Review

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Reviews

Comprehensive Survey of Combinatorial Library Synthesis: 2000

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Publications from both academic and industry on the synthesis and application of chemical libraries continued at a rapid pace in 2000. The total number of libraries cited was 284, comparable to the 297 figure for 1999, bringing the cumulative total to over 1250 libraries published since 1992.[1] Of the 284 new libraries, 25% were accompanied by biological screening results, 82% were prepared on solid phase, and 65% came from academic laboratories.[2−258] This is the first year that published library output from academia outpaced that from industry. There were a number of significant advances for the year with respect to design strategy, solid- and solution-phase methodology, and the discovery of biologically active agents. Three independent research groups disclosed "ligand dimerization" libraries yielding novel c-Src kinase inhibitors,[141] adrenergic receptor agonists,[257] and agents active against vancomycin-resistant bacterial strains.[168] The development of tetrafluorophenol (TFP)-activated resins was reported.[76,208] This new class of amine derivatizing reagent, which represents a stable and convenient source of reactive acid and sulfonyl chlorides, has rapidly gained popularity and is commercially available from several vendors. In a joint program between Pharmacopeia and Berlex Biosciences, potent in vivo active inhibitors of inducible nitric oxide synthetase (iNOS), an important but previously intractable molecular target, were discovered from an 8649-member library of imidazolylpyrimidines.[149] Finally, Ontogen Corporation reported that OC144-093, a P-glycoprotein modulator, was tested in man.[254] The diarylimidazole lead structure emerged from a solid-phase discovery library and was optimized by solution-phase chemistry. This is the second publicly known example (Agouron's rhinoviral 3C-protease inhibitor being the first example)[259] of a library compound, or derivative thereof, that has entered clinical trials.

In keeping with previous years' format,[1] libraries are divided into two major categories: those that have been evaluated against a molecular target and whose biological results are reported and those that have no accompanying biological data. The screened libraries are further subdivided according to molecular target class: proteases (Table 1), nonproteolytic enzymes (Table 2), G-protein-coupled receptor (GPCR) agonists and antagonists (Table 3), non-GPCR ligands (Table 4), and cytotoxic and antiinfective agents (Table 5). Libraries without associated biological activity are subdivided according to construct type and mode of synthesis (solid-phase vs solution-phase): scaffold derivatization (Table 6), acyclic synthesis (Table 7), monocyclic synthesis (Table 8), bicyclic and spirocyclic synthesis (Table 9), and polycyclic and macrocyclic synthesis (Table 10). For each of the libraries listed in Tables 1−5, the name, size, affiliation (company or senior academic author), and generic library

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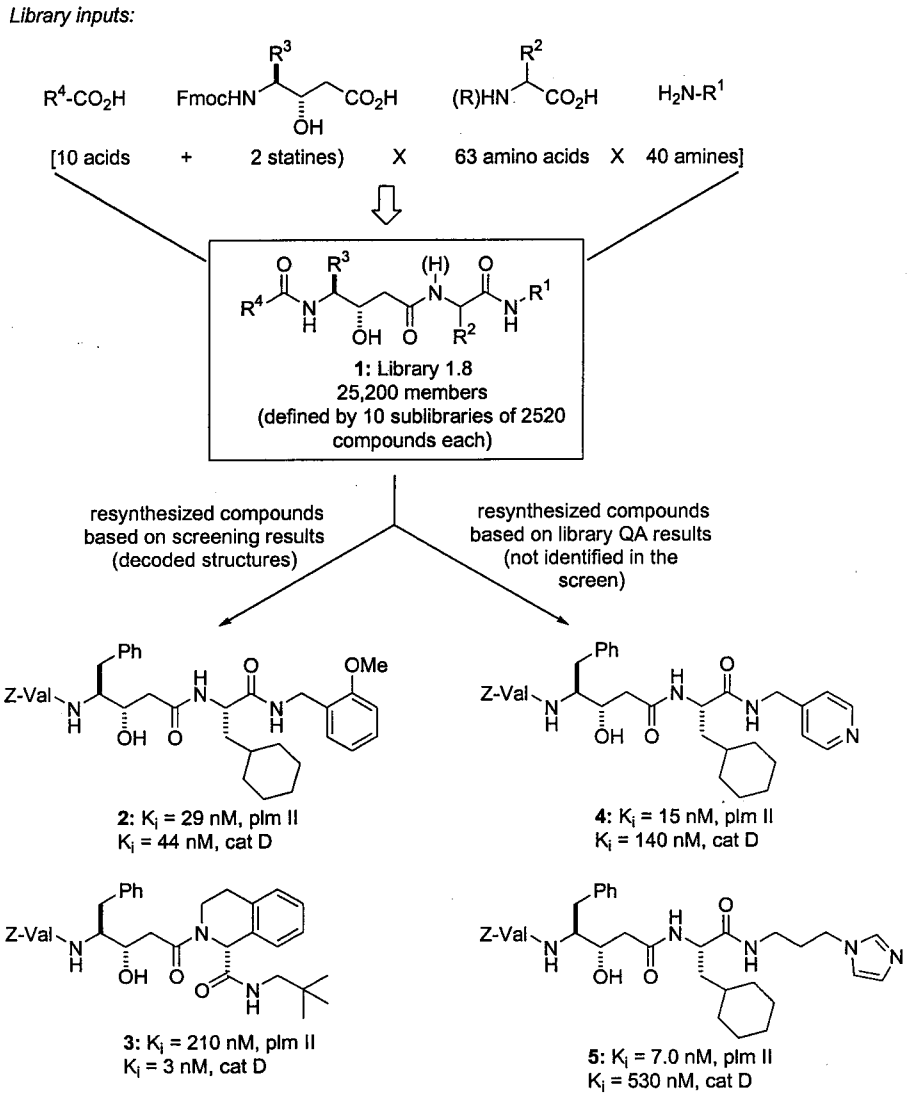


Figure 1. Statine amides as cathepsin D and plasmepsin II inhibitors.[57]

structure are given along with the most active library member identified from screening. The affiliation, number of examples, yield, and a brief synthesis description are provided for those libraries listed in Tables 6−10.

Biologically Active Libaries

The quality control (QC) of libraries prepared by split-pool synthesis has been a concern for many years. Unlike parallel synthesis in which discrete compounds are synthesized in milligram amounts and characterized by traditional methods, split-pool libraries contain mixtures of >10 000 compounds prepared in multifold redundancy utilizing millions of resin beads. The amount of compound per bead is typically <1 nM; hence, traditional characterization of library compounds is impossible. Historically, the QC of split-pool libraries is carried out indirectly by careful reaction optimization, extensive synthon profiling, and rigorous analysis of a handful of QC compounds. It is generally taken on faith that the "library rehearsal" is reproduced during the construction of a full library. It is highly desirable to know whether chemistry actually took place as planned and the assurance that putative compounds eluted from the beads are physically present in the wells of assay plates. As a unique solution to this problem, Pharmacopeia developed a statistical sampling protocol (library QA) to assess the overall fidelity of large encoded libraries and the performance of individual synthons.[57] Library QA is an analytical method in which beads, totaling 10×, the largest synthon set (typically 500 beads per library), are randomly retrieved, compound detached, and the bead decoded. The presence or absence of a discrete compound is established by comparing its molecular weight as predicted by its tag decode to the molecular weight of the cleaved compound as determined by LC/MS. In a proof of principle library of 25 200 statine amides (library 1.8, Figure 1), the 1900 beads subjected to QA analysis revealed an overall 85% positive confirmation rate, indicating that only ∼21 400 compounds were actually synthesized. Library 1.8 was screened against two aspartyl proteases, cathepsin D and plasmepsin II. Some 200 active beads were decoded, and a synthon frequency analysis indicated a preference for

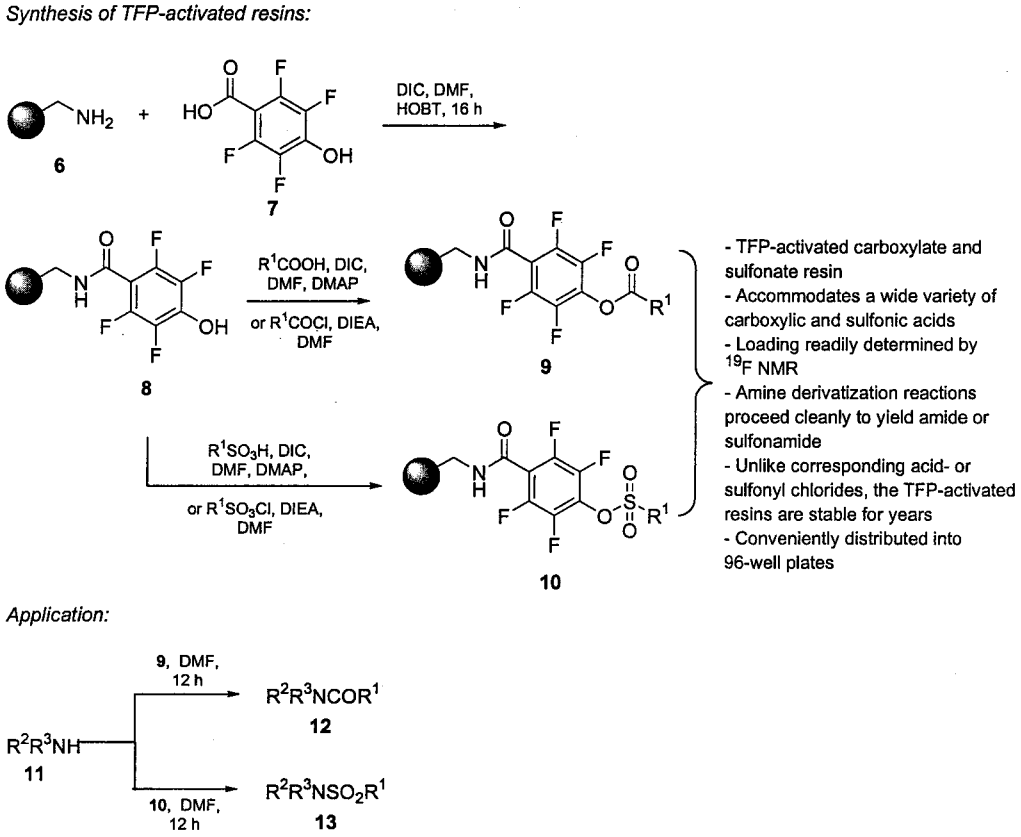


Figure 2. Synthesis and application TFP-activated resins for amine derivatization.[208]

hydrophobic synthons at the R^1 and R^2 positions. The library appeared to be more active against cathepsin D than plasmepsin II. Compounds **2** and **3** nicely represent the nascent structure−activity relationship (SAR) that emerged from screening. Library QA, however, revealed hydrophobic synthons as strongly performing synthons, while hydrophilic synthons (particularly at R^1) displayed mediocre or poor performance. Compounds containing hydrophilic R^1 and R^2 synthons make up the majority of the 15% unconfirmed QA results. Because these compounds were underrepresented in the library, their full biological activity would not be detected in the screen. For this reason compounds **4** and **5** were synthesized. These compounds are analogues of **2** (library members) but were not found in decoded structures. Introducing basic polar residues at R^1 led to a remarkable increase in the inhibitory potency and selectivity for plasmepsin II verses cathepsin D. In the absence of corroborating QA data, this salient SAR information would have been lost.

Salvino and co-workers at Rhone-Poulenc Rorer (now Aventis) developed a novel set of tetrafluorophenol (TFP)-activated resins for amine derivatization (Figure 2). TFP resin **8** is readily prepared by coupling 4-hydroxy-2,3,5,6-tetrafluorobenzoic acid **7** to amine polystyrene resin **6**. Resin **8** is activated by either acylating (**8** → **9**) or sulfonylating (**8** → **10**) the phenolic OH with carboxylic or sulfonic acids, their anhydrides or acid chlorides. Resins **9** and **10** are suspended in DMF and reacted with an amine nucleophile to cleanly provide the corresponding amide or sulfonamide derivative (**11** → **12**, **13**). The major advantage of using the TFP-activated resins over other known activated resins is that ^{19}F NMR conveniently determines loading. This is important because it allows the amine to be accurately used as a limiting reagent, thus negating the need to scavenge excess amine (consumed) or acylating/sulfonylating reagent (remains resin-bound). A wide variety of carboxylic and sulfonic acids may be loaded onto the resin, creating a "reagent kit" which can be used on demand for a derivatization campaign. Activated TFP resins may be kept for years without decomposition. By simple distribution of TFP resins **8** and **9** into 96-well plates, suspension of the resin in DMF, and addition of a limiting amount of amine, hundreds to thousands of amides and sulfonamides can be rapidly generated. The derivatives are sufficiently pure (>85%) for direct evaluation in biological screens. By way of application, TFP-activated sulfonate resins were used to further delineate the SAR in a series of factor Xa inhibitors (Figure 3).[76] Library 1.10, composed of 52 discrete compounds derived from the reaction of the amine set **16**−**19** with resin **10**, furnished several submicromolar inhibitors including **21**: $IC_{50} = 15$ nM.

MAP kinase p38 is a putative mediator of cytokine signaling. SmithKline Beecham's (now GlaxoSmithKline) pioneering efforts in this area identified pyridylimidazoles **22** as agents that disrupt cytokine signaling in cells (Figure 4). Subsequently, Vertex reported ureas **23** and **24** as potent p38 kinase inhibitors. During a screening program, research-

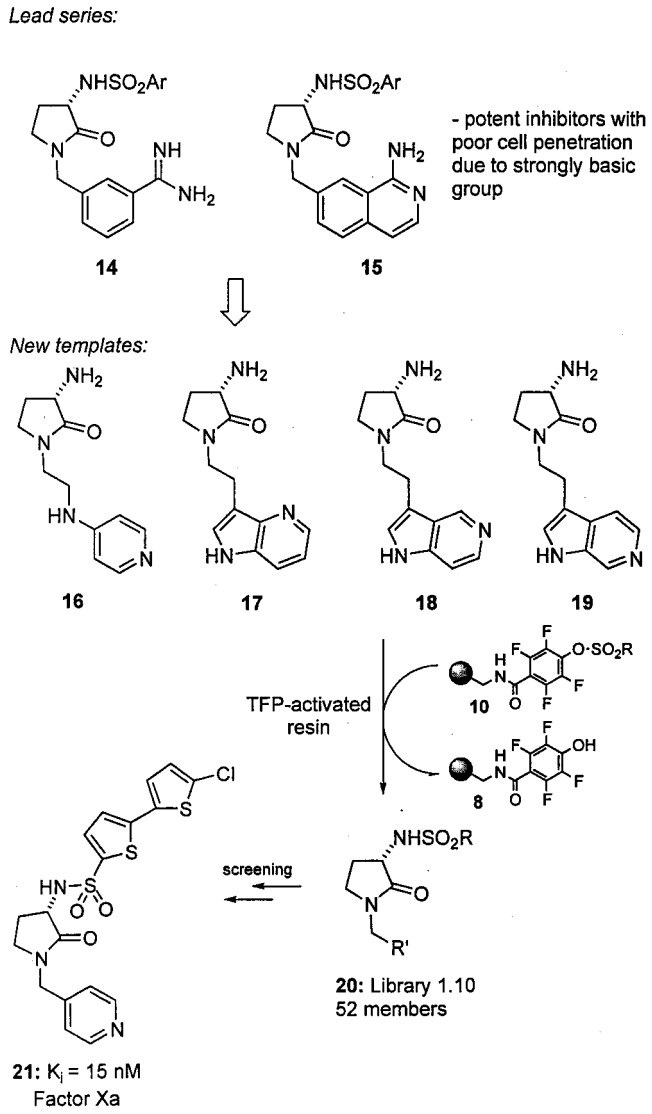


Figure 3. Factor Xa inhibitors via TFP-activated sulfonate esters.[76]

ers at Bayer discovered pyrazole urea **25** as a reversible p38 kinase inhibitor.[60,61] A parallel library (library 2.1) of over 1000 analogues of **25** was generated to develop SAR around the lead structure. The solution-phase synthesis was achieved by reacting heterocyclic amines **26** with aryl isocyanates **27** in DMF at 80−95 °C for 18 h. Instrumentation used in the synthesis included a Gilson 215 robotic liquid handler and a J-KEM reaction block. Heterocyclic amines (aminopyrazoles, -isoxazoles, -thiadiazoles, and others) were derived from α-cyanoketones and synthesized in bulk as separate templates. The biological evaluation of the library compounds revealed a rather steep SAR for the class. Increase in affinity was only observed upon replacing the *N*-methyl group in **25** with a phenyl ring as in **32**−**35**. Although computational analysis of library 2.1 indicated the compounds were druglike in terms of molecular weight, clogP, and satisfying Lipinski rules, the vast majority of the compounds were water-insoluble. The exception was aniline **34** (solubility in water is 594 μg/mL), some 4-fold more potent than lead **25**. No compounds were reported in which the urea nitrogen atoms were alkylated or the urea linkage was replaced by classical bioisosteres.

Ellman conceived of "combinatorial target-guided ligand assembly" as a novel method for identifying ligands of biological targets in the absence of any mechanistic or structural information about the target, or a preexisting pharmacophore (Figure 5).[141] This is accomplished by screening a set of molecules containing a common chemical linkage group and then tethering together the subset of molecules that bind to the target of interest. Tethering or dimer formation occurs through the common chemical linkage group. As a proof of concept, a collection of ca. 300 *O*-methyloximes **38**, derived from *O*-methylhydroxylamines **37** and aryl aldehydes **36** in DMSO, were screened against c-Src tyrosine kinase. Some 66 oximes were identified displaying >70% inhibition at a screening concentration of 0.5 M. Notable examples of the active oximes found include **39** and **40**. The corresponding aldehydes (e.g., **42** and **43**) of the weakly binding oxime ethers were combined in library 2.2 by reacting the aldehydes with mixtures of bis-hydroxylamines **41** to give all possible bis-oxime dimer permutations **44**. When library 2.2 was screened against c-Src tyrosine kinase, an intriguing SAR was found with activity highly dependent on the length and structure (acyclic or cyclic) of the tether and on the specific aldehyde. Remarkably, bis-oxime **45** was identified as a 64 nM inhibitor of the enzyme and possessed excellent selectivity over other tyrosine kinases (Fyn, Lyn, Lck). This methodology holds out the possibility of finding ligands against other hitherto recalcitrant targets such as phosphatases and protein−protein interactions.

Nicolaou reported another library dimerization strategy dubbed "target-accelerated combinatorial synthesis". In this approach, library building blocks are covalently ligated (dimerized) in the *presence* of their molecular target. Capturing the "preorganized assembly" will invariably lead to enhanced potency of the newly created dimers vs their monomeric starting materials. In a fascinating demonstration of this concept, the modified vancomycin building blocks **47** and the Ac_2-L-Lys-D-Ala-D-Ala substrate were combined in physiological buffer (Figure 6). Since the formation constant of vancomycin dimers ($K_d = 7 \times 10^2\ M^{-1}$) is much greater in the presence of the peptide target ($K_d \approx 10^4\ M^{-1}$), it was anticipated (and verified by experiment) that the target-bound dimer assembly would ligate more quickly than the unbound dimer. Disulfide formation and olefin metathesis were the ligating reactions used in this dimerization process. Antibacterial activity of some 30 vancomycin dimers (library 5.13) strongly correlated reaction rate enhancement with biological activity.

