. D. [302]
• enantioselective ketone reduction



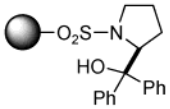
• Benaglia, M. [33]
• enantioselective Diels-Alder catalyst



• Guo, H. [153]
• Sharpless epoxidation catalyst



• Brase, S. [49]
• Suzuki and Sonogashira catalyst



• Zhao, G. [411]
• enantioselective reduction of β–ketosulfones

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