As a final example of bivalent ligand libraries, a series of yohimbine dimers **52** were prepared and evaluated at the human α_{2a} and α_{2b} adrenergic receptors (library 3.3, Figure 6).[257] Yohimbine **50** is a potent antagonist of the α_{2a} (K_i =

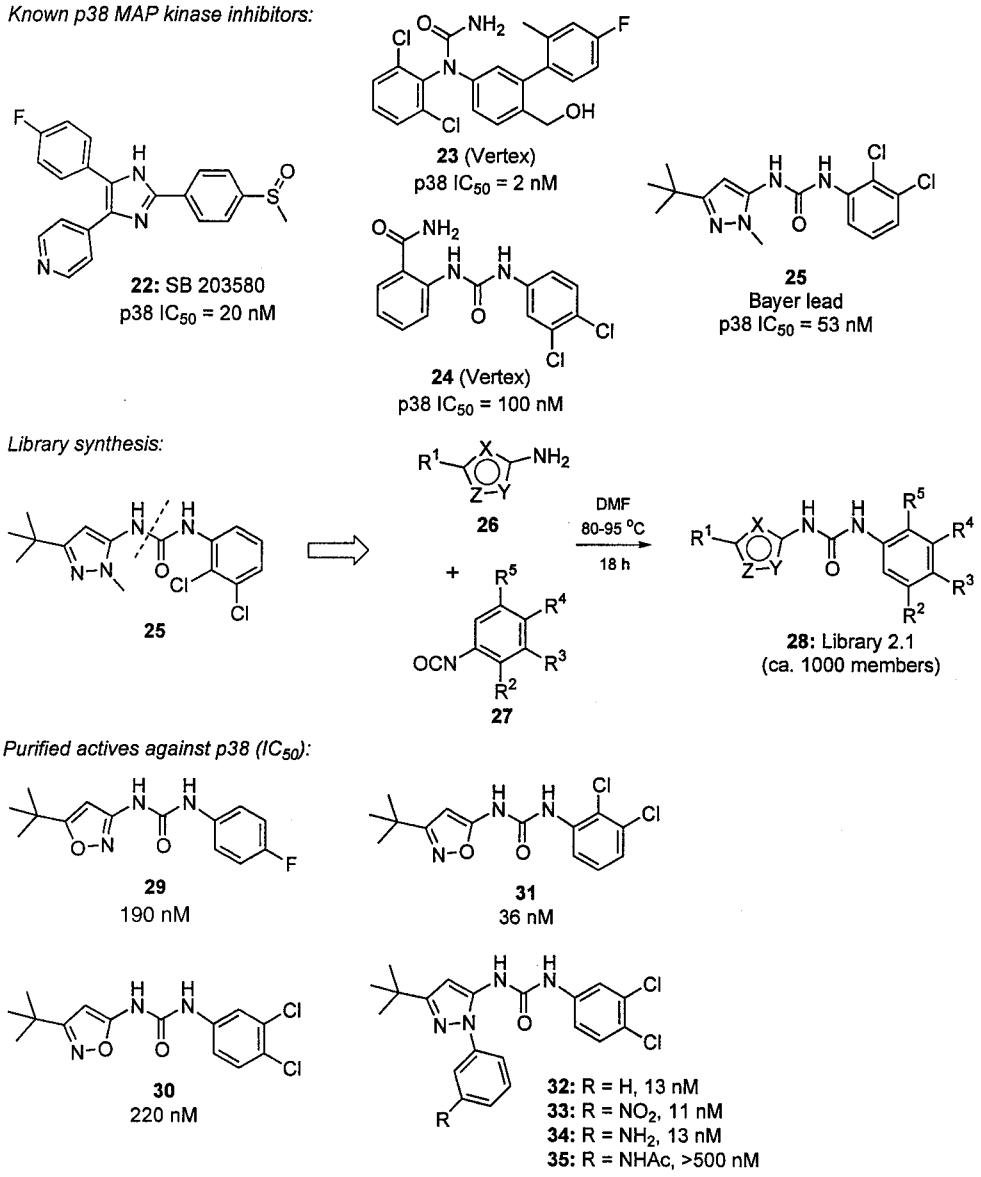


Figure 4. p38 MAP kinase inhibitors.[60,61]

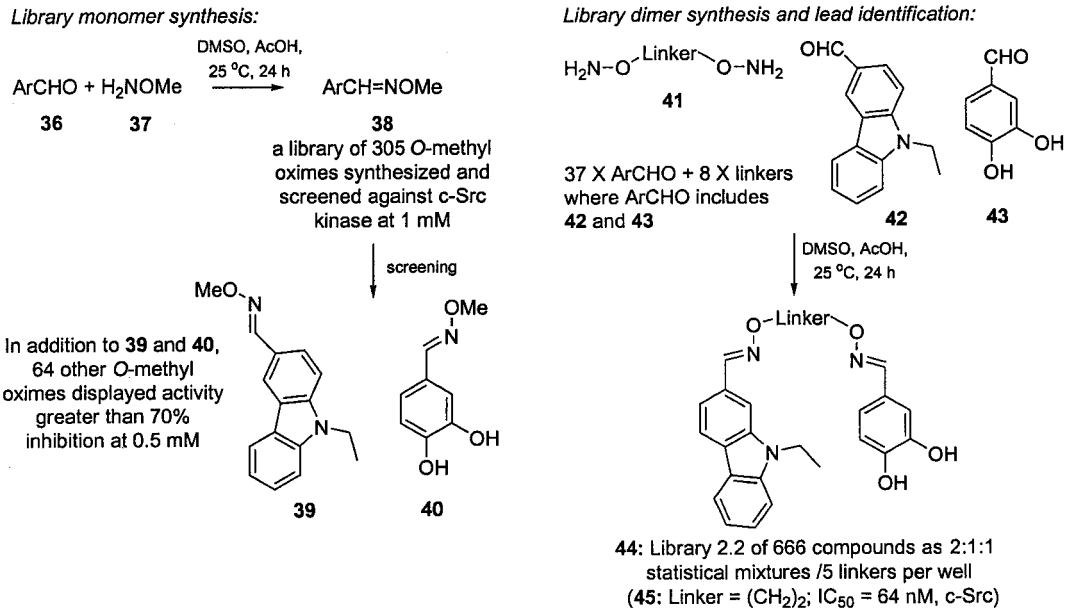


Figure 5. Ellman's "target-guided ligand assembly" and the identification of c-Src kinase inhibitors.[141]

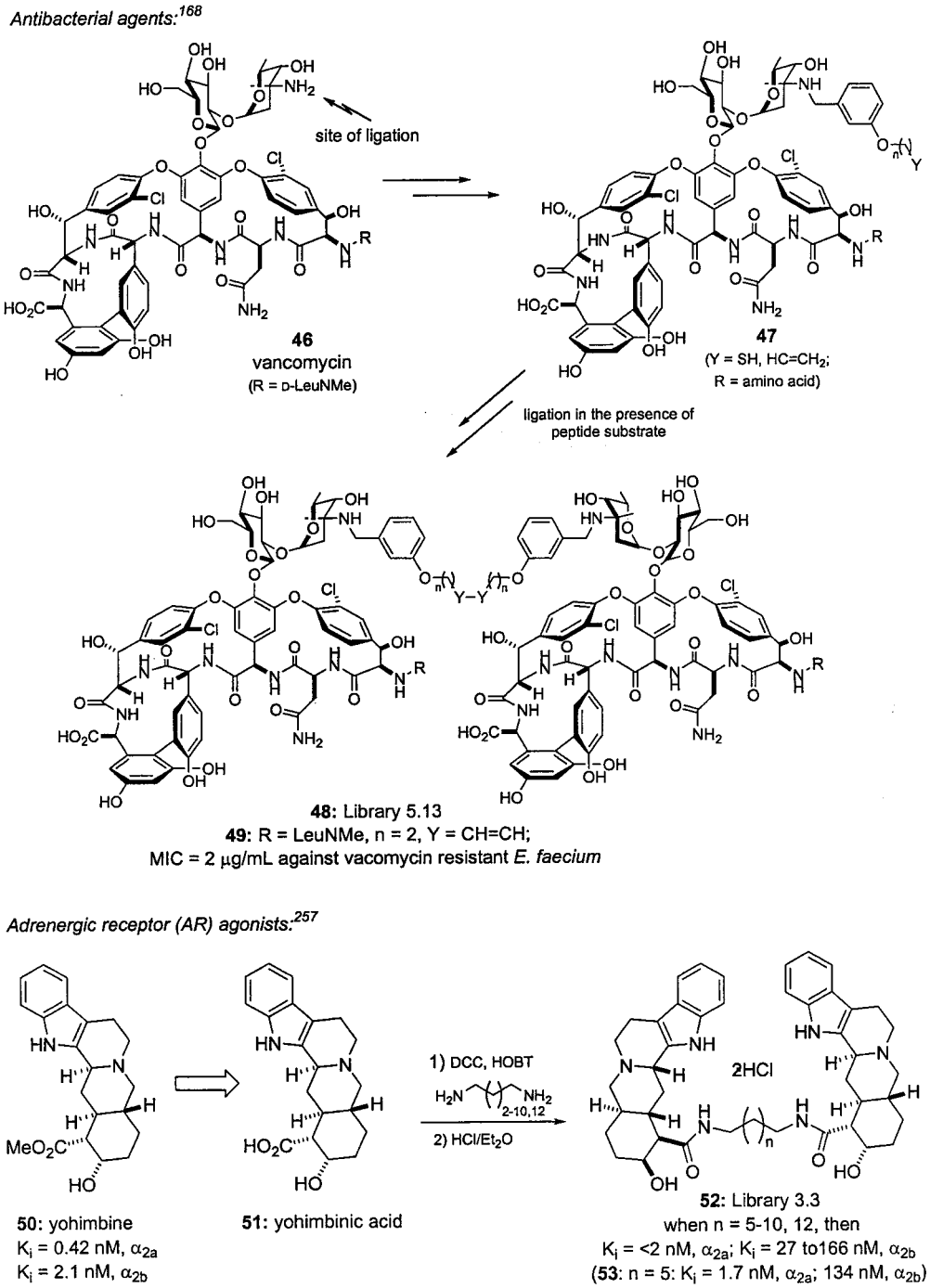


Figure 6. Further examples of ligand dimer libraries.

0.42 nM) and α_{2b} (K_i = 2.1 nM) adrenergic receptors (α_{2a}/α_{2b} = 4.8). Despite the large number of yohimbine analogues that have been made over the years, potent selective antagonists have not been described. The rationale for creating yohimbine dimers is based on the success of the bivalent ligand strategy for developing selective high-affinity ligands of other receptor systems (opioid, serotonergic, growth factor). The enhanced activity of the ligand dimers may be a consequence of the bridging between either vicinal receptors or the pharmacophore binding site and another accessory site in the same receptor molecule. As in the case of the other two dimer libraries described above, the SAR was dependent on the length of the tether. In this specific instance, potent and highly selective α_{2a}-AR antagonists were identified from library 3.3, e.g., **52**, K_i = 1.7 nM α_{2a} with 123-fold selectivity vs α_{2b}.

A family of naturally occurring 2,2-dimethylbenzopyrans is the active constituent in Cubé resin, a century old botanical insecticide (Figure 7). The mechanism of action is the disruption of oxidative phosphorylation (ATP synthesis), which occurs through inhibition of mitochondrial NADH/ubiquinone oxidoreductase, one of a cascade of enzymes operating in the electron-transport system. As seen by Nicolaou, the common structural feature or pharmacophore

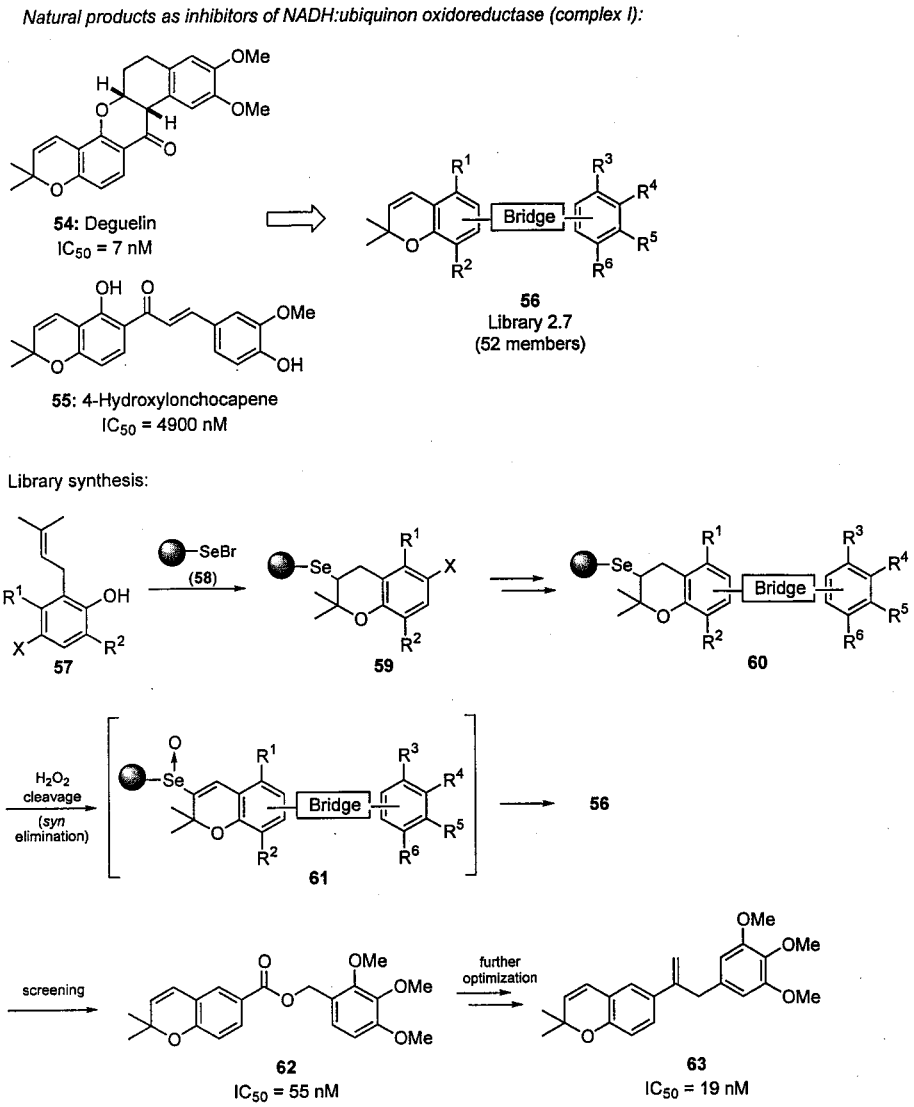


Figure 7. Nicolaou's natural product-like benzopyran libraries.[171]

found throughout this class is a benzopyran nucleus with a pendant electron-rich aromatic ring.[171] By use of these natural products as a guide, a 52-member (library 2.7) of 2,2-dimethylbenzopyrans with a tethered (or bridged) aromatic ring was screened for oxidoreductase activity. Library 2.7 is a subset of a several-thousand-member combinatorial library of 2,2-dimethylbenzopyrans prepared previously by the Scripps group. The salient methodology for constructing these compounds is the so-called "cycloloading" strategy, a clever solid-phase variant of the intramolecular seleno-etherification reaction.[169−172,174,175] In this chemistry, selenyl bromide resin **58**[170] is reacted with *o*-phenylphenols **57**, which undergo cycloloading, i.e., simultaneous cyclic ether formation and resin attachment. Because resin **59** is stable to Lewis and Bronsted acids, organometallics, reducing reagents, bases, electrophiles, HF pyridine, Pd and Ru catalysts, and many other reagents, broad structural diversification of the benzopyran nucleus is possible. Cleavage occurs upon selenoxide formation (treatment with *m*-CPBA or H_2O_2) and syn elimination to yield 3,4-dihydrobenzopyrans. The resin is not compatible with sulfide-containing synthons unless sulfone products are desired. Several actives, for example, **62** (IC_{50} = 55 nM), were identified from library 2.7, and biological activity was highly dependent on the bridging element. Five followup libraries were then synthesized to define the SAR and to optimize potency, ultimately yielding a family of potent 2,2-dimethylbenzopyran inhibitors (**63**: IC_{50} = 19 nM) with IC_{50} values against NADH/ubiquinone oxidoreductase in the range 18−55 nM.

Inducible nitric oxide synthetase (iNOS) is one of three enzyme isoforms that catalyzes the NAPDH-dependent oxidation of L-arginine to NO• and citrulline. Functional iNOS is a heterodimer comprising oxidoreductase and oxygenase monomeric units. Under normal physiological conditions, NO• production is highly regulated, functioning as a reversible, local signal transduction molecule. In disease states where release of reactive NO• is unrestrained, non-specific tissue damage results. Since the discovery of the enzyme over a decade ago, there has been much interest in finding specific iNOS inhibitors because such agents are

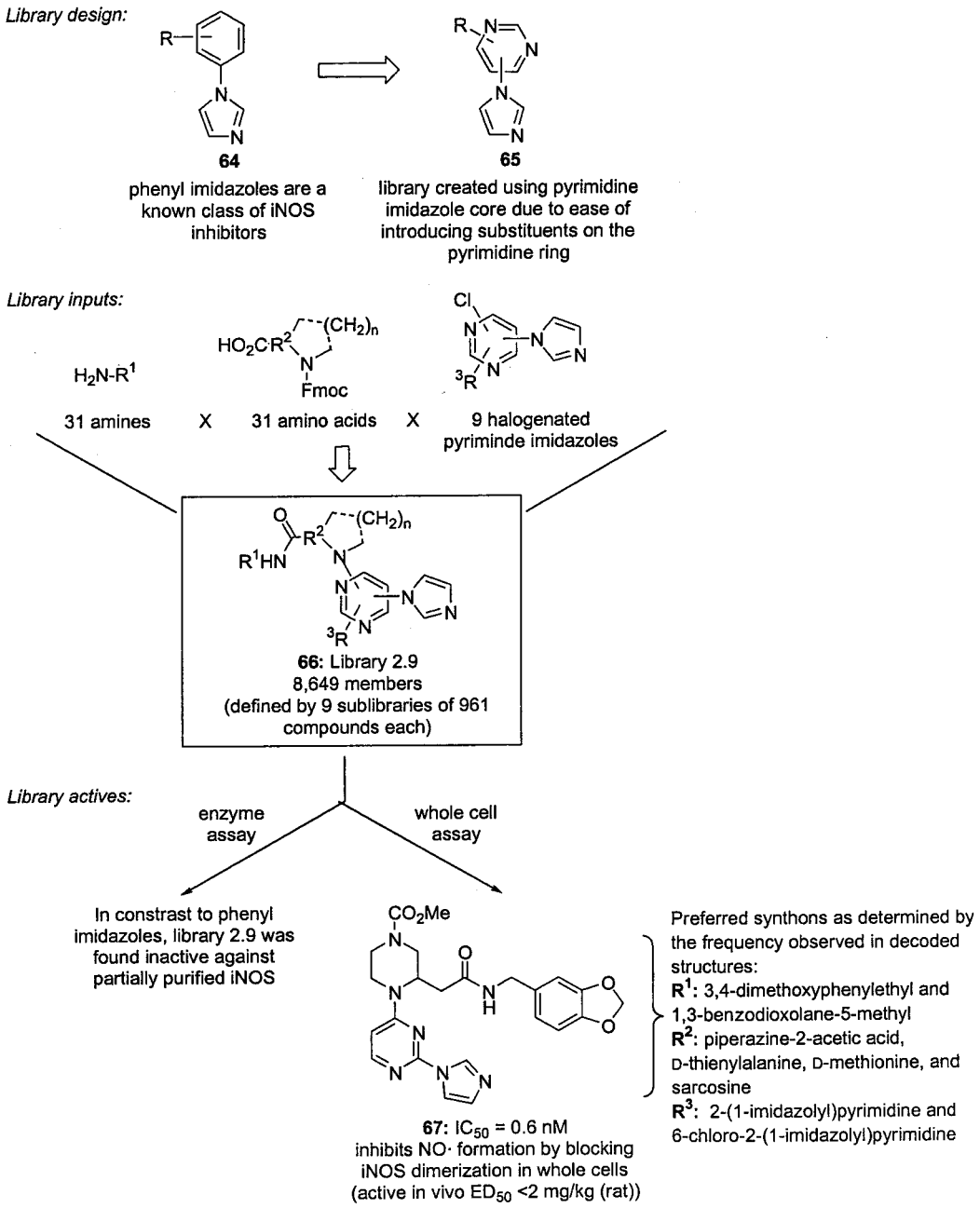


Figure 8. iNOS inhibitors from Pharmacopeia's encoded library.[149]

thought to have broad therapeutic potential in treating a variety of inflammatory and autoimmune pathologies. Mechanism-based approaches to the design of iNOS inhibitors by modifying its substrate (arginine) or product (citrulline) have met with limited success. Phenylimidazoles **64** (Figure 8), a known class of iNOS inhibitors possessing low micromolar activity and modest selectivity, were the inspiration for creating an encoded library (library 2.9) of substituted pyrimidineimidazoles **65**.[149] Core **65** permitted facile introduction of substituents into the pyrimidine ring, which was believed to be important in enhancing the potency and selectivity of the literature series **64**. The library was constructed on a photolabile linker by first generating a set of 961 fully encoded amino acid amides and then capping the amino group with nine reactive chloro-substituted pyrimidineimidazoles. The resulting 8649-member library was initially screened against the iNOS enzyme, but no appreciable activity was observed. However, NO• production in cytokine-stimulated intact cells (human A-172 cells) was blocked in three of nine sublibraries. A total of 53 compounds having >60% inhibition at an inhibitor screening concentration of 200 nM were decoded (hit rate of 0.6%). Strong preferences were observed for the R^1, R^2, and R^3 synthons (see summary in Figure 8). One of the more potent cell-based inhibitors was compound **67**, IC_{50} = 0.6 nM. Biochemical studies revealed that **67** caused accumulation of iNOS monomers in intact cells. The exact mechanism of action was understood in terms of an iNOS-inhibitor **67** crystal structure. The imidazole nitrogen of **67** binds to the heme and allosterically perturbs the molecular interactions

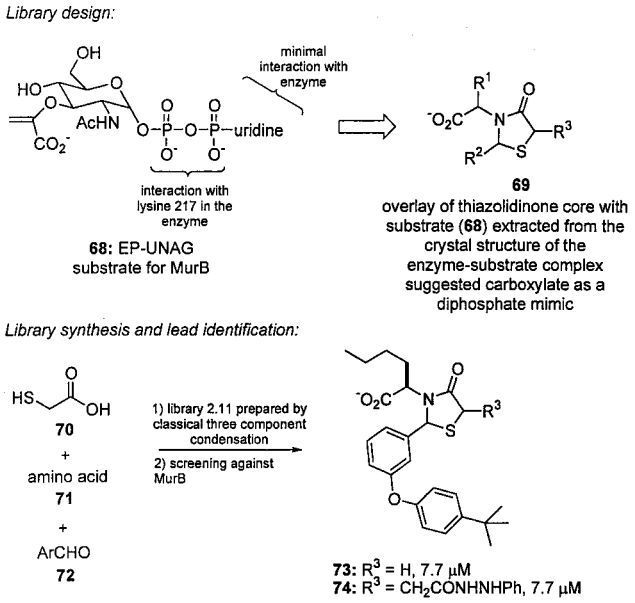


Figure 9. 4-Thiazolidinones as inhibitors of bacterial enzyme MurB.[4]

at the oxidoreductase−oxidase dimer interface, preventing functional iNOS heterodimer formation. Compound **67** was active in vivo with an ED_{50} less than 2 mg/kg in a rat model of endotoxin-mediated systemic iNOS induction. The research project was a collaborative effort between Berlex Biosciences and Pharmacopeia.[149]

Bacterial enzyme MurB is one of a cascade of enzymes required for the biosynthesis of peptidoglycan, an essential cell wall component of both Gram-positive and Gram-negative bacteria. Bacterial MurB carries out the reduction of enol pyruvyl uridine diphosphate *N*-acetylglucosamine (EP-UNAG, **68**) to uridine diphosphate *N*-acetylmuramic acid (UNAM), an intermediate in cell wall assembly. MurB is unique to prokaryotic cells, and inhibitors of this enzyme represent potential antibacterial agents, active against a broad range of pathogens. An X-ray crystal structure of MurB with its bound substrate **68** was used as a starting point for small-molecule inhibitor design (Figure 9). Researchers at Bristol Myers Squibb noted that the thiazolidinone core **69** over-

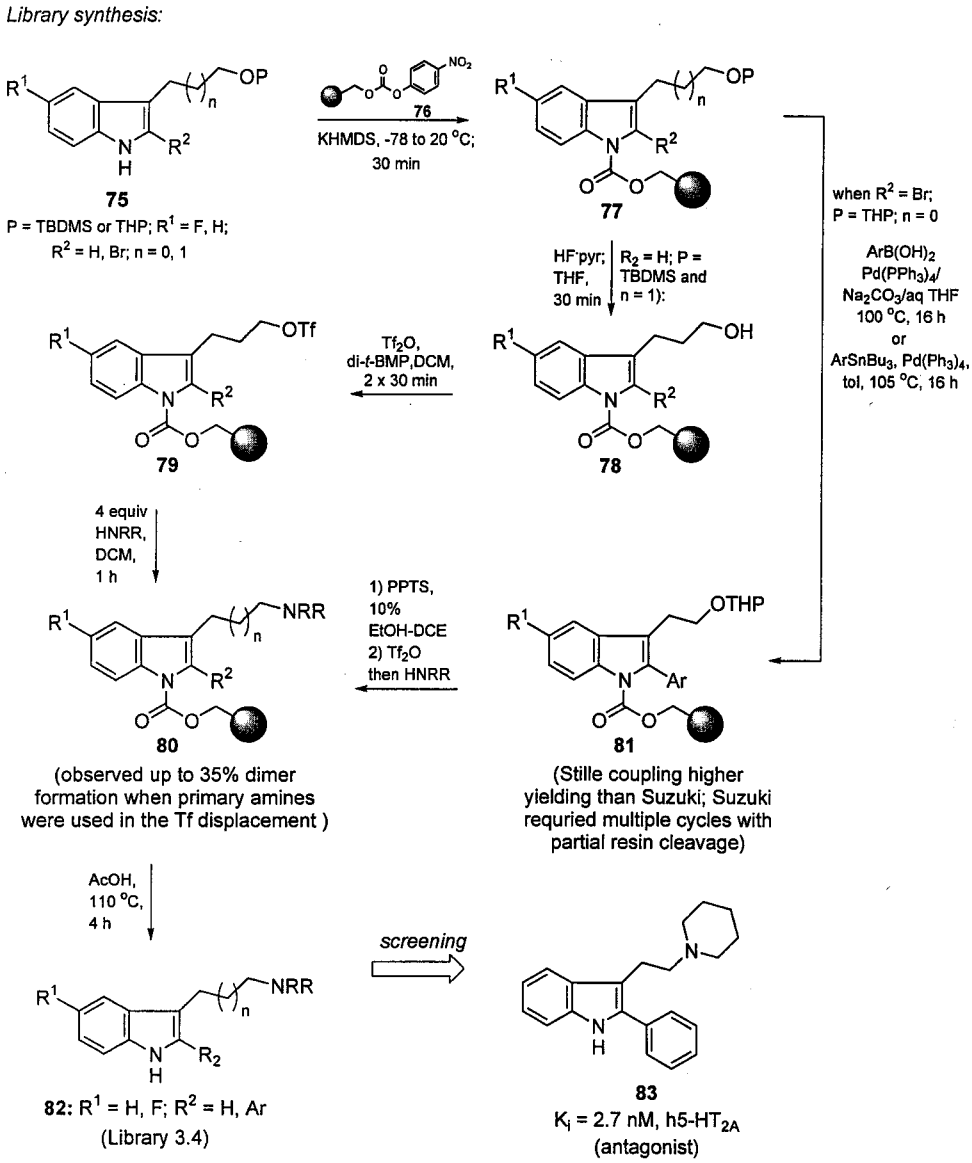


Figure 10. Indole derivatives via carbamate linker on solid support yielding h5-HT_{2A} antagonists.[220]

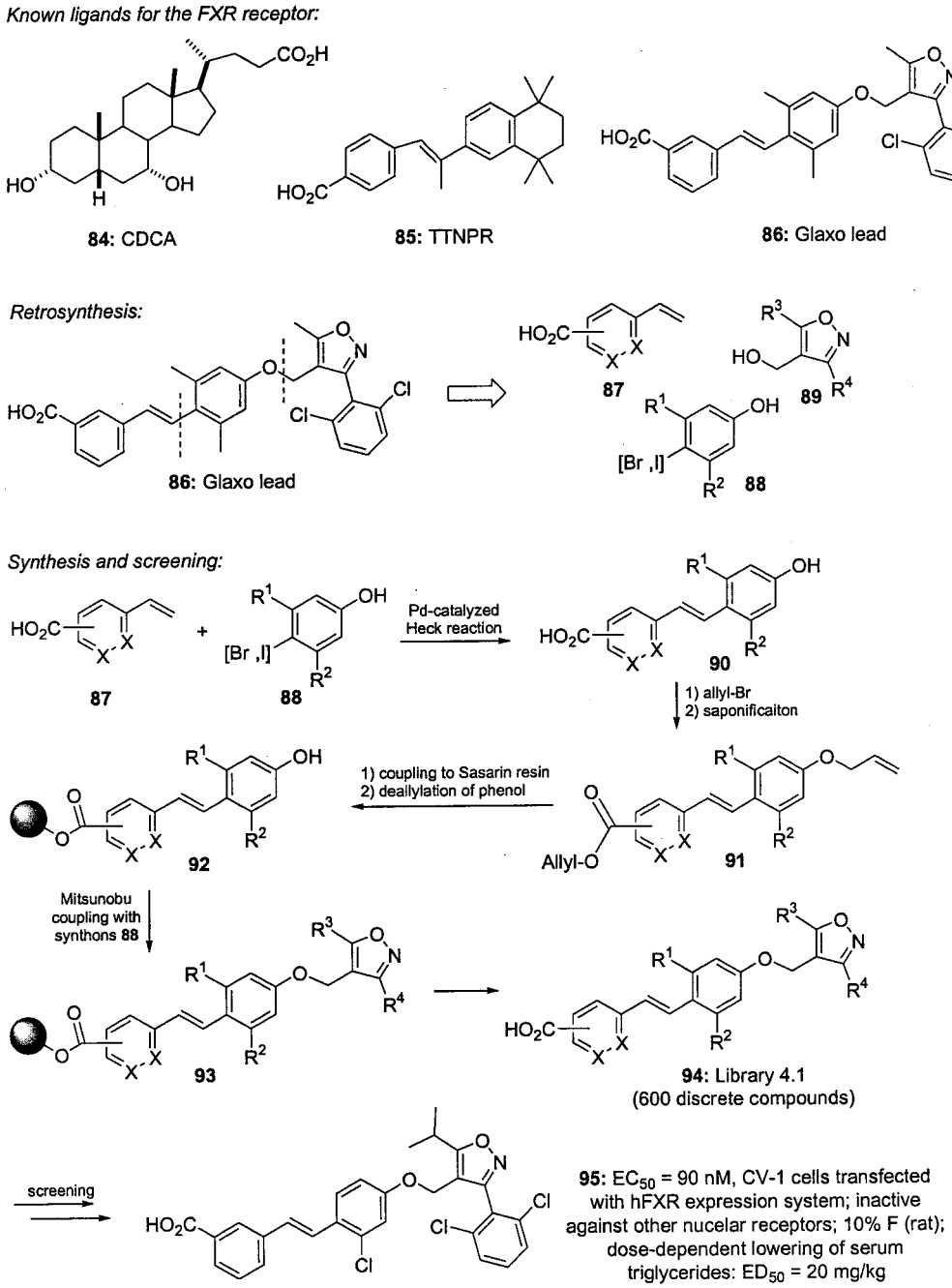


Figure 11. Orphan nuclear receptor FXR agonists.[139]

lapped nicely with enzyme-bound **68**.[4] The R^1 and R^2 side chains in **69** extend to occupy the region of glucosamine binding with the negatively charged carboxylic acid mimicking the ionic diphosphate. In their overlay, the side chain R^3 extended over the uridine base, and because of the lack of strong, definable contacts of this base with the enzyme, the R^3 side chains in **69** were not postulated to be particularly important for binding. As a result, library 2.11 of 4-thiazolidinones was prepared. The classical protocol of condensing thioglycolic acid **70**, an amino acid **71**, and an aromatic aldehyde **72** in one pot was used in library synthesis. Multiple sublibraries defined by **72** were likely prepared, but the screening results of only 21 compounds were given as derived from a 3 (**70**) × 7 (**71**) × 1 (**72**) matrix. The SAR obtained from screening indicated that a bulky R^2 aryl group, e.g., *tert*-butyl-*m*-phenoxyphenyl, was essential for activity (when R^2 = phenyl, no activity was observed). D-Amino acids possessing hydrophobic aliphatic side chains were the preferred groups at R^1. Consistent with the original hypothesis, R^3 appeared to be the least important for activity because R^3 = H and hydrazone possessed identical affinity. Thiazolidinones **73** and **74** are the first examples of small-molecule in vitro inhibitors of bacterial MurB.

Indoles arguably represent one of the most pharmaceutically important structural classes of compounds. Numerous solution- and solid-phase syntheses of the indole ring and its derivatives have appeared in the literature over the past 10 years. Merck has been particularly active in this area and

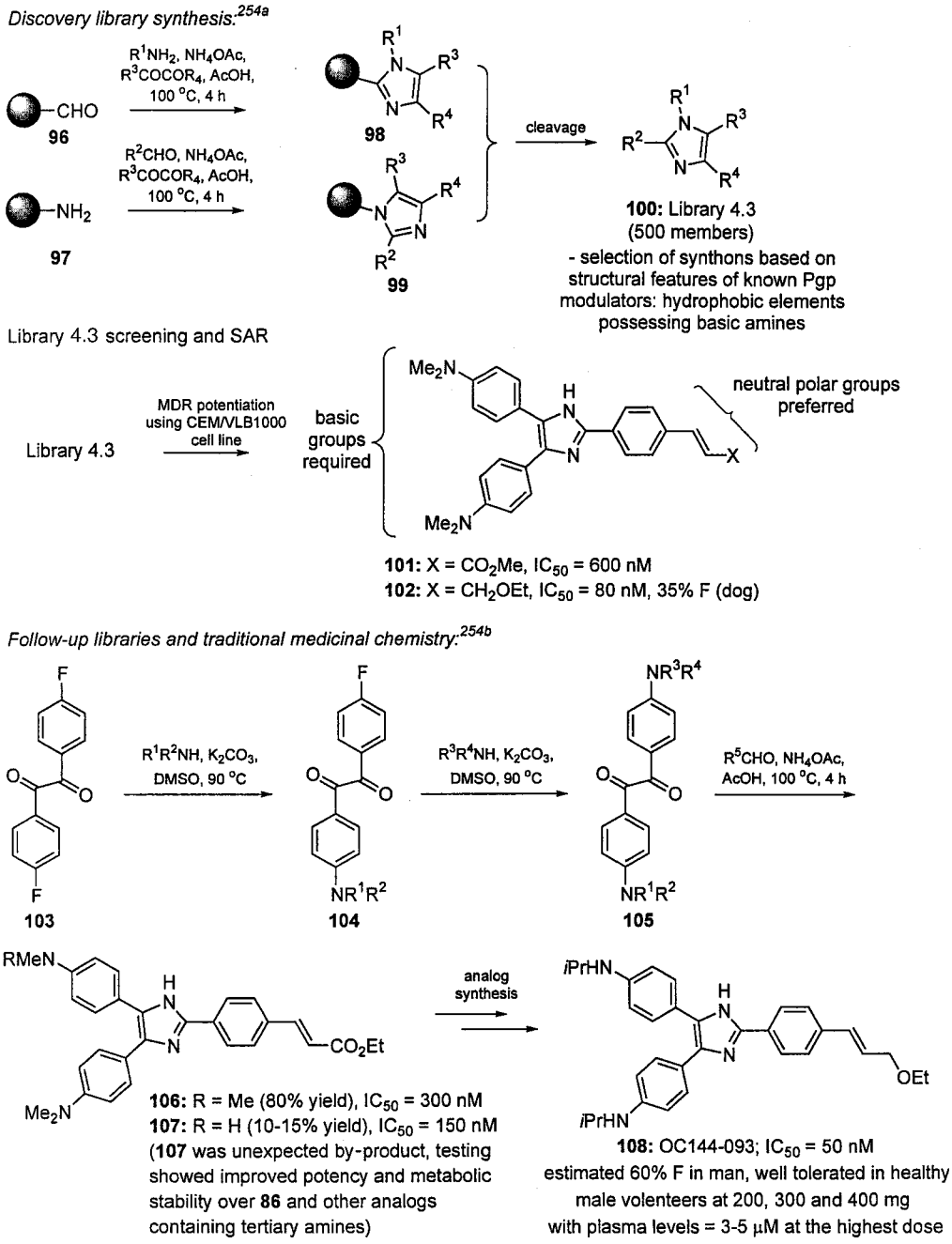


Figure 12. Modulators of P-glycoprotein-mediated MDR evaluated in man.[254]

recently described a solid-phase synthesis of a 2,3-disubstituted indole library (library 3.4, Figure 10).[220] The key feature of their work was the development of a new carbamate linker strategy for immobilizing indoles. By premixing of indole **75** with *p*-nitrophenyl carbonate modified Wang resin **76**, the azeotroping with toluene, resuspension in toluene, and treatment of the heterogeneous mixture with potassium hexamethyldisilazane (KHMDS, 1.05 equiv, −78 °C), clean conversion of resin-bound indole **77** was achieved. Release of indoles from resin was carried out by heating either in 5% pyrrolidine in DMF at 90 °C or in glacial acetic acid at 110 °C. Standard TFA-mediated cleavage was reportedly not possible because of unwanted reaction between the in situ generated resin-bound carbonium ion and the indole nucleus. The carbamate-linked indole was stable to HF pyridine, PPTS/EtOH, triflate formation (Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine), primary and secondary amines in DCM at room temperature, and the Stille (aryl stannane, Pd^0) coupling reaction. The resin was somewhat sensitive to Suzuki coupling conditions ($ArB(OH)_2$, $Pd(Ph_3)_4/Na_2CO_3$/aqueous THF, elevated temperature), since premature cleavage was observed. Biological evaluation of library 3.4 of 2,3-disubstituted indoles furnished **83**, a potent antagonist of the human $5HT_{2A}$ receptor, $K_i = 2.7$ nM.

Maloney and co-workers at Glaxo Wellcome (now GlaxoSmithKline) have identified the first nonsteroid agonist for the orphan nuclear receptor FXR (Figure 11).[139] FXR is believed to be involved in the regulation of bile acid and

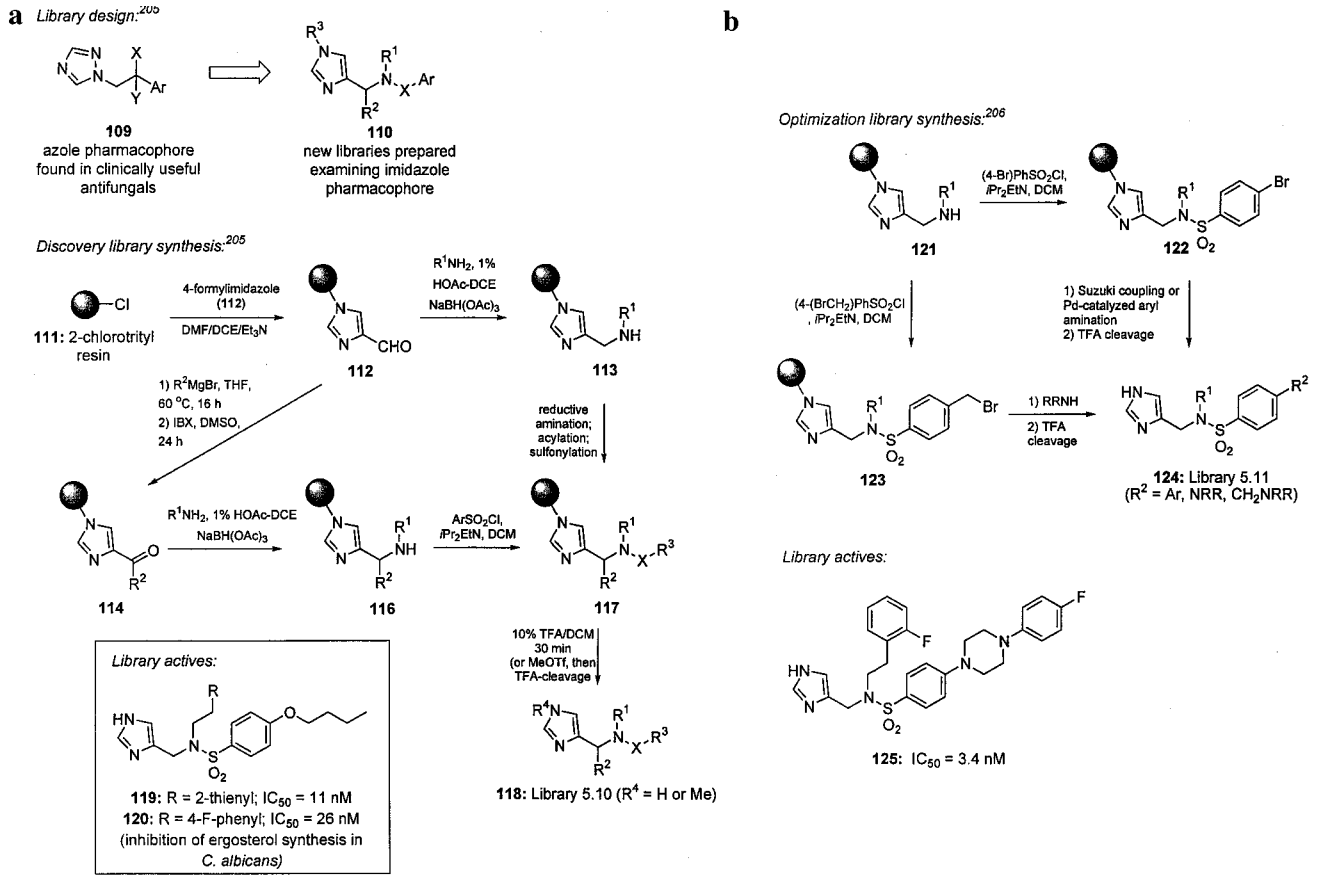


Figure 13. (a) 4-Substituted imidazoles active as antifungal agents.[205,206] (b) Optimization of antifungal agents.[206]

cholesterol homeostasis. The only known ligands for the receptor are chendeoxycholic acid (CDCA, **84**) and the retenoic acid receptor agonist, TTNPB **85**. Both **84** or **85** are inadequate as pharmacological tools to study the orphan receptor because of the interaction of **84** with bile acid binding and transport proteins and its metabolic instability and because of the weak potency and poor selectivity of **85** ($EC_{50} > 1\ \mu M$). Glaxo's lead, isoxazole **86**, for FXR was identified from a combinatorial library of 10 000 stilbine-containing carboxylic acids (unpublished results). Compound **86** was a weak FXR agonist ($EC_{50} = 4.1\ \mu M$) in a cell-based assay, and enhancement of the lead's potency and selectivity was desired. Retrosynthetic library analysis of **86** led to its dissection into three sets of building blocks: vinyl-substituted acids **87**, bromo/iodo-substituted phenols **88**, and hydroxymethyl isoxazoles **89**. Four olefins were combined with five phenols via the Heck reaction to give, after a two-step phenol protection sequence, 20 stilbene carboxylic acids **90**. The 20 templates were then loaded onto Sasarin resin, the phenol deprotected, and coupled with 40 hydroxymethyl isoxazoles (Mitsunobu coupling reaction). Cleavage of the final products from resin with TFA gave 600 discrete acids **94** on a 2−3 mg scale with >80% purity (library 4.1). The acids as obtained directly from cleavage were evaluated against FXR, and 31 of them were discovered with a cell-based activity equal to that of CDCA at 50 μM. Several of the actives were resynthesized and purified on a 50 mg scale. Isoxazole **95** is a full agonist with $EC_{50} = 90$ nM in CV-1 cells transfected with the human FXR. In further studies, **95** possessed an oral bioavailability of 10% in the rat ($t_{1/2} = 3.5$ h), and upon a 7-day dosing in Fisher rats, a dose-dependent lowering of serum triglycerides was observed ($ED_{50} = 20$ mg/kg).

Ontogen Corporation published a two-part report on the identification of 2,4,5-trisubstituted imidazoles as novel nontoxic modulators of P-glycoprotein (Pgp)-mediated multidrug resistance (MDR).[254] Pgp modulators are of interest as an adjunct to enhancing the oral bioavailability of certain chemotherapeutic agents, which are substrates for Pgp in the intestine. A discovery library of 500 substituted imidazoles was prepared using classical solid-phase protocols starting from resin-bound aldehyde **96** or amino-functionalized Wang resin **97** (Figure 12). Hydrophobic aldehydes, amines, and diaryldiones with dialkylamine and methoxy substituents were selected as part of the synthon set. This was in keeping with the desire to create a collection of hydrophobic imidazoles with multiple amine groups because such structural features are characteristic of known Pgp substrates and modulators. Library **100** was screened in a whole-cell MDR potentiation assay. Several 2,4,5-trisubstituted imidazoles represented by compounds **101** and **102**, were identified as potent Pgp modulators. As might be expected, pharmacokinetic studies indicated rapid metabolism of **101** and **102** through P_{450}-mediated N-demethylation and *N*-oxide forma-

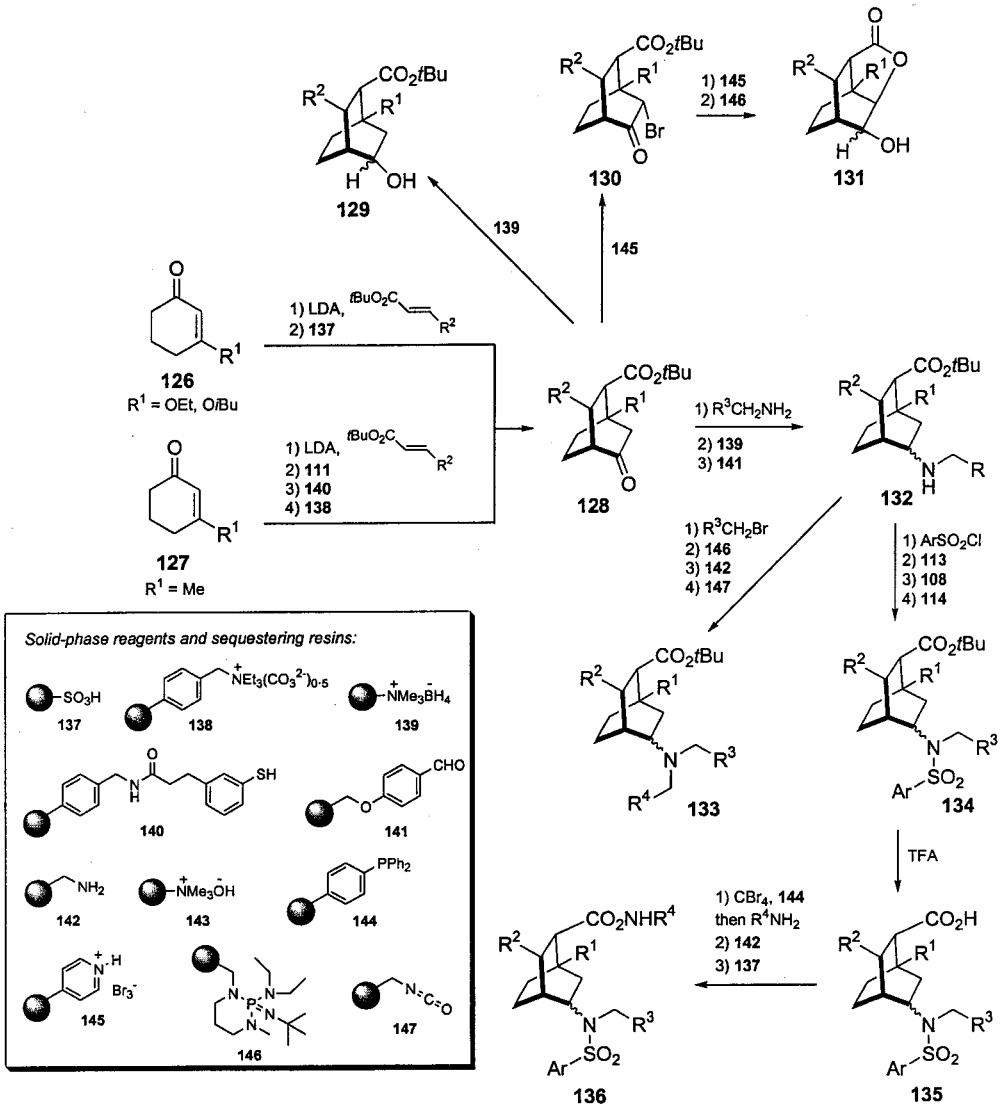


Figure 14. Ley's solution-phase synthesis of bicyclo[2.2.2]octane derivatives.[124,125]

tion. It was thought that metabolism could be attenuated by bulking up the substituents around the anilino nitrogen atom(s) in **102**. With this strategy in mind, solution-phase optimization was undertaken. A variety of amine groups was conveniently introduced via stepwise nucleophilic displacement of the fluorine atoms in difluorobenzil **103**, yielding symmetrical and unsymmetrical imidazoles. The reaction of **103** with dimethylamine gave the symmetrical product **106** in 80% yield accompanied by 10−15% of the monodemethylated compound **107**, the latter being an unexpected byproduct of cyclodehydration. The activity and pharmacokinetic profile of byproduct **107** was superior to those of the previously synthesized tertiary anilines. This fortuitous result led to the synthesis of other imidazoles containing secondary anilines and the identification of **108** (OC144-093) as a clinical candidate. OC144-093 possesses an IC_{50} = 50 nM in the MDR potentiation assay and is relatively nontoxic, with an estimated oral bioavailability of 60% in man. OC144-093 was well tolerated in healthy male volunteers at 200, 300, and 400 mg doses. Plasma levels reached 3−5 μM at the highest dose. Clinical studies are in progress examining **108** as an enhancer of the oral bioavailability of selected chemotherapeutic agents.

At Janssen Research, Saha and co-workers developed a new class of antifungal agents based on 4-substituted imidazoles **110**.[205,206] The design of these compounds was loosely based on the azolyl phenethylamine pharmacophore **109** uniquely found in several of the clinically useful antifungals including itraconazole and voriconazole. The initial discovery library 5.10 was prepared in a straightforward manner by immobilizing 4-formylimidazole **112** onto 2-chlorotrityl resin **111** (Figure 13a). The aldehyde functional group in **112** was either reductively aminated directly to yield resin **113** or subjected to Grignard addition, IBX oxidation, and then reductive amination to yield the α-substituted amine resin **116**. Derivatization of the amine in **113**/**116**, principally acylation, sulfonylation, or a second reductive amination, furnished the penultimate resin-bound intermediate **117**. A final diversity element was introduced into library 5.10 upon the choice of cleavage cocktail, TFA or MeOTf and then

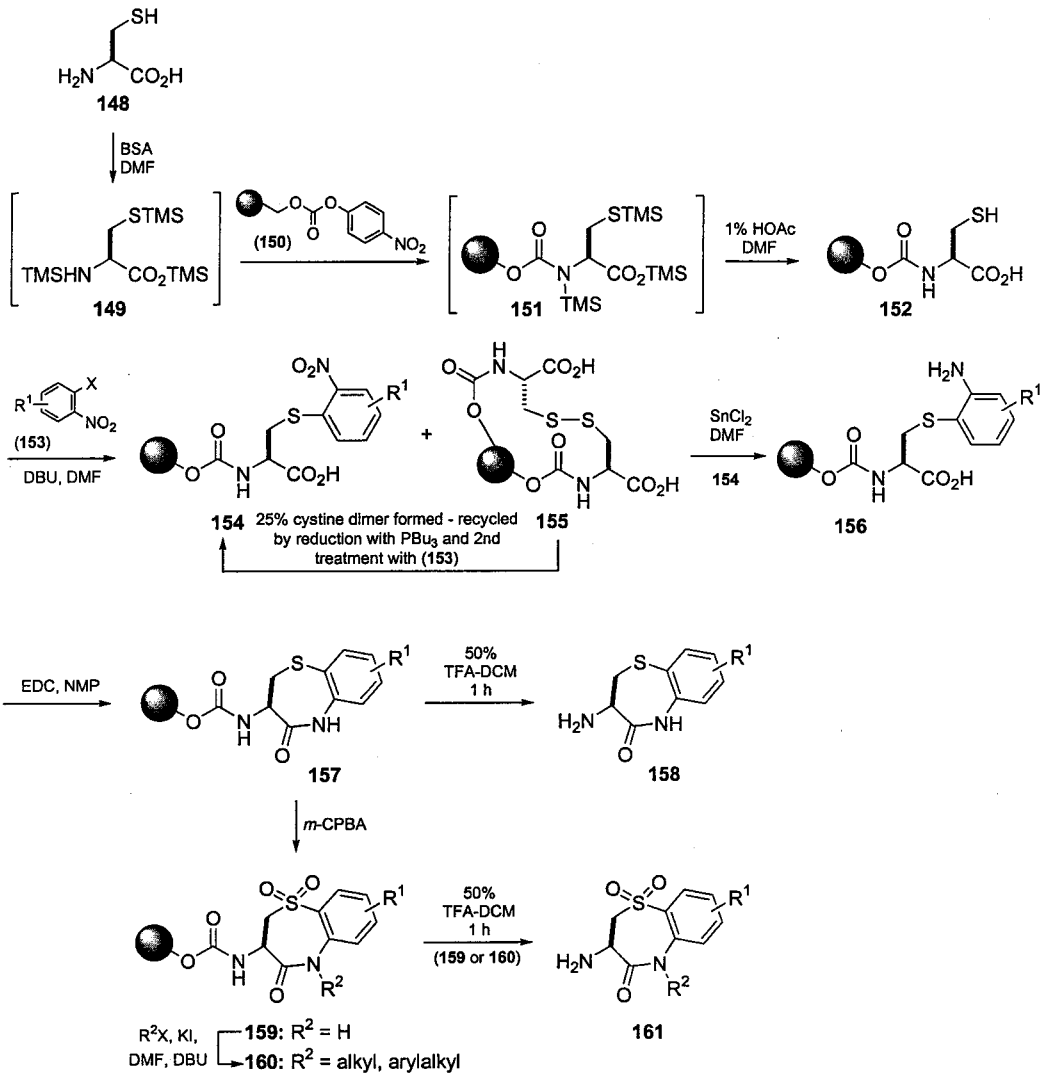


Figure 15. Herpin's solid-phase synthesis of 1,5-benzothiazepin-4-one derivatives.[157]

TFA, to provide imidazoles or *N*-methylimidazoles, respectively (R^4 = H, Me). A biological survey of the library indicated that the imidazole sulfonamides, e.g., **119** and **120**, possessed significant activity. A followup library 5.11 (Figure 13b), focusing on further optimization of the sulfonamide leads in library 5.10, gave compound **125**, IC_{50} = 3.4 nM, active against a range of fungi.

Library Constructs without Accompanying Biological Data

Approximately 30% of the libraries reported in the literature this past decade have been synthesized by solution-phase techniques. Polymer-supported reagents and sequestering agents are indispensable for this purpose. One of the more elegant demonstrations of the power of this approach is Ley's solution-phase synthesis of bicyclo[2.2.2]octane derivatives (Figure 14).[124,125] In this example, 11 solid-phase reagents and/or sequesterants were used 20 times throughout the multistep sequence to generate some 40 library compounds on a milligram scale in yields of 40−60% and purities in excess of 90% without resorting to chromatographic purification. The synthesis proceeds through Michael addition of *tert*-butyl acrylate to 3-substituted cyclohexenones **126**/**127**. Bicyclic ketone **128** is subjected to a host of reactions including reduction, bromination, intramolecular lactonization, reductive amination, amine alkylation, sulfonamidation, ester hydrolysis, acid bromide formation, and amidation. This same library was first prepared on solid phase, requiring over 2 years of optimization, while the solution-phase approach was completed in a fraction of that time. In addition, there were few restrictions in terms of decorating the bicyclic scaffold in the solution-phase route, since the "handle" required for solid-phase synthesis is rendered superfluous.

Herpin and co-workers described the synthesis of 1,5-benzothazepine-4-ones Figure 15).[157] This heterocyclic ring system has turned up as a pharmacophore in a number of enzyme inhibitors and GPCR antagonists. The synthesis used the 3-amino group in the heterocycle as the point of resin attachment, permitting the use of a variety of *o*-halonitrobenzenes to introduce diversity into the benzene ring. The synthesis began with immobilizing L-cysteine **148** to *p*-

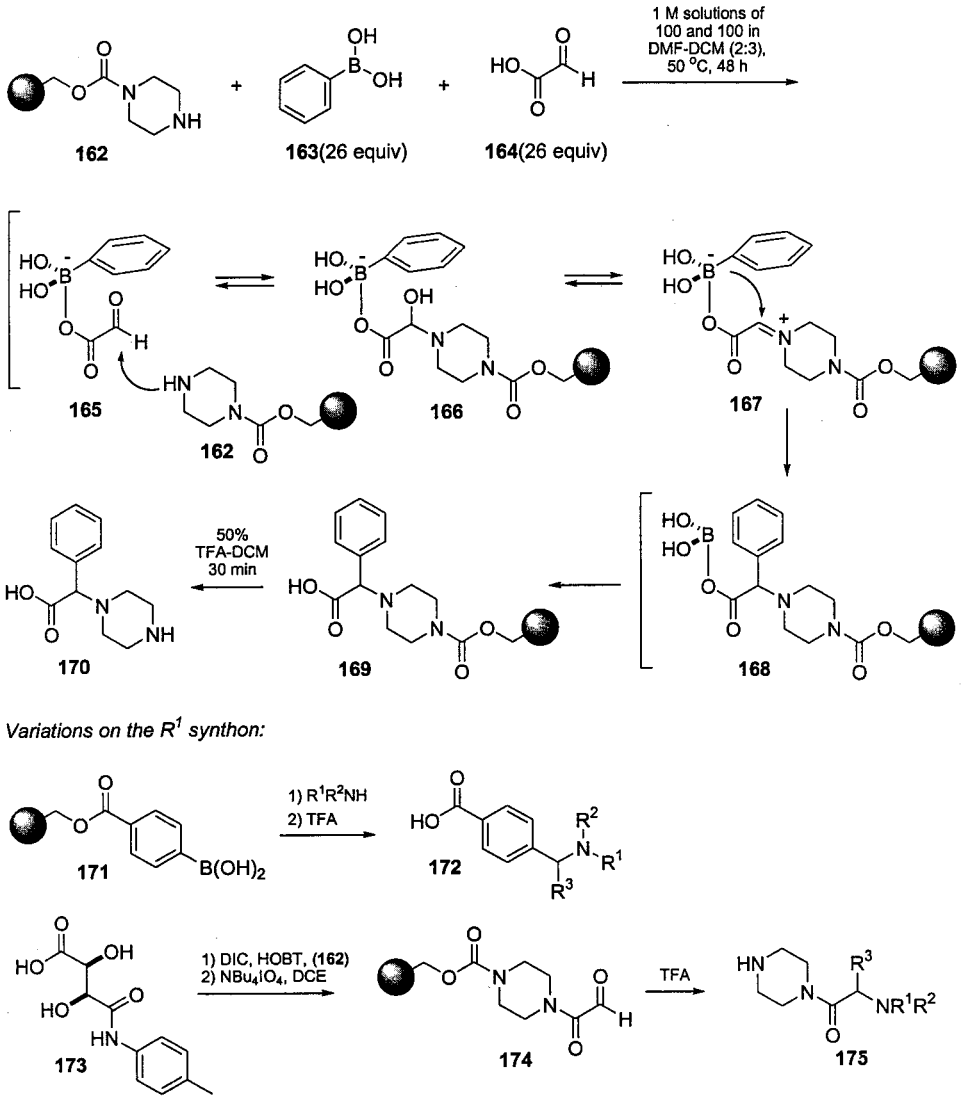


Figure 16. Solid-phase version of the boronic acid Mannich reaction.[213]

nitrocarbonate-derivatized Wang resin **150**. Because of the poor solubility of the free amino acid in DMF, **148** was converted in a separate step into its tris-TMS derivative **149** by exhaustive treatment with bis(trimethylsilyl)acetamide (BSA). Silylated amino acid **149** now readily dissolved and reacted with resin **150** in DMF under argon. Exposure of the resin intermediate **151** to 10% AcOH in DMF regenerated the free thiol and carboxylate residues (**151** → **152**). The thiol in **152** was then reacted with a host of halonitrobenzenes **153** using DBU as the base in DMF at room temperature to give predominantly **154**. Formation of up to 25% cystine dimer **155** was observed and was optionally cycled back to **154** by reductive treatment with PBu_3 and reaction with a second portion of **153**. Reduction of the nitro group in (**154** → **156**) was achieved with $SnCl_2$, and cyclization was effected with EDC to yield the benzothiazepine derivative **157**. Cleavage of **157** with TFA gave 3-amino derivatives **158** in good yield and purity. Alternatively, resin **157** was oxidized to the sulfone with *m*-CPBA in DCM and optionally N-alkylated with a variety of alkyl bromides/iodides or benzyl chlorides to furnish **161** (R^2 = H, alkyl, arylalkyl) after exposure of **159**/**160** to TFA.

A solid-phase version of the Petasis three-component boronic acid Mannich reaction (BMR) was reported by Hansen et al. at Novo Nordisk.[213] In their scheme, an aryl boronic acid was combined with an aldehyde and a secondary amine (Figure 16). Several examples were given in which each of the three components was alternately linked onto Wang resin. Expected products were obtained in high yields in most instances. In the case of resin-bound secondary amine substrates **162**, reactions were best carried out at 50 °C over 24−48 h in 1 M solution of both aldehyde and boronic acid. The BMR reaction was sensitive to the aldehyde substrate used. Preferred solvent mixtures for the reaction with salicylaldehyde were either DMF/DCE (2:3) or 2,2,2-trifluoroethanol/dioxane/DMF (5:1:4), while protonated as well as nonprotonated solvents could be used with glyoxylic acid. *Interestingly, BMR products were not obtained with*

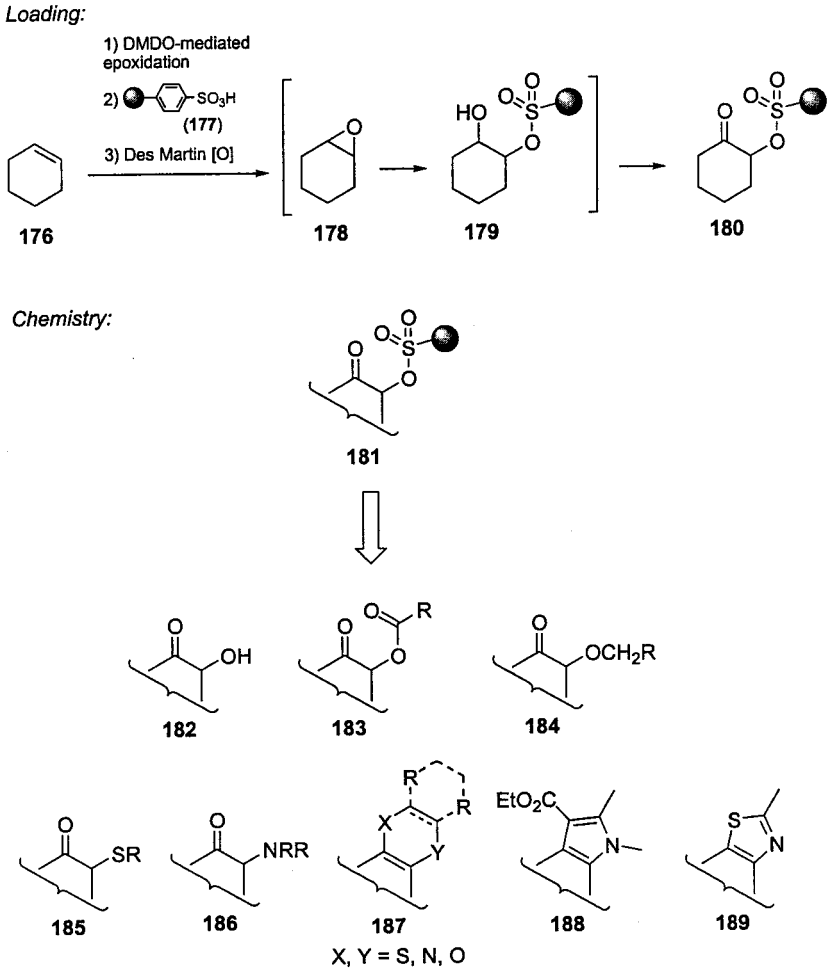
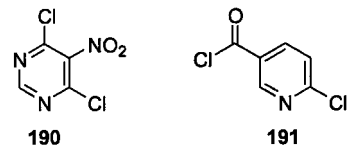


Figure 17. Application of resin-bound α-sulfonated ketones.[166]

the resin-bound primary amine substrates examined. Both immobilized glyoxylic acid **174** and boronic acid **171** substrates linked through an ester or amide bond to the resin performed as expected in the three-component condensation.

Nicolaou described the preparation and utility of resin-bound α-sulfonated ketones (Figure 17).[166] Loading of α-sulfonated ketones onto resin was readily accomplished upon treatment of polystyrene sulfonic acid resin **177** (a solid-phase version of toluenesulfonic acid) with epoxides (e.g., **178**) in DCM at room temperature for 24 h and subsequent oxidation with Dess−Martin periodinane. A one-pot entry into **181** could be achieved directly from olefins via in situ olefin oxidation with dimethyldioxirane (DMDO) followed by the two-step addition/oxidation sequence. Resin **181** was remarkably stable and underwent a variety of nucleophilic cleavage reactions generating α-hydroxy-, α-acyloxy-, α-phenoxy-, α-alkoxy-, α-amino-, α-anilino, and α-thioaryl ketones. Reaction of **181** with bis nucleophiles including thioamides, catechols, dithiols, and diamines gave rise to a series of diverse fused heterobicyclic rings. Over 20 functionalizing cleavage options were reported.

In recent years, commercially available *o*-halonitrobenzenes have found wide application in the solid-phase synthesis of heterocyclic systems.[260] Their enormous popularity stems from the fact that the reactive halogen atom is easily displaced by O, N, and S nucleophiles and that the facile reduction of the nitro group unmasks a latent nucleophilic anilino nitrogen, which in turn may participate in intramolecular acylation-, sulfonylation-, or alkylation-style ring closures. Surprisingly absent from the literature are examples of heterocycles derived from *o*-halonitropyridines and -nitropyrimidines. One would anticipate an enhanced reactivity of these halogenated aromatics toward nucleophiles due to the electron-deficient nature of the pyridine/pyrimidine ring relative to benzene. It is interesting to note that in this past year three research groups independently disclosed a solid-phase synthesis of pyridine- and pyrimidine-based heterocycles (purines,[53] dihydropteridinones,[13] and 7-aza-benzimidazoles[66]) from **190** and **191**, respectively.



Gilbert's synthesis of purines began by attaching **190** to Rink amide resin **192**, which proceeded smoothly to give

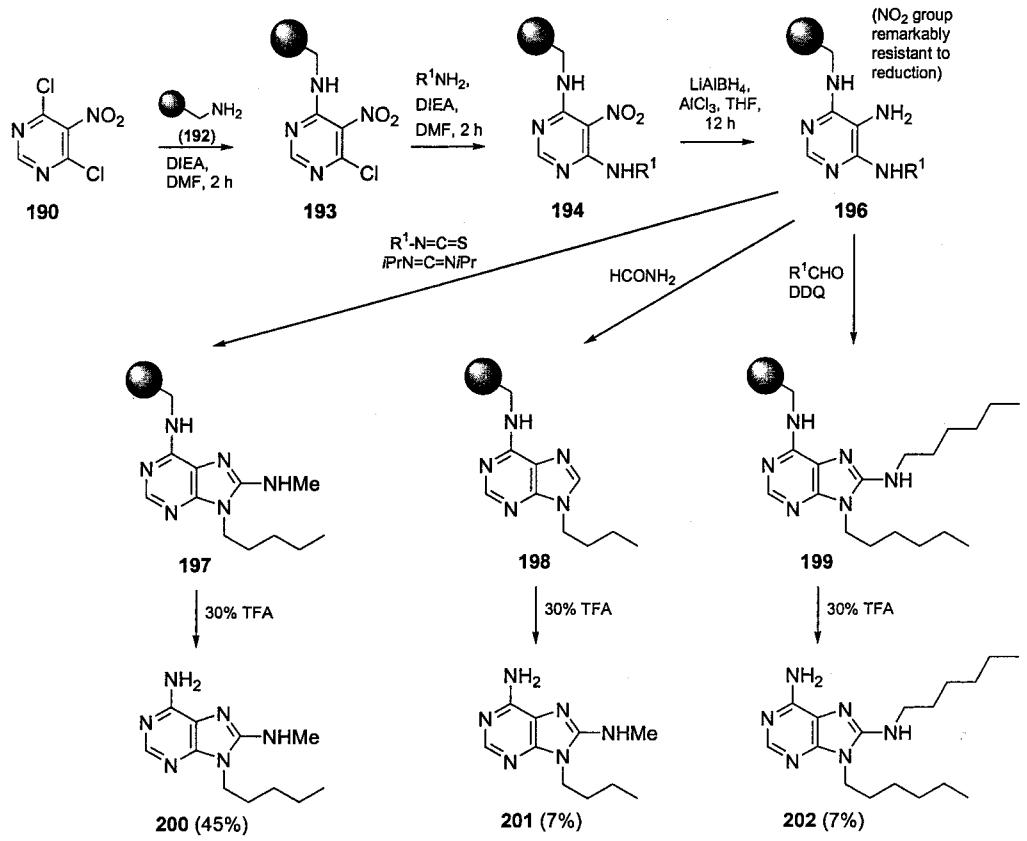
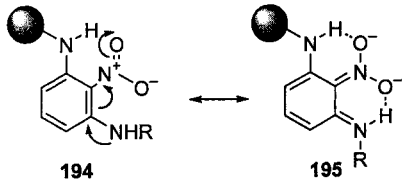


Figure 18. Solid-phase synthesis of purines from pyrimidines.[53]

193 (Figure 18).[53] Displacement of the second chlorine in **193** with a primary amine was quite rapid and also proceeded in good yield, as determined by cleaving the diaminonitropyrimidine from the resin with TFA. Problems started with the reduction of the nitro group to the corresponding amine. Conventional reagents and reaction conditions, e.g., $SnCl_2$, $NaBH_4/CoCl_2$, $Na_2S_2O_4$, hydrazine/carbon, failed to reduce the nitro group. In all, 16 different reagent/condition combinations were investigated and the only reagent pair found to be effective was $LiAlH_4/AlCl_3$ in THF at 25 °C for 12 h. Although these rather harsh reaction conditions did not appear to decrease the loading of **196**, the major drawback of the reagent pair was the contamination of the cleaved products with inorganic salts, leading to low overall yields. The remarkable resistance of the nitro group to reduction is hypothesized to be caused by extensive conjugation of the adjacent amino groups to the nitro group and the large number of intramolecular hydrogen bonds that must be broken for reduction to proceed (**195** → **196**). Reduction notwithstanding, resin-bound triamine **196** was subjected to several cyclization protocols to furnish purine ring systems **200**−**202** with variation at the 8- and 9-positions. These transformations were also a struggle in that the reaction of **196** with methyl isothiocyanate or ethyl isothiocyanate (ca. 7.5 equiv) in the presence of dicyclohexylcarbodiimide (DCC; ca. 7.5 equiv, benzene, reflux, 12 h) gave **197** (45% yield) contaminated with dicyclohexylurea after cleavage. This particular problem was circumvented by using diisopropylcarbodiimide (DIC) in place of DCC. Cyclization of **196** with formamidine (neat, 160 °C, 12 h) and oxidative cyclization of **196** with an aliphatic aldehyde (3 equiv) and DDQ (1.5 equiv, DMF, 25 °C, 5 h) furnished **201** and **202**, respectively, each in only 7% isolated yield following TFA-mediated release.

4,6-Dichloro-5-nitropyrimidine **190** was employed in a novel, flexible solid-phase synthesis of dihydropteridinones **207** as reported by Cox from Oxford Asymmetry International.[13] The reaction sequence is outlined in Figure 19. Fmoc amino acids were coupled to Wang resin, and the Fmoc protecting group was removed using standard conditions. Resin **203** so obtained was treated with **190** (3 equiv) in the presence of Hunigs base using DCM as solvent (16 h), furnishing **204** in high yield and purity (as determined by cleavage of a small sample with 50% TFA−DCM, 1 h). The fully functionalized pyrimidine resin **206** was obtained via a second S_NAr reaction, displacing the chlorine atom with a variety of amino acid esters **205**. Resin-bound methyl ester substrates **206** underwent efficient reductive cyclization upon exposing it to a solution of $SnCl_2 \cdot H_2O$ (5 equiv) in oxygen-free ethanol−DMF (1:1) and heating the mixture at 70 °C



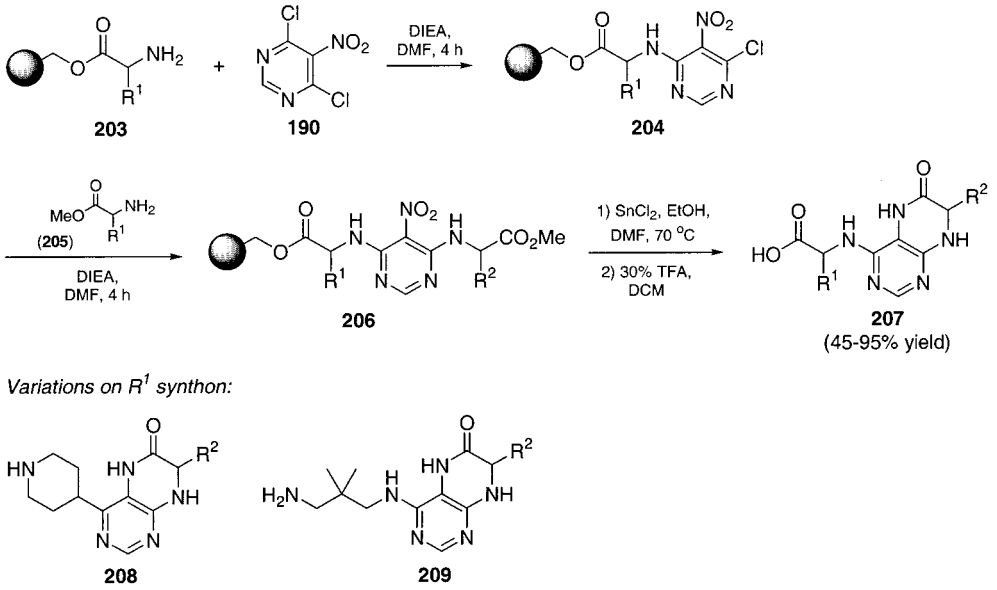


Figure 19. Solid-phase synthesis of dihydropteridinones from pyrimidines.[13]

for 16 h. The smooth reduction of the nitro group in **206** is in stark contrast to the problematic reduction of **194** to **196** experienced by Gilbert[53] in the purine synthesis described above. Gilbert's hypothesis that conjugation and H-bonding in **195** is responsible for making the nitro group resistant to reduction is inconsistent with the result of Fox. The analogous intermediate of **195** can be drawn for substrate **206**. Subtle differences in the substrate, reaction conditions (reduction conditions of Gilbert that are closest to those of Cox was $SnCl_2 \cdot H_2O$ in water or EtOAc at 70 °C), or linker attachment must account for the difference in the nitro group's behavior in **194** and **206**. Cleavage of the reductively cyclized intermediate with 50% TFA−DCM completed the dihydropteridinone synthesis. Further diversity could be achieved by using other diamine-functionalized Wang resins (e.g., **208** and **209**). In total, eight dihydrodpteridinones were synthesized. Yields ranged from 45% to 95% with an average purity of 70−75%.

As a final example of using an *o*-halonitro heterocycle in solid-phase synthesis, Rahman at SmithKline Beecham developed a route to 1,2,5-substituted 7-azabenzimidazole derivatives (**217**, Figure 20).[66] Primary amines were attached to 4-formyl-3-methoxyphenyloxymethyl polystyrene resin **210** by reductive amination. It was originally thought that resin-bound amines **211** could be acylated with 6-chloro-5-nitropyrimidine-3-carboxylic acid **212** using standard amide coupling reagents and conditions. Empirically, this was not the case because the competing S_NAr reaction between amine **211** and the 6-chloro group in **212** occurred in preference to acylation. Ultimately reaction conditions for this transformation were found by using the nicotinoyl chloride **191** and carrying out the reaction at −78 °C (Et_3N, DCM). Under these conditions no evidence of competing S_NAr was observed between **191** and the amine nucleophile. The immobilized intermediate **214** was converted to the 7-aza-

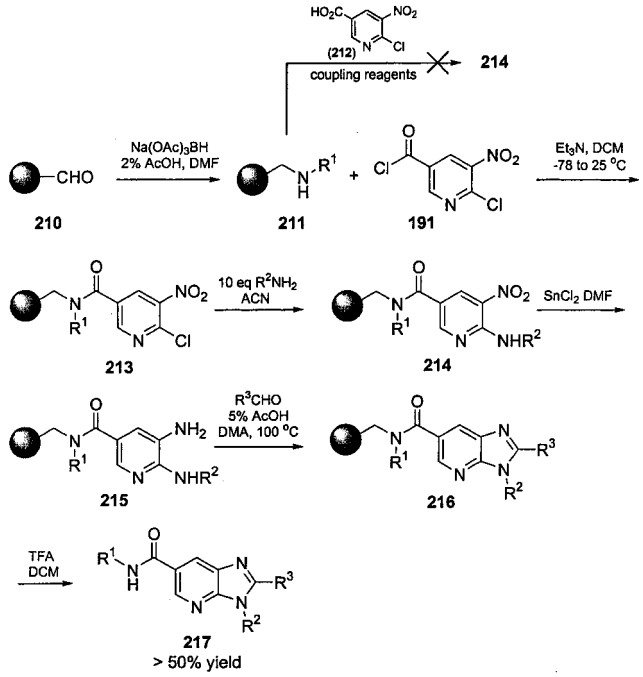


Figure 20. Solid-phase synthesis of 7-azabenzimidazoles.[66]

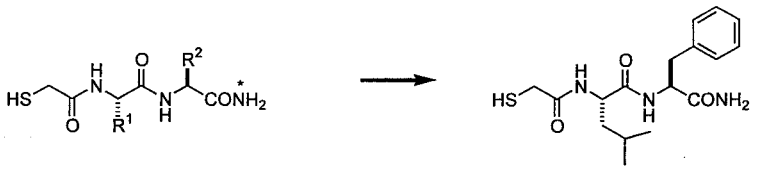
benzimidazole by the following four-step sequence: (1) alkylation with a second set of amine synthons (10 equiv of R^2NH_2, CH_3CN, 25 °C, 12 h), (2) nitro group reduction ($SnCl_2 \cdot H_2O$, DMF, 25 °C, 25 h), (3) cyclization with aldehydes (10 equiv of R^3CHO, 5% AcOH−DMA, 160 °C, 5 h), and (4) product cleavage (TFA−DCM−water (6:3:1), 25 °C, 1 h). Eight examples showcasing the chemistry were given, with yields of products ranging from 50% to 94% and purities averaging >90%.

Acknowledgment. A special thank you is expressed to Ms. Rebecca (Becca) Schaefer for her helpful assistance in drawing chemical structures and in the preparation of other portions of this manuscript.

Table 1. Chemical Libraries Targeted for Proteases (∗ Indicates Point of Attachment to the Resin)

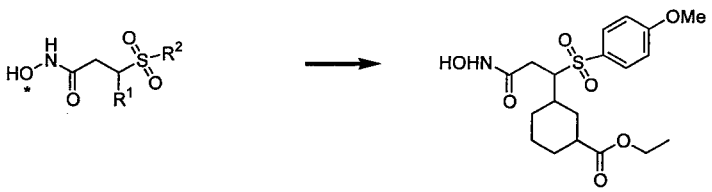
Metallo-proteases

Library: 1.1
Name: Mercaptoacylpeptide
Size: 36 members
Affiliation: Lynas, J. F.; *et al.* [134]
Note: 2 x 18 member libraries prepared on automated synthesizer.



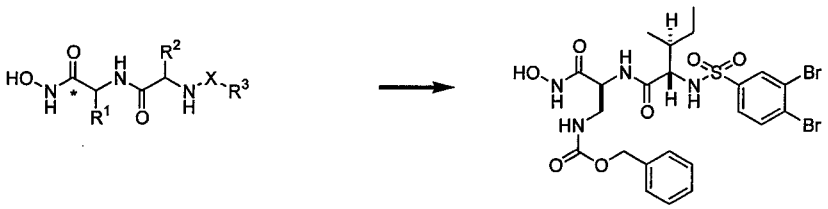
Enzyme: MMP-1
Activity: IC_{50} = 50 nM

Library: 1.2
Name: Arylsulfone hydroxamate
Size: ca. 48 members
Affiliation: Rhone-Poulenc Rorer [209]



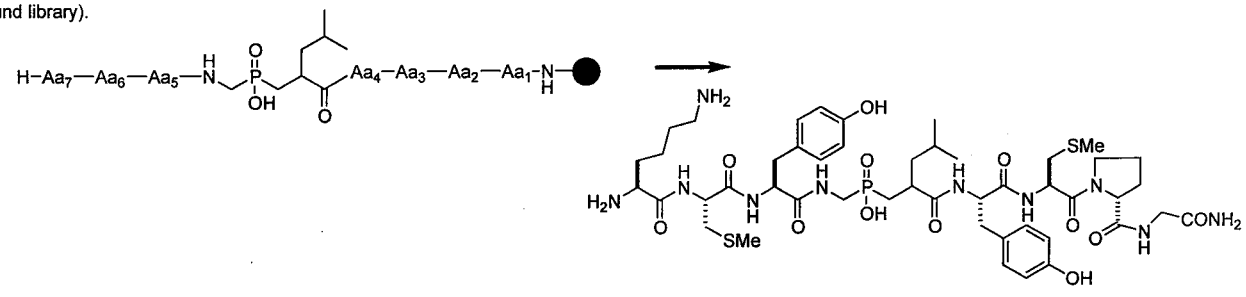
Enzyme: MMP-2
Activity: K_i = 0.8 nM, MMP-2;
K_i = 1010 nM, MMP-1;
K_i = 60 nM, MMP-3

Library: 1.3
Name: Peptide hydroxamate
Size: ca. 1000 members
Affiliation: Roche Biosci. [50]



Enzyme: Procollagen C-protease
Activity: IC_{50} = 26 nM

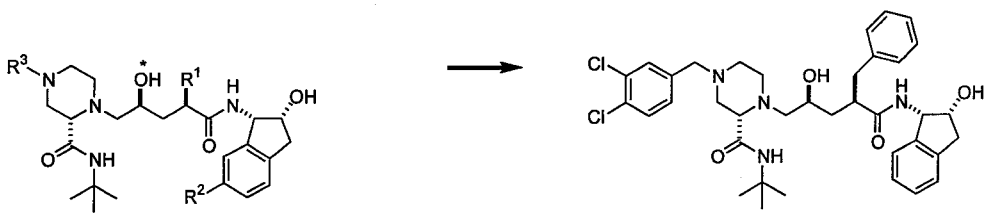
Library: 1.4
Name: Phosphinic peptide
Size: 165,000 members
Affiliation: Meldol, M.; *et al.* [37]
Note: On-bead screening with fluorogenic substrate also on the bead (one-bead-two-compound library).



Enzyme: MMP-12
Activity: K_i = 6.0 nM

Aspartic acid proteases

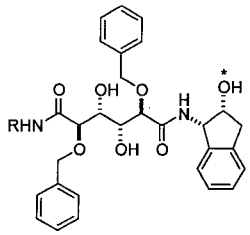
Library: 1.5
Name: Indinavir analog
Size: ca. 50 members
Affiliation: Merck [200]

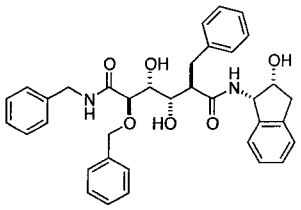


Enzyme: HIV-1 protease
Activity: IC_{50} = 1.0 nM

Table 1. (Continued)

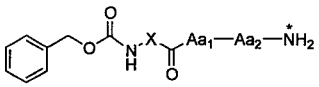
Library: 1.6
Name: L-Mannaric diamide
Size: 11 members
Affiliation: Oscarsson, K.; *et al.* [182]

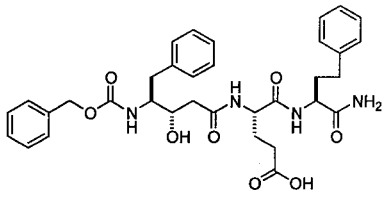




Enzyme: HIV-1 protease
Activity: K_i = 0.1 nM

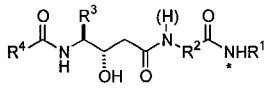
Library: 1.7
Name: Pseudopeptide
Size: 11,520 members
Affiliation: Rinnova, M.; *et al.* [203]
Note: X = aspartic acid protease pharmacophore.

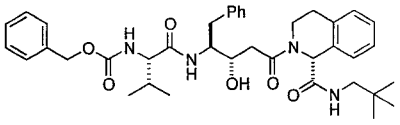




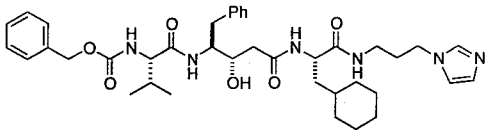
Enzyme: HIV-1 protease^{SAQ}
Activity: K_i = 0.18 nM

Library: 1.8
Name: Statine amide
Size: 25,200 members
Affiliation: Pharmacopeia [57]
Note: Encoded with molecular tags.





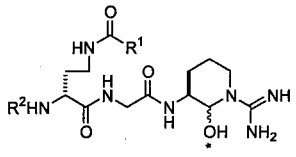
Enzyme: Cathepsin D
Activity: K_i = 3 nM, cathepsin D;
K_i = 210 nM, plasmepsin II

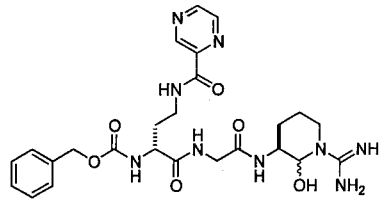


Enzyme: Plasmepsin II
Activity: K_i = 7 nM, plasmepsin;
K_i = 530 nM, cathepsin D

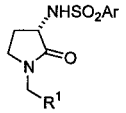
Serine proteases

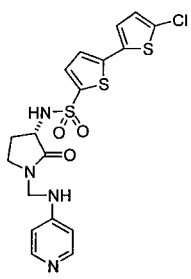
Library: 1.9
Name: Argininal peptide
Size: ca. 20 members
Affiliation: Corvas Int. [94]





Library: 1.10
Name: Azarene pyrrolidinone
Size: 56 members
Affiliation: Rhone-Poulenc Rorer [76]
Note: Use of sulfonyl-activated TFP resins for N-derivatization.

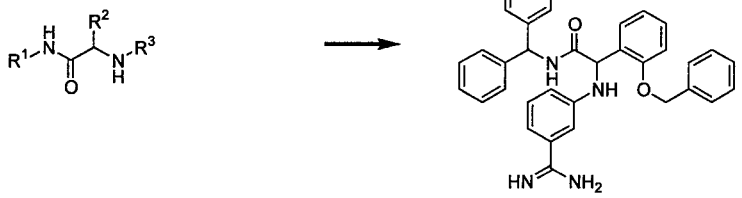




Enzyme: Factor Xa
Activity: K_i = 15 nM

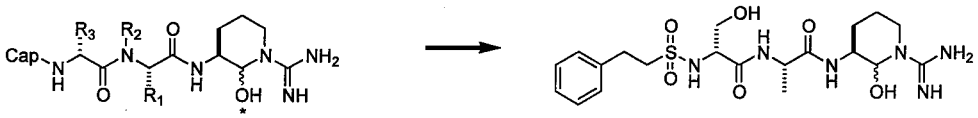
Table 1. (Continued)

Library: 1.11
Name: Amino acid amide
Size: 15,360 members
Affiliation: Hoffmann-La Roche [102]
Note: Ugi chemistry.



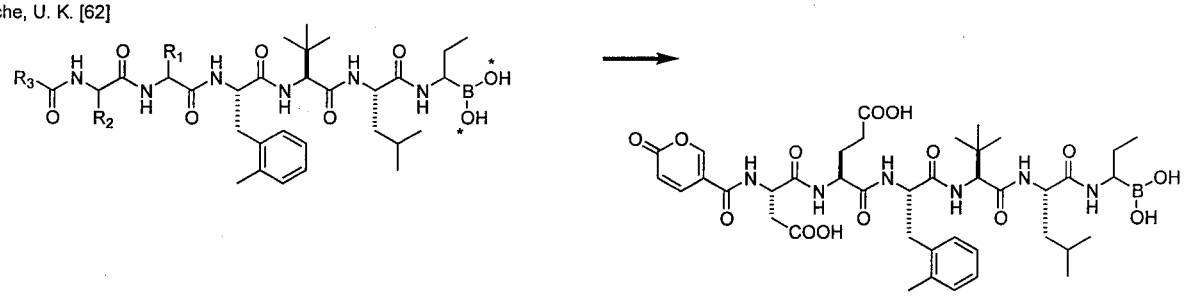
Enzyme: Thrombin
Activity: K_i = 2.0 nM

Library: 1.12
Name: Peptidyl argininal
Size: 11 members
Affiliation: Corvas Int. [228]



Enzyme: Urokinase
Activity: IC_{50} = 3.1 nM

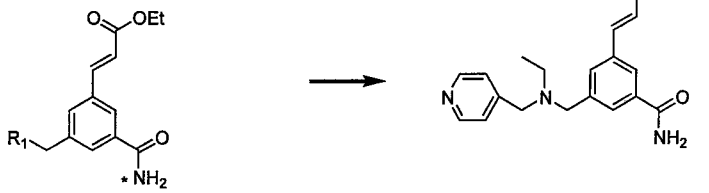
Library: 1.13
Name: Peptidyl boronic acid
Size: 42 members
Affiliation: Roche, U. K. [62]



Enzyme: HCV NS3 protease
Activity: K_i = 80 nM

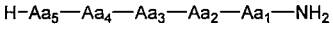
Cysteine proteases

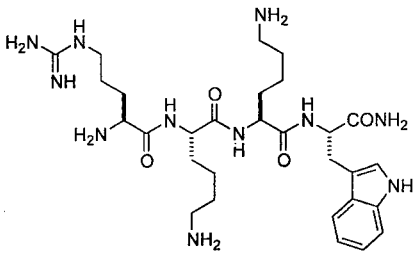
Library: 1.14
Name: Cinnamate
Size: 784 members
Affiliation: Agouron Pharm. [201]



Enzyme: Human rhinovirus 3C protease
Activity: $K_{obs}/[I]$ = 96 $M^{-1}s^{-1}$

Library: 1.15
Name: Pentapeptide
Size: ca. 17 million members
Affiliation: Brinker, A.; *et al.* [32]



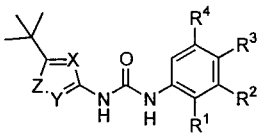


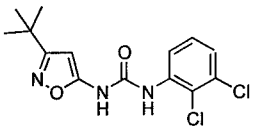
Target: Cathepsin L (human)
Activity: K_i = 130 nM

Table 2. Chemical Libraries Targeted for Non-proteolytic Enzymes (∗ Indicates Point of Attachment to the Resin)

Kinases and phosphatases

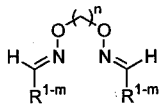
Library: 2.1
Name: Heterocyclic urea
Size: ca. 1000 members
Affiliation: Bayer [60, 61]
Note: Focused library based on a pyrazole urea. Solution-phase synthesis.

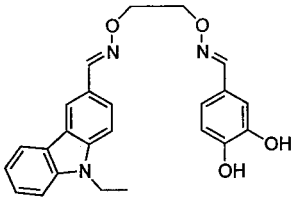




Enzyme: MAP kinase p38 α2 (human)
Activity: IC_{50} = 36 nM

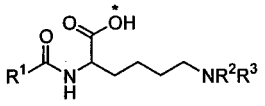
Library: 2.2
Name: Oxime dimer
Size: ca. 600 members
Affiliation: Ellman, J. A.; *et al.* [141]
Note: Target-guided ligand assembly.

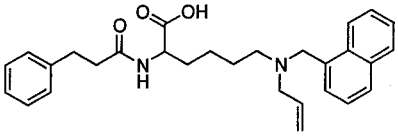




Target: c-Src tyrosine kinase
Activity: IC_{50} = 64 nM: > 75x selective versus Fyn, Lyn, Lck

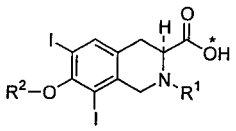
Library: 2.3
Name: Lysine derivative
Size: ca. 30 members
Affiliation: Wipf, P.; *et al.* [243]
Note: Library design based on natural product inhibitors of PSTPases.

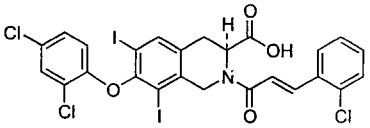




Enzyme: VHR phosphatase (dual-specificity)
Activity: IC_{50} = 156 μM

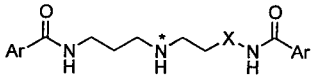
Library: 2.4
Name: Tetrahydroisoquinoline
Size: 24 members
Affiliation: Pharmacia; Upjohn [67]
Note: Focused library based on 70 μM lead.

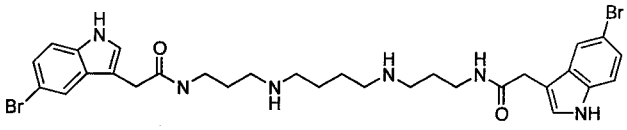




Enzyme: Protein phosphatase CDC25B
Activity: IC_{50} = 15 μM

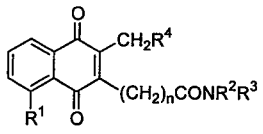
Library: 2.5
Name: Polyamide
Size: ca. 160 members
Affiliation: Chitkul, B.; *et al.* [44]
Note: Based on Kukoamine, known natural product inhibitor of TR.
X = CH_2; CH_2CH_2; $CH_2CH_2N(CH_2)_3$

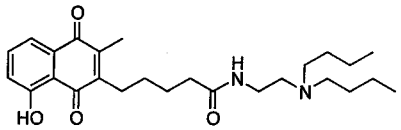




Taget: Trypanothione reductase (TR)
Activity: K_i = 76 nM

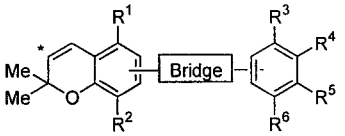
Library: 2.6
Name: 1,4-Naphthoquinone
Size: 1360 members
Affiliation: Davioud-Charvet, E.; *et al.* [207]

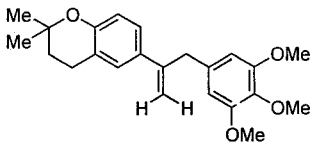




Enzyme: Trypanothione reductase
Activity: IC_{50} = 0.3 μM

Library: 2.7
Name: Benzopyran
Size: ca. 130 members
Affiliation: Nicolaou, K.C.; *et al.* [171]
Note: Inital screening library of 52 members then a series of three follow-up libraries.

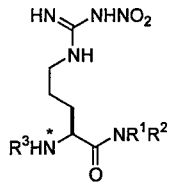


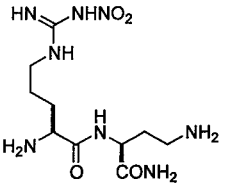


Enzyme: NADH:ubiquinone oxidoreductase
Activity: IC_{50} = 18 nM

Table 2. (Continued)

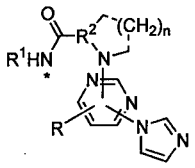
Library: 2.8
Name: Nitro-L-arginine peptidomimetic
Size: ca. 17 members
Affiliation: Silverman, R. B.; *et al.* [96]
Note: Multiple attachment points to enhance diversity of active site probes.

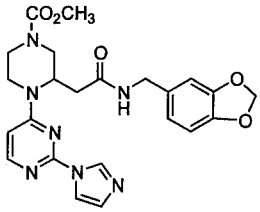




Enzyme: Nitric oxide synthetase
Activity: K_i = 0.33 μM, nNOS;
K_i = 97 μM, iNOS;
K_i = 245 μM, eNOS

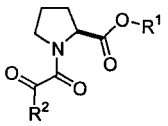
Library: 2.9
Name: Pyrimidine imidazole
Size: 8649 members
Affiliation: Pharmacopeia [149]
Note: 31 x 31 x 9 library encoded with molecular tags.

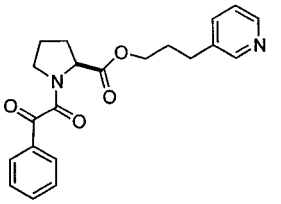




Enzyme: Inducible nitric oxide synthetase (iNOS)
Activity: IC_{50} = 0.6 nM (inhibition of cytokine-stimulated NO-production in human glioblastoma A-172 cells).[3]

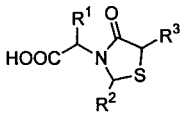
Library: 2.10
Name: Proline pyruvic amide
Size: 880 members
Affiliation: Glaxo Wellcome [196]
Note: Solid-phase proline esterification, then solution-phase amide formation.

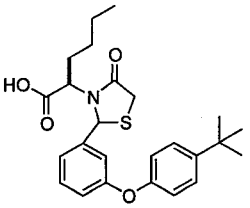




Enzyme: FKBP12
Activity: pIC_{50} = < 5 (spa assay)
(napamycin pIC_{50} = 8.5)

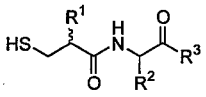
Library: 2.11
Name:Thiazolidinone
Size: 27 members
Affiliation: Bristol-Myers Squibb [4]
Note: Three-component condensation.

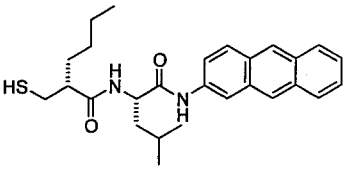




Enzyme: Bacterial MurB
Activity: IC_{50} = 7.7 μM

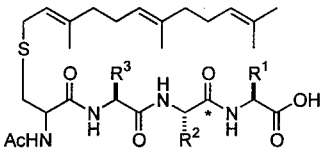
Library: 2.12
Name: Peptide thiol
Size: 750 members
Affiliation: Pei, D.; *et al.* [241]
Note: Most potent inhibitor from this library was further optimized by solution-phase chemistry to yield a 15 nM inhibitor.

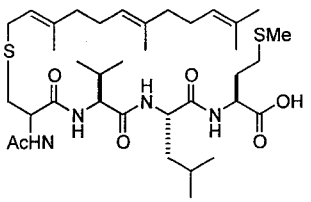




Enzyme: Peptide deformylase (*E. coli*)
Activity: K_i = 500 nM

Library: 2.13
Name: Farnesylated tetrapeptide
Size: ca. 60 members
Affiliation: Poulter, D. C.; *et al.* [56]
Note: Cleavage of tripeptide bound to Kaizer oxime resin with amino acid benzyl esters, then hydrolysis.

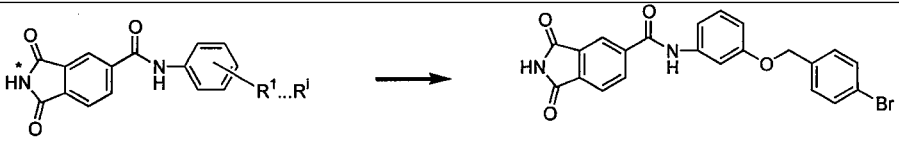




Enzyme: Ras and α-factor converting enzyme (RCE) (Ras CaaX endopeptidase; yeast)
Activity: IC_{50} = 103 nM

Table 2. (Continued)

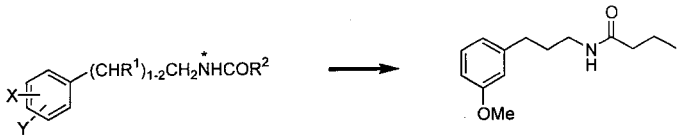
Library: 2.14
Name: Phthalimide
Size: 32 members
Affiliation: Wang, C. C.; *et al.* [6]



Enzyme: Hypoxanthine-guanine-xanthine phosphoribosyltransferase (*T. foetus*)
Activity: K_i = 490 nM (>30x selective over human enzyme)

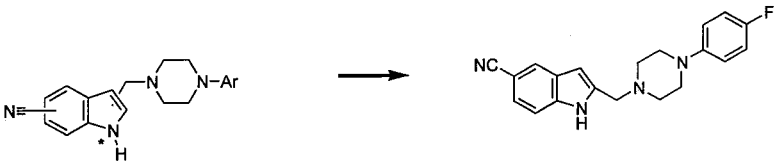
Table 3. Chemical Libraries Targeted for G-Protein-Coupled Receptors (∗ Indicates Point of Attachment to the Resin)

Library: 3.1
Name: Phenylalkylamide
Size: 108 members
Affiliation: Langlois, M.; *et al.* [188]



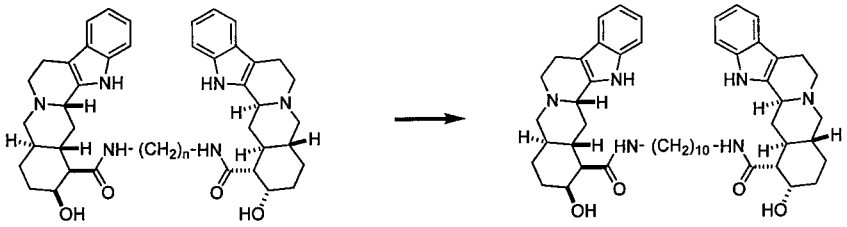
Receptor: Melatonin (human)
Activity: K_i = 0.6 nM (hmt_1);
K_i = 0.7 nM (hmt_2)

Library: 3.2
Name: Cyanoindole
Size: 13 members
Affiliation: Gmeiner, P.; *et al.* [97]



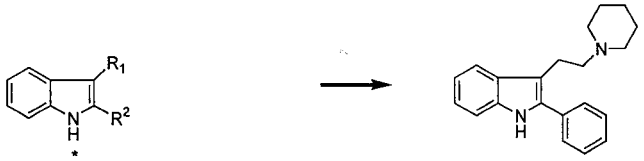
Receptor: Dopamine-4 (human D_4)
Activity: 1.0 nM (>8600x selective versus D_1-D_3 receptors)

Library: 3.3
Name: Yohimbine dimer
Size: 10 members
Affiliation: Miller, D. D.; *et al.* [257]



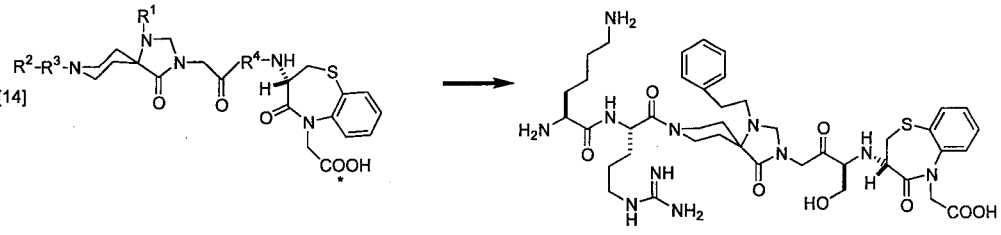
Receptor: α_{2a}-adrenergic
Activity: K_i = 0.39 nM, α_{2a};
K_i = 18.6 nM, α_{2b}

Library: 3.4
Name: 2,3-Disubstituted indole
Size: Not defined (>12 members)
Affiliation: Merck [220]



Receptor: 5-HT_{2A} (human)
Activity: K_i = 2.7 nM (antagonist);
K_i = 900 nM, hD_2

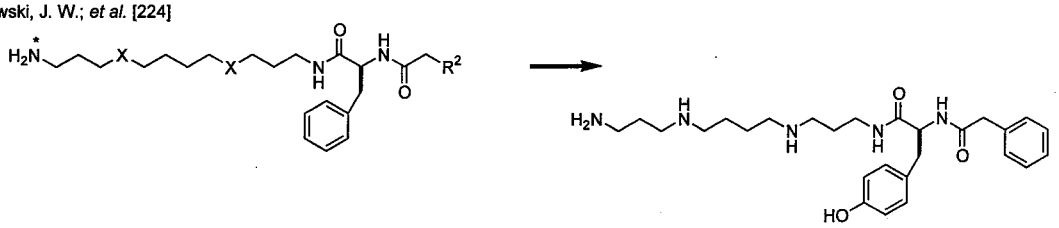
Library: 3.5
Name: Pseudopeptide
Size: 11 members
Affiliation: Martinez, J.; *et al.* [14]



Receptor: Bradykinin B_1 (human)
Activity: K_i = 24 nM; pA_2 = 6.1, human umbilical vein (antagoinst)

Table 3. (Continued)

Library: 3.6
Name: Philanthotoxin analogue
Size: 18 members
Affiliation: Jaroszewski, J. W.; *et al.* [224]

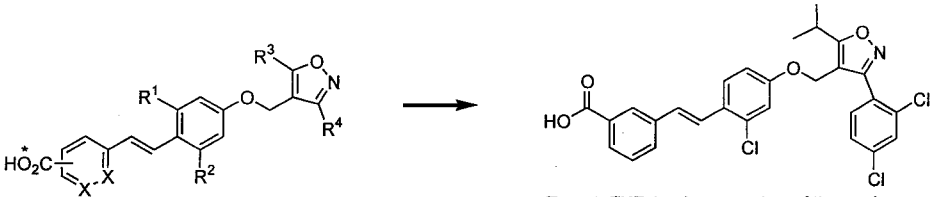


Receptor: Non-NMDA glutamate (rat)
Activity: IC_{50} = 15 nM (antagonist)

Table 4. Chemical Libraries Targeted for Non-G-Protein-Coupled Receptors (∗ Indicates Point of Attachment to the Resin)

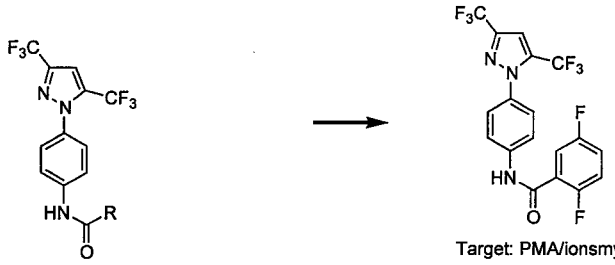
Integrins

Library: 4.1
Name: Arylisoxazole
Size: 600 members
Affiliation: Glaxo Wellcome [139]
Note: Focused library based on 70 nM lead.



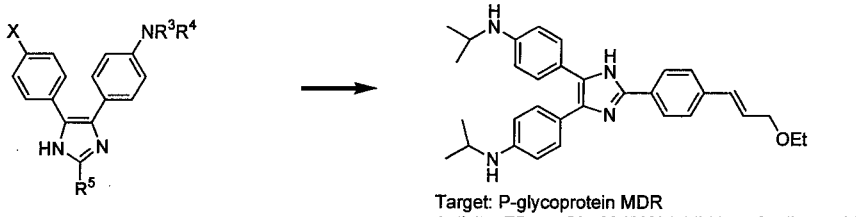
Target: FXR (orphan member of the nuclear receptor gene family)
Activity: EC_{50} = 12 nM (agonist)

Library: 4.2
Name: Pyrazolyl aniline
Size: 350 members
Affiliation: Abbott Lab. [55]
Note: Solution-phase parallel synthesis.



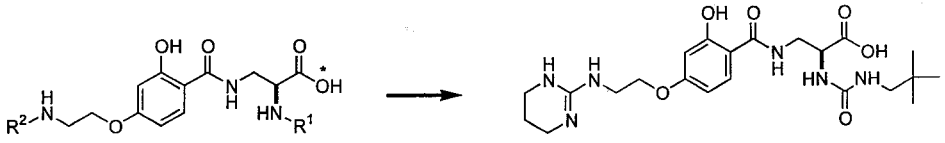
Target: PMA/ionsmycin induced IL-2 synthesis in human whole blood.
Activity: IC_{50} = 372 nM

Library: 4.3
Name: 2,4,5-Trisubstituted imidazoles
Size: ca. 12 members
Affiliation: Ontogen Corp. [254]



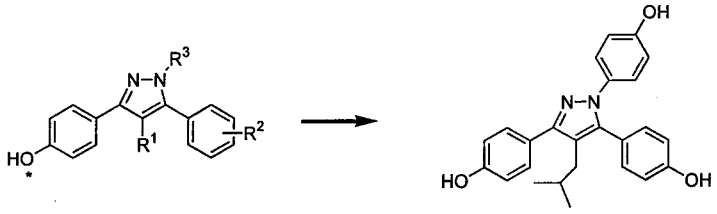
Target: P-glycoprotein MDR
Activity: ED_{50} = 50 nM (50% inhibition of cell growth)

Library: 4.4
Name: Acyl resorcinol
Size: ca. 120 members
Affiliation: Wyeth-Ayerst Rsh. [78]



Receptor: αVβ3 (vitronectin)
Activity: not explicitly given; >100x selectivity versus GPIIb/IIIA.

Library: 4.5
Name: Diarylpyrazole
Size: 108 members
Affiliation: Katzenellenbogen, J. A.; *et al.* [223]



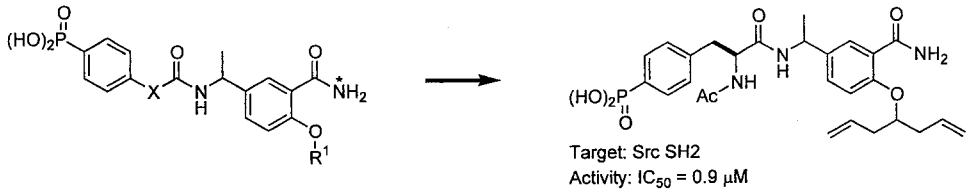
Receptor: Estrogen (lamb cytosol)
Activity: 23% RBA (relative binding affinity derived from competative [^{3}H] estradiol binding assay).

Table 4. (Continued)

Library: 4.6
Name: Imidazole amine
Size: Not defined
Affiliation: Procter & Gamble Pharm. [23]
Note: Solution-phase parallel synthesis.

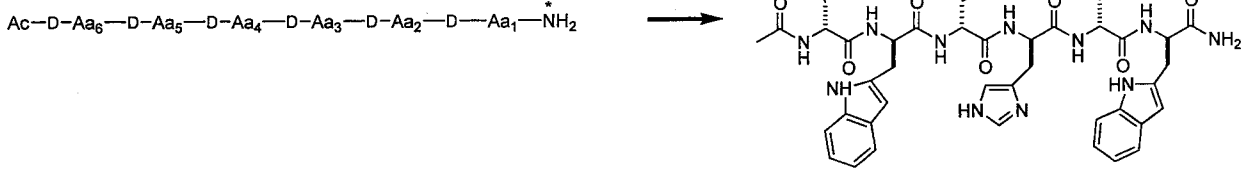
Target: Na^+/K^+ ATPase
Activity: IC_{50} = 1.3 μM

Library: 4.7
Name: Salicylic amide ether
Size: ca. 12 members
Affiliation: ARIAD Pharm. [151]



Target: Src SH2
Activity: IC_{50} = 0.9 μM

Library: 4.8
Name: Hexapeptide
Size: >52,000,000 members
Affiliation: Blondella, S.E.; *et al.* [24]
Note: All D-amino acids.

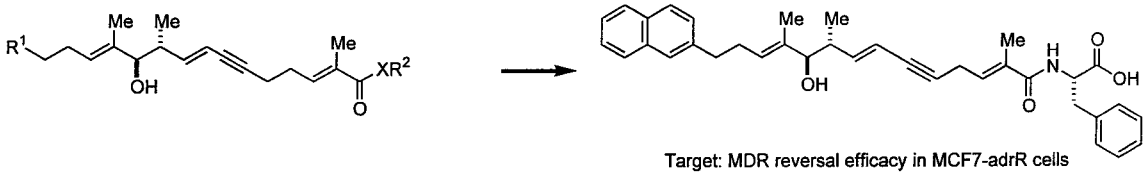


Target: Calmodulin
Activity: IC_{50} = 8.2 μM

Table 5. Chemical Libraries Displaying Cytotoxic and Antiinfective Activity (∗ Indicates the Point of Attachment to the Resin)

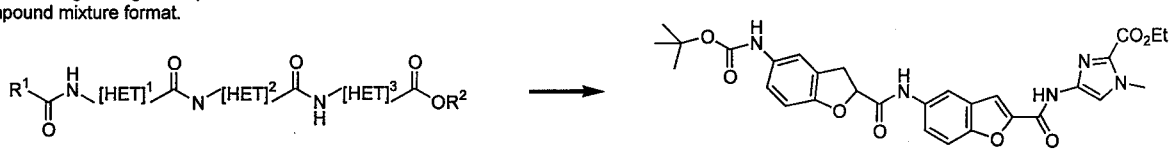
Cytotoxic agents

Library: 5.1
Name: Stipiamide analogs
Size: 42 members
Affiliation: Andrus, M.B.; *et al.* [5]
Note: Solution-phase mixture synthesis.



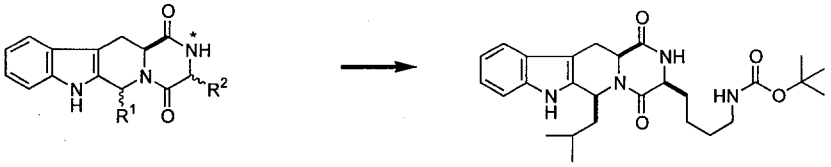
Target: MDR reversal efficacy in MCF7-adrR cells
Activity: ED_{50} = 1.45 μM

Library: 5.2
Name: Distamycin A
Size: 1000 members
Affiliation: Boger, D.L.; *et al.* [25, 26]
Note: Solution-phase synthesis of two 1000 member positional scanning libraries; comparison of screening at single compound versus 10-compound mixture format.



Target: L1210 cytotoxicity
Activity: IC_{50} = 29 nM (1000x more potent than distamycin A)

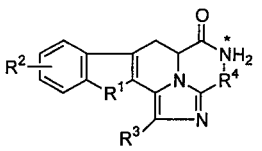
Library: 5.3
Name: Indolyl diketopiperazine
Size: 42 members
Affiliation: Koomen, G. J.; *et al.* [234]

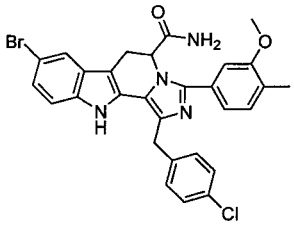


Target: Breast cancer resistant protein (BCRP) inhibition
Activity: 1.0 μM in mito xantrone accumulation assay in T6400 cell line.

Table 5. (Continued)

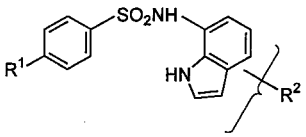
Library: 5.4
Name: Imidazo-pyridindole
Size: 23,375 members
Affiliation: Reixach, N.; *et al.* [202]

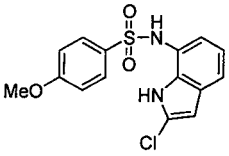




Target: Aβ25-35 and Aβ1-42 (β-amyloid) neurotoxicity (rat pheochromo-cytoma PC-12 cell line)
Activity: IC_{50} = 42 μM, Aβ25-35; IC_{50} = 40 μM, Aβ1-42

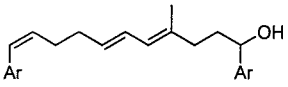
Library: 5.5
Name: (Indolyl)benzenesulfonamide
Size: ca. 33 members
Affiliation: Eisai Co., Ltd. [184]
Note: Solution-phase synthesis.

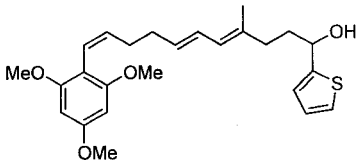




Target: P388 murine leukemia cells
Activity: IC_{50} = 0.11 μg/mL

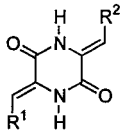
Library: 5.6
Name: Curacin A analog
Size: ca. 50 members
Affiliation: Wipf, P.; *et al.* [244]
Note: Solution-phase synthesis using flourous quenching.

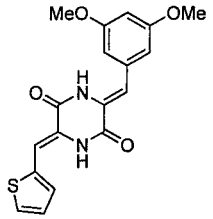




Target: Tubuline-polymerization (bovine)
Activity: IC_{50} = 1.4 μM

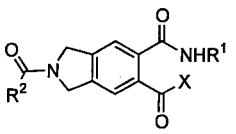
Library: 5.7
Name: Piperazine-2,5-dione
Size: 35 members
Affiliation: Loughlin, W.A.; *et al.* [133]
Note: Solution-phase synthesis.

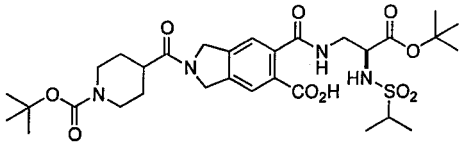




Target: Brine shrimp larvae
Activity: IC_{50} = 18 μg/mL

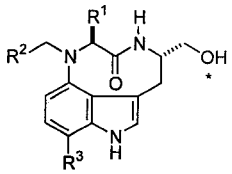
Library: 5.8
Name: Triamide
Size: 120 compounds
Affiliation: Boger, D.L.; *et al.* [27]
Note: Two libraries prepared as individual compounds and as full mixtures to compare the performance of scanning and deletion convolution.
X = OH, NHMe

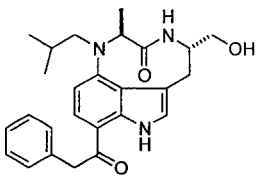




Target: L-1210 (mouse leukemia) cells
Activity: IC_{50} = 5 μM

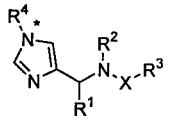
Library: 5.9
Name: Indole lactam
Size: ca. 50 members
Affiliation: Waldmann, H.; *et al.* [150]
Note: Library based on known PKC activator, (-)-indolactam V.

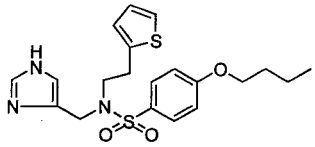




Target: PKC activation in Swiss 3T3 cells
Activity: increase in MARKS translocation at 200 nM; efficient as (-)-indolactam V.

Library: 5.10
Name: Imidazole sulfonamide
Size: ca. 1000 members
Affiliation: Janssen Res. [206]

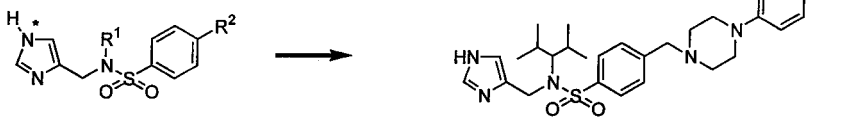




Target: *C. albicans*
Activity: IC_{50} = 11 nM for inhibition of ergosterol synthesis in subcellular screen.

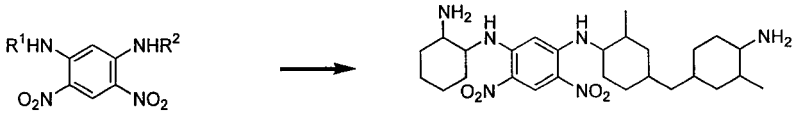
Table 5. (Continued)

Library: 5.11
Name: Imidazole sulfonamide
Size: ca. 28 members
Affiliation: Janssen Res. [205]
Note: Follow-up to library 5.11.



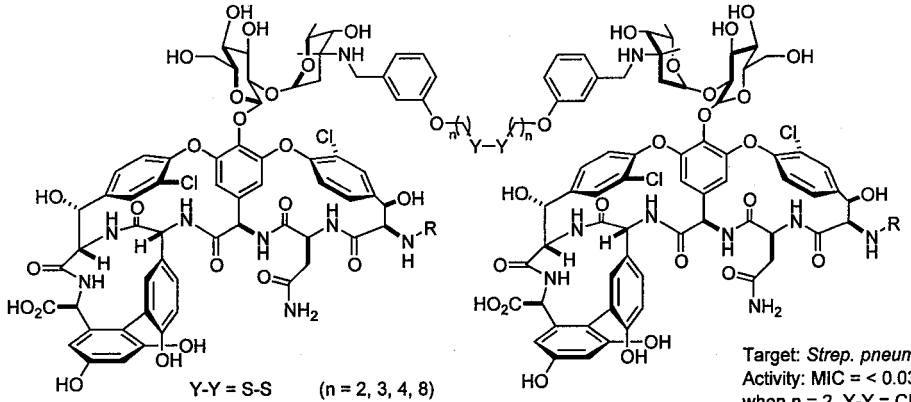
Target: *C. albicans*
Activity: IC_{50} = 8.7 nM for inhibition of ergosterol synthesis in subcellular screen.

Library: 5.12
Name: 1,5-Dialkylamino-2,4-dinitrobenzene
Size: 2485 members
Affiliation: Lam, K. S.; *et al.* [129]



Target: *S. aureus (ATCc25923)*
Activity: MIC = 11 μg/mL

Library: 5.13
Name: Vancomycin dimers
Size: 8 members
Affiliation: Nicolaou, K.C.; *et al.* [168]

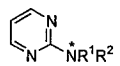


Y-Y = S-S (n = 2, 3, 4, 8)
Y-Y = cis/trans CH = CH (n = 1, 2, 3, 7)

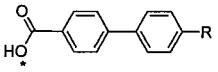
Target: *Strep. pneumoniae*
Activity: MIC = < 0.03 μg/mL
when n = 2, Y-Y = CH=CH, R = LeuNMe

Table 6. Scaffold Derivatization (∗ Represents Point of Attachment to the Resin)

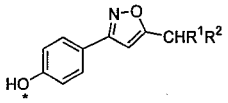
(a) Solid-Phase Scaffold Derivatization



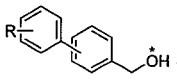
- Kessler, H. [71]
- 7 ex; >95%
- reaction of amines with 2-fluoropyrimidine and DIEA



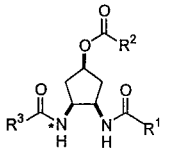
- Hiyawa, T. [95]
- 8 ex; 30-100%
- Pd-catalyzed coupling of aryl(fluoro)silanes with resin-bound aryl iodides



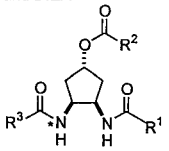
- Barta, S. [11]
- 46 ex; 65-90%
- derivatization of resin-bound 3-(4-hydroxyphenyl)-5-isoxazolecarboxaldehyde



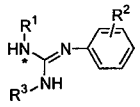
- Yoo, S. [249]
- 4 ex; 60-70%
- Suzuki coupling with resin-bound bromobenzyl alcohols (vinyl ether linker)



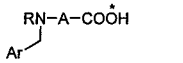
- Bergstrom, D. E. [83]
- 27 members
- derivatization of 3,4-diaminocyclopentanol



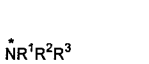
- Bergstrom, D. E. [83]
- 27 members
- derivatization of 3,4-diaminocyclopentanol



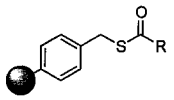
- Selectide [186]
- 880 members
- from resin-bound pyrazole-based guanylating agent



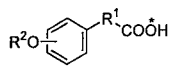
- Novo Nordisk [252]
- 5 ex; 66-97%
- Mitsunobu coupling of benzyl alcohols with resin-bound ammonium iodides



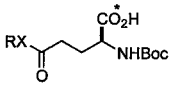
- Janda, K. D. [232]
- 15 ex; 0-71%
- multi-polymer strategy for cleavage of tertiary amines from REM resin



- Bradley, M. [145]
- 5 ex; good yield
- thioesters synthesis on resin to yield alcohols, ketones, lactones

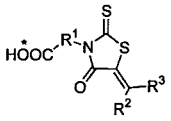


- Bradley, M. [9]
- 20 members
- Mitsunobu coupling of alcohols to resin-bound phenols (dendrimer beads)

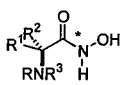


- Dominguez, E. [51]
- 40 ex; 12-100%
- nucleophilic ring opening of resin-bound N-Boc pyroglutamate with heteronucleophiles

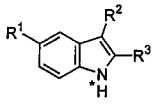
- Carreaux, F. [195]
- 12 ex; 30-90%
- protodeboronation of resin-bound arylboronic acids as a traceless-linker strategy



- Sim, M. M. [119]
- 12 ex; 68%-88%
- condensation of resin-bound rhodanine -3-acetic acid with RCHO and RCOR



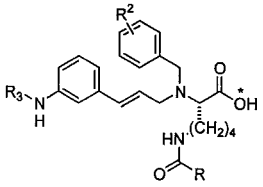
- Lubell, W. D. [230]
- 9 ex; good yield
- displacement of resin-bound oxime esters with $HONH_2$



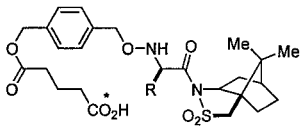
- Kraxner [115]
- 2 ex; 66+99%
- Mannich and Stille reactions on resin-bound diethoxymethyl (DME) protected indoles

Table 6. (Continued)

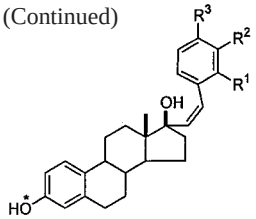
(a) Solid-Phase Scaffold Derivatization (Continued)



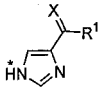
- R. W. Johnson [46]
- 17 ex; 35-85%
- from lysine



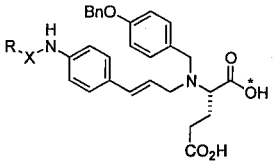
- Kobe Pharm. [154]
- 3 ex; 40-70%
- radical addition to resin-bound oxime ether



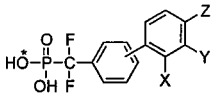
- Hanson, R. N. [120]
- 6 ex; 17-75%
- Stille coupling with resin-bound phenyl-seleno vinyl estradiol



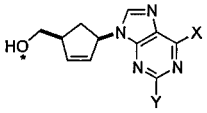
- Timmerman, H. [69]
- 27 ex; 50-89%
- resin-bound 4-iodoimidazole subjected to metal/halogen exchange then an electrophile; X = O, S, OH/H



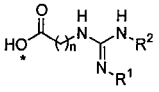
- R. W. Johnson [46]
- 14 ex; 31-77%
- from glutamic acid



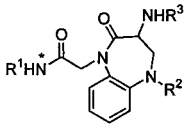
- Taylor, S. D. [101]
- 28 ex; 43-89%
- Suzuki reaction of soluble polymer-bound phosphonates then cleavage with TMSI



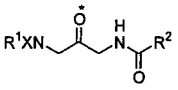
- Crimmins, M. T. [48]
- 9 ex; 60-75%
- Pd-catalyzed coupling of purines to resin-bound allylic benzoate



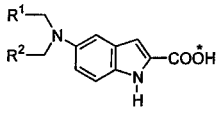
- Burgess, K. [41]
- 50 ex; 53-99%
- reaction of resin-bound amines (or carbodiimides) with carbodiimides (or amines)



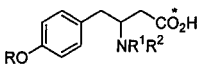
- RPR [92]
- 10,000 members
- derivatization of 3-amino-1,5-benzodiazepine-2-one



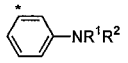
- Pfizer [225]
- 8 ex; 20-60%
- from resin-bound orthoganal protected 1,3-diamine alcohol then oxidation; X = CO, SO_2



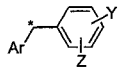
- Franzen, R. [231]
- 8 ex; 40-74%
- reduction of resin-bound 5-nitro-2-carboxy-indole then reductive amination/alkylations



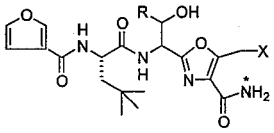
- Aventis [156]
- 1932 members
- tyrosine as scaffolds; IRORI technology



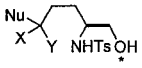
- Maiorana, S. [136]
- 3 ex; ca. 80%
- reaction of resin-bound fluorobenzene chromium dicarbonyl isocyanide complex with amines



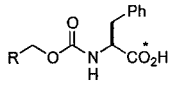
- Mioskowski, C. [235]
- 15 ex; 24-99%
- Pd-catalyzed coupling of arylboronic acids to resin-bound benzylsulfonium salts and simultaneous release



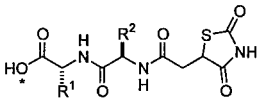
- Peptide Therp. [81]
- 20 ex; high purity
- derivatization of 5-(hydroxymethyl) isoxazole scaffold



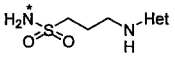
- Cossy, J. [47]
- 8 ex; 59-91%
- ring opening of resin-bound N-tosyl lactam



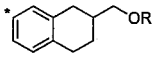
- Novo Nordisk [253]
- 8 ex; 40-82%
- direct conversion of resin-bound Fmoc amino acids to *O*-alkyl carbamates via Mitsunobu reaction



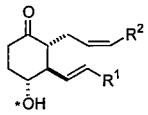
- Mohler, D. L. [155]
- 9 ex; good purity
- standard peptide coupling using 2-chlorotrityl resin



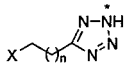
- Millan, D. S. [153]
- 16 ex; good yield
- reaction of resin-bound 3-bromopropane sulfonamide with amines



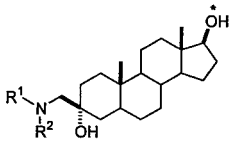
- Jones, G. B. [107]
- ca. 15 members
- etherification or esterification of resin-bound tri-carbonyl Cr complex of corresponding alcohol; R = estrogenic moieties



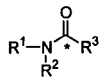
- Janda, K. [131]
- 5 ex; 71-88%
- from resin-bound hydroxy enone



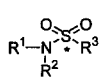
- Eli Lilly [144]
- 30 ex; 24-100%
- reaction of resin-bound chloroalkyl tetrazoles with nucleophile (X)



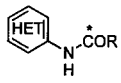
- Poirier, D. [140]
- 4 ex; 45-64%
- from resin-bound steroid expoxide



- RPR [208]
- ca. 35 ex; high yield/purity
- derivatization using TFP activated carboxylate esters



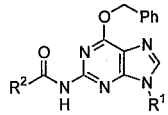
- RPR [208]
- 3 ex; high yield/purity
- derivatization using TFP activated sulfonate esters



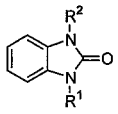
- Hoffmann-La Roche [112]
- 9 ex; 12-94%
- acylation of heterocylic amines by polymeric acyl-transfer reaction

Table 6. (Continued)

(b) Solution-Phase Scaffold Derivatization

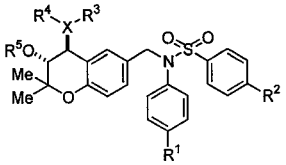


- Hoffmann-La Roche [148]
- 16 ex; 37-99%
- alkylation then acylation of O-benzyl-2-aminopurine using solid-supported reagents

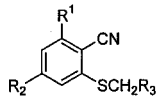


- Roberts, S. M. [64]
- 24 ex; 60-99%
- thiol scavenger to remove alkylating reagents

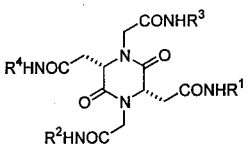
- Wyeth-Ayerst [189]
- 16 ex; 33-100%
- Mitsunobu without chromatography



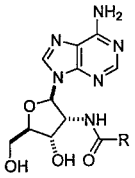
- Nicolaou, K. C. [169]
- 120 members
- Nu ring opening of epoxy benzopyran derivatives



- Semenov, V. V. [218]
- 19 ex; 17-91%
- S-alkylation of CF_3-3-cyano-2(1H)-pyridinethiones



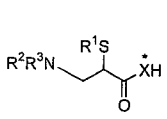
- Taddei, M. [65]
- 21 memebrs



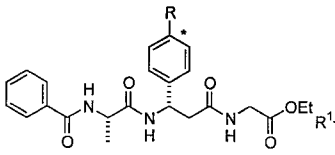
- Link, A. [73]
- 30 ex; 87-98%
- acylation of corresponding amine

Table 7. Acyclic Synthesis (∗ Represents Point of Attachment to the Resin)

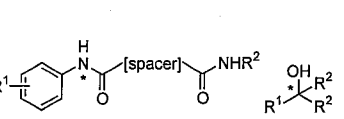
(a) Solid-Phase Acyclic Synthesis



- Novo Nordisk [251]
- 10 ex; 31-94%
- sequential nucleophilic substitution using resin-bound 2,3-dichloropropionic acid

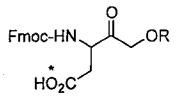


- Silverman, R. B. [122]
- 3 ex; good purity
- traceless silyl linker strategy

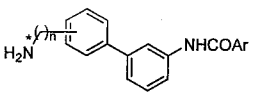


- Astra Zeneca [63]
- 400 members
- diamide synthesis on RINK resin

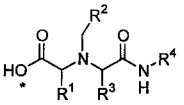
- Chandrasekhar, S. [40]
- 20 ex; 65-90%
- Grignard addition to resin-bound esters



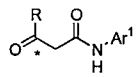
- Jung, G. [158]
- 7 ex; 55-85%
- (acyloxy)methyl ketones via resin-bound Fmoc-protected aspartic acid



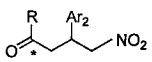
- Hall, D. G. [82]
- 6 ex; 75-100%
- resin-to-resin Suzuki coupling of resin-bound arylboronic acids



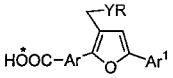
- P & G Pharm. [113]
- 9 ex; 35-91%
- Petasis reaction using resin-bound α-amino acids



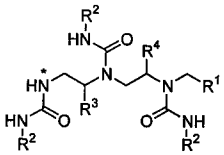
- Aznar, F. [7]
- 9 ex; 51-77%
- reaction of resin-bound enamines with isocyanates



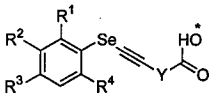
- Aznar, F. [7]
- 10 ex; 0-57%
- reaction of resin-bound enamines with nitroolefins



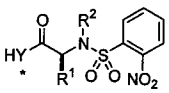
- Merck Frosst [86]
- 19 ex; 0-74%
- cross-coupling of resin-bound aryl halides and zincate derived from THP-protected furan derivatives



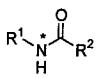
- Houghten, R. A. [164]
- 135 members
- exhaustive reduction of resin-bound amides then treatment with isocyanates and cleavage



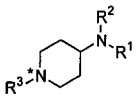
- Diaz, P. [70]
- 16 ex; 5-45%
- Cu-mediated coupling selenyl bromides and resin-bound terminal alkynes



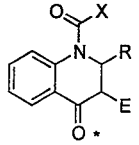
- Chiron [127]
- 11 ex; 90-99%
- Mitsunobu coupling of alcohol with amino acid derived Fukuyama sulfonamides



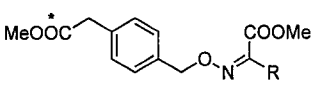
- Abell, C. [159]
- 8 ex; 31-54%
- amides and ureas via SmI_2-mediated cleavage of hydroxyl amino linkage



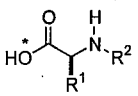
- Abbott [236]
- 12 ex; 8-41%
- N-quaternization then β-elimination of sulfone-based resin



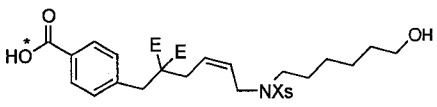
- Novantic [242]
- Ca 25 ex; 50-100%
- attachment of 4-chloroquinoline to resin via ether linkage, carbamylation, Grignard addition and electrophilic cleavage



- Kim, S. S. [106]
- 6 ex; 22-50%
- radical addition of phenylsulfonyl oxime ether on solid support



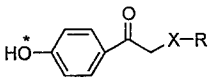
- Chiron [127]
- 7 ex; 85-96%
- derived from Fukuyama sulfonamides



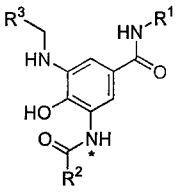
- Dory, Y. L. [68]
- 2 ex; 40-95%
- malonate anion addition to resin-bound 4-chloromethylbenzoic acid (intermediates for macrocycle synthesis

Table 7. (Continued)

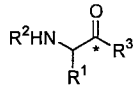
(a) Solid-Phase Acyclic Synthesis (Continued)



- Shionogi [103]
- ca. 12 ex; 40-65%
- insertion reaction of resin-bound α-TMS diazoketones; X = O, S, NH

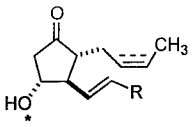


- Nielsen, J. [179]
- 12 members
- chemoselective derivatization of resin-bound 3-amino-4-hydroxy-5-nitrobenzoic acid

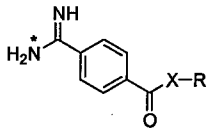


- O'Donnell, M. J. [177]
- 24 ex; 27-87%
- alkylation of benzophenone imine-activated Weinreb resin-bound amino acid then Nu or reductive cleavage

- Organon [193]
- ca. 8 ex; 30-50%
- Grignard and metal hydride compatible REM resin

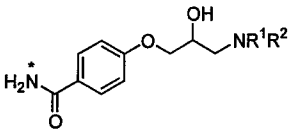


- Janda, K. D. [142]
- 5 ex; 19-32%
- from resin-bound 4-hydroxycyclopentenone

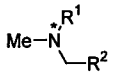


- Bradley, M. [10]
- 5 ex; >50%
- from resin-bound 4-amidinobenzoate

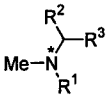
- Deloisy, S. [20]
- 1 ex; 49%
- [4+2] cycloaddition of resin-bound furan with yne-type dienophile, then addition of Nu and retro-[4+2]



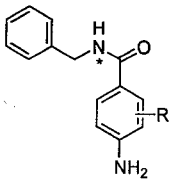
- SKB [36]
- 5800 members
- ring opening of resin-bound expoxide



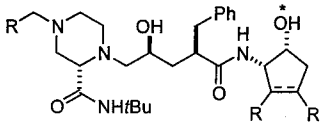
- Grigg, R. [22]
- 15 ex; 34-80%
- methyl tertiary amines via reductive alkylation framentation via hydroxylamine linker



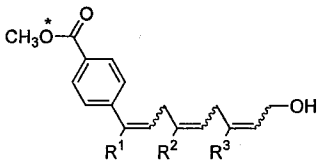
- Grigg, R. [21]
- 22 ex; 18-72%
- displacement of benzotriazole Mannich adducts with Grignard reagent



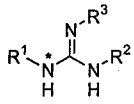
- Affymax [212]
- ca. 75 ex; high yield
- reduction of resin-bound nitro aromatics via sodium hydrosulfite



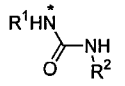
- Merck [42]
- 12 ex; 71-87%



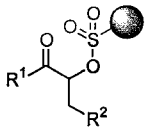
- Dvorak, D. [89]
- ca. 9000 members
- 3-(Bu_3Sn)allyl alcohols used for skipped dienes and trienes



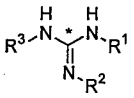
- Brase, S. [49]
- 9 ex; 41-100%
- reaction of diazonium resin-bound thioureas with amines and HgO



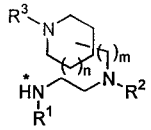
- Ibis
- 8 ex; 50-81%
- one pot Curtius rearrangement of $RCON_3$, trapping with resin-bound amine and cleavage



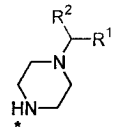
- Nicolaou, K. C. [166]
- 7 ex; high loading
- loading via reaction of sulfonic acid resin and olefins/epoxides



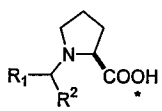
- Mioskowski, C. [74]
- 14 ex; 25-66%
- from resin-bound chlorothioformamidine



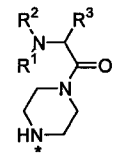
- Ibis [105]
- >20,000 members
- from resin-bound 2-nitrobenzenesulfonyl-protected ethylenediamine



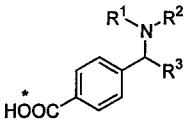
- Novo Nordisk [213]
- 8 ex; 0-81%
- multi-component boronic Mannich reaction



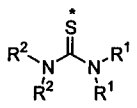
- Novo Nordisk [213]
- 8 ex; 0-81%
- multi-component boronic Mannich reaction



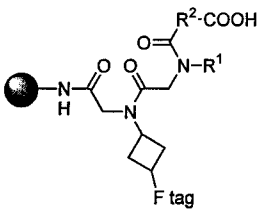
- Novo Nordisk [213]
- 3 ex; 77-90%
- multi-component boronic Mannich reaction



- Novo Nordisk [213]
- 6 ex; 14-29%
- multi-component boronic Mannich reaction



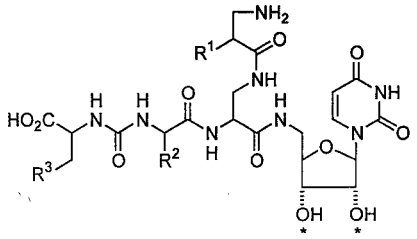
- Mioskowski, C. [75]
- 12 ex; 33-81%
- thermolytic cleavage of dithiocarbamates



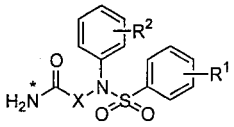
- Pirrung, M. C. [191]
- 90 members

Table 7. (Continued)

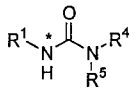
(a) Solid-Phase Acyclic Synthesis (Continued)



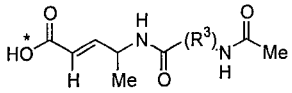
- Glaxo Wellcome [28]
- 80 members
- Mureidomycin analogs; no antibacterial activity observed



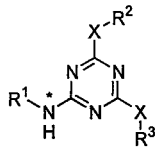
- DuPont [45]
- ca.12 ex; 0-81%
- N-arylation of sulfonamides via $Cu(OAc)_2$ mediated coupling of aryl boronic acids



- Brase, S. [30]
- 60 members
- T2 triazene linker

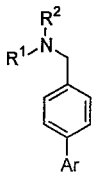


- RPR [39]
- ca. 20 ex.; 62-84%
- derived from resin-bound Horner-Emmons reagent and amino acid aldehydes

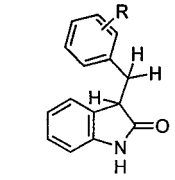


- Germeroth, L. [211]
- 8000 members
- microwave-assisted nucleophilic substitution on cellulose

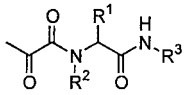
(b) Solution-Phase Acyclic Synthesis



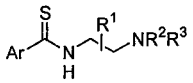
- Organ, M. G. [181]
- 13 ex; 44-63%
- Nu-substitution and Suzuki coupling of 4-bromo benzylbromide



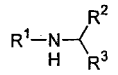
- Argonaut [250]
- 8 ex; good yield
- condensation of indoline-2-one with ArCHO then parallel hydrogenation



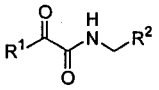
- Senju Pharm. [160]
- 100 members
- Ugi four-component condensation then PDC oxidation



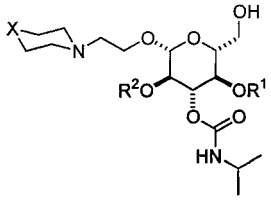
- ACADIA [180]
- 25 members
- microwave-assisted solvent free thioamide synthesis



- Hemming, K. [90]
- 20 ex; 58-99%
- aza-Wittig reaction of R^1N_3 and R^2CHO with resin-bound PPh_3, then reduction (or organo-metallic addition) of imines



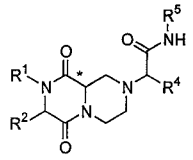
- Searle [221]
- 28 members
- from α-hydroxy acids



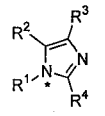
- Hirschmann, R. [93]
- ca. 7 ex; >50%
- multi-step functionalization of β-D-glucose

Table 8. Monocyclic Synthesis (∗ Represents Point of Attachment to the Resin)

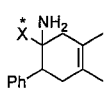
(a) Solid-Phase Monocyclic Synthesis



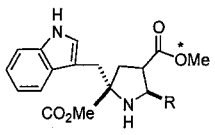
- P & G Pharm. [72]
- 6 ex; 56-96%
- Petasis reaction then diketopiperazine formation



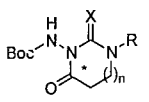
- Balasubramanian, S. [121]
- 19 ex; 23-84%
- from resin-bound N-alkyl-N-(β-keto) amides



- Scheeren, H. W. [117]
- 2 ex; good yield
- high pressure Diels-Alder cycloaddition using resin-bound nitroalkenes; X = H, CH_2OH



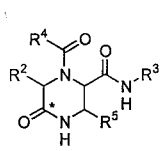
- Grigg, R. [58]
- 2 ex; ca. 50%
- Ag-mediated imine cycloaddition to Wang resin acrylate



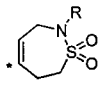
- P & G Pharm. [245]
- 24 ex; 22-69%
- intracyclative cleavage; X = O, S

Table 8. (Continued)

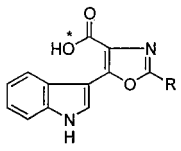
(a) Solid-Phase Monocyclic Synthesis (Continued)



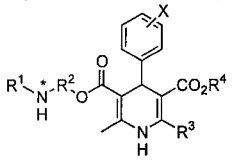
- RPR [100]
- 3 ex; good purity
- resin-bound amino acids subjected to Ugi/deBOC/cyclize strategy



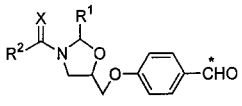
- Brown, R. C. D. [34]
- 3 ex; 49-59%
- ring-closing metathesis cleavage strategy



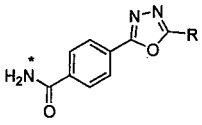
- Nishida, A. [176]
- 8 ex; 9-41%
- oxidative cyclization of resin-bound tryptophan dipeptide



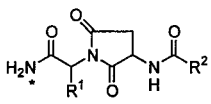
- Axys [31]
- 272 members
- Hantzsch condensation



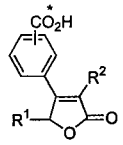
- Oh, H. S. [178]
- 16 ex; 0-92%
- ring opening of resin-bound expoxides then oxidative cleavage with DDQ



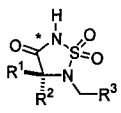
- Glaxo Wellcome [33]
- 10 ex; 60-78%
- diisopropyl carbodiimide mediated cyclodehydration of resin-bound 1,2-diacylhydrazines



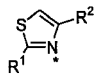
- Houghten, R. A. [3]
- 12 ex; 85->95%
- intramolecular cyclization of aspartic acid containing dipeptide



- Ma, S. [135]
- 12 ex; 82-100%
- Pd-catalyzed cyclization of 1,2-allenic carboxylic acids with resin-bound aryl iodides

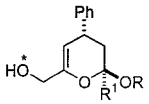


- Albericio, F. [2]
- 10 ex; 7-31%
- sulfamoylation and intracyclative cleavage

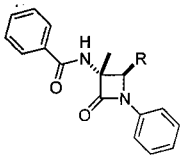


- OSI [194]
- 25 ex; 20-98%
- traceless cleavage of Rink thioamides upon reaction with 2-haloketon

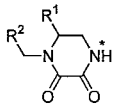
- Kappe, C. O. [108]
- 12 ex; 41-71%
- condensation of resin-bound thiouronium salt with unsaturated β-keto esters; Z = O, S



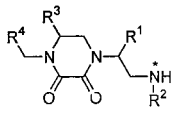
- Brown, E. [118]
- 8 ex; 82-100%
- $Eu(fod)_3$-catalyzed [4+2] heterocycloaddition of resin-bound benzylidene pyruvic acid then LAH



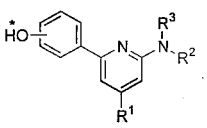
- Enders, D. [215]
- 8 ex; 53-71%
- ester enolate-imine condensation, traceless cleavage for T1-triazene linker



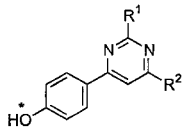
- Houghten, R. A. [161]
- 19 ex; good purity
- reduction of resin-bound acylated amino acid then treatment with oxalyl-diimidazole



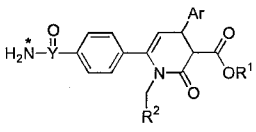
- Houghten, R. A. [161]
- 24 ex; good purity
- reduction of resin-bound acylated dipeptides then treatment with oxalyldiimidazole



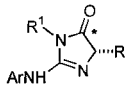
- Katritzky, A. R. [109]
- 10 ex; good purity
- condensation of bromo-methyl amidines with resin-bound chalcones



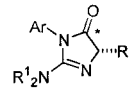
- Katritzky, A. R. [109]
- 3 ex; good purity
- condensation of acetamidines with resin-bound chalcones



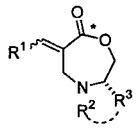
- Chiron [237]
- 25 ex; 30-98%
- from resin-bound acetophenones via chalcone intermediates



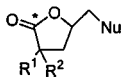
- Glaxo Wellcome [59]
- 6 ex; 34-62%
- reaction of resin-bound amino acids with isothio-cyanates then conversion to carbodiimides and reaction of amines



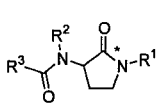
- Glaxo Wellcome [59]
- 5 ex; 44-94%
- reaction of resin-bound amino acids with isothio-cyanates then conversion to carbodiimides and reaction of amines



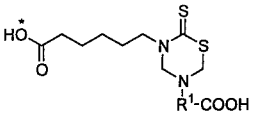
- Reiser, O. [197]
- 6 ex; 51-79%
- Baylis-Hillman reaction of soluble supported acrylate then amino addition and intracyclative cleavage



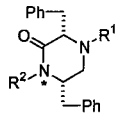
- David, M. [80]
- ca. 20 ex; 13-71%
- nucleophilic ring opening of resin-bound epoxides then intra-cyclative cleavage



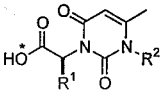
- RPR [99]
- 9 ex; good purity
- Ugi reaction using resin-bound isocyanate



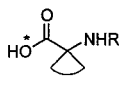
- Perez, R. [190]
- 6 ex; 30-80%
- from resin-bound ε-amino acid



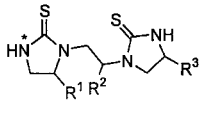
- Glaxo Wellcome [16]
- 4 ex; 34-76%
- use of latent aryl hydrazine safety-catch linker



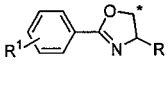
- Wahhab, A. [238]
- 12 ex; 45-90%
- condensation of resin-bound unsymmetrically substituted ureas with diketone in HOAc



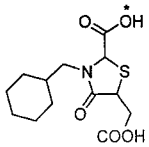
- Chai, C. L. L. [38]
- 7 ex; ca. 50%
- [4+2] cycloaddition of resin-bound Fmoc-dehydroalanine then N-derivatization



- Houghten, R. A. [163]
- 8 ex; good purity
- reduction of resin-bound tripeptides then reaction with thiocarboxyl-diimidazole



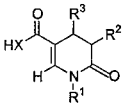
- Pirrung, M. C. [192]
- 28 ex; 32-75%
- intracyclative cleavage of resin-bound N-acylamino alcohol tosylates



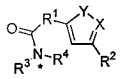
- Novo Nordisk [214]
- 1 ex; 33%
- from resin-bound glyoxylic acid, benzylamine and mercaptosuccinic acid

Table 8. (Continued)

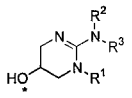
(a) Solid-Phase Monocyclic Synthesis (Continued)



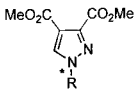
• Affymax [187]
• 18 ex; 45-92%
• aza-annulation of resin-bound enamines (from amines and propynoic acid derivatives) with unsaturated acids and/or anhydrides and Et_3N



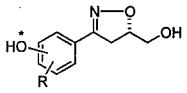
• Merck [217]
• ca. 10 ex; good yield
• condensation of esters with resin-bound acetyl carboxylic acids followed by cyclization with hydrazines or hydroxylamine, activation of the linker, and cleavage using amines



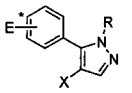
• SIDDCO [104]
• 96 members
• conversion of resin-bound 3-azidopropan-2-ol-1-tosylate to carbodiimides with arylisothiocyanate and Ph_3P then reaction with amine



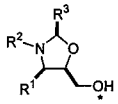
• Komatsu, M. [240]
• 6 ex; 5-70%
• 1, 3-dipolar cycloaddition of polymer-supported azomethine imines with DMAD
R = H, -C(CO_2Me)CHCO_2Me



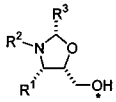
• Jiang, B. [258]
• 7 ex; 38-78%
• asymmetric 1,3-dipolar cycloaddition



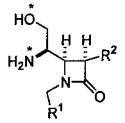
• Spivey, A. C. [222]
• ca. 40 ex; good purity
• Ge-based linker and electrophilic cleavage



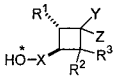
• Janda, K. [233]
• 48 members
• resin-bound epoxides; plus minor R^3 diastereomer



• Janda, K. [233]
• 48 members
• resin-bound epoxides; plus minor R^3 diastereomer

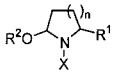


• Balasubramanian [79]
• 7 ex; 45-62%
• β-lactams derived from chiral oxazolidine aldehyde



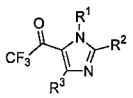
Brown, R. C. D. [35]
ca. 12 ex; 36-97%
from resin-bound cyclobutanone iminium salts;
= alkyl, aryl; Y, Z = R^4, OH/NR; = O

(b) Solution-Phase Monocyclic Synthesis

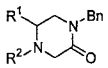


• Yudin, A. K. [219]
• 20 ex; 61-95%
• electrolysis of cyclic carbonates

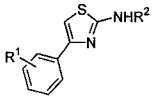
• AstraZeneca [12]
• 1500 members
• reaction of chalcones with hydrazine then derivatization; use of scavenger resins; X = CO, COO, CONH, SO_2



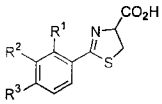
• Monsanto [85]
• 200 members
• conversion of N-acylglycines to munchnones and reaction with benzamidines



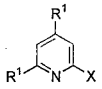
• Merck [54]
• 14 ex; 27-85%
• tandem reductive coupling and S_N2-cyclization of 2-chloro-N-(2-oxoalkyl)acetamide and primary amine



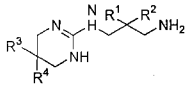
• Bayer AG [204]
• 14 ex; 0-99%
• one-pot synthesis from aryl bromomethyl ketones



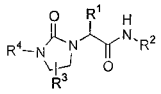
• Loughlin, W. A. [132]
• 7 ex; 16-39%
• from nitrile and cysteine



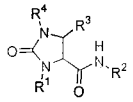
• Ward, T. R. [29]
• ca. 300 members
• Co-catalyzed cyclotrimerization of alkynes and nitriles (2,4,6- and 2,5,6-isomers generated)



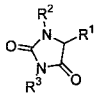
• Escale, R. [143]
• 81 members
• from 2-substituted monoprotected diamines



• RPR [98]
• 4 ex; good purity
• Ugi five-component condensation



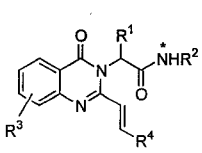
• RPR [98]
• 10 ex; good purity
• Ugi five-component condensation



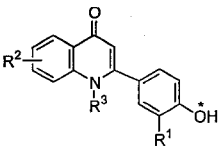
• RPR [98]
• 10 ex; good purity
• Ugi five-component condensation

Table 9. Bicyclic and Spirocyclic Synthesis (∗ Represents Point of Attachment to the Resin)

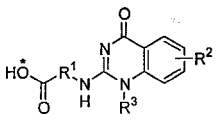
(a) Solid-Phase Bicyclic and Spirocyclic Synthesis



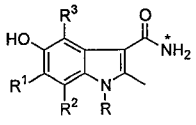
- Houghten, R. A. [229]
- 13 ex; >60% purity
- from resin-bound amino acids, acylation with anthranilic acid derivatives and cyclization



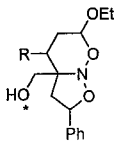
- Sato, S. [210]
- 14 ex; 17-59%
- aqueous ammonia treatment of resin-bound flavylium salts



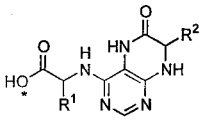
- Wyeth-Ayerst [77]
- 11 ex; 80-95%
- condensation of resin-bound S-methylthiopseudourea with isatoic anhydrides



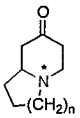
- Ketcha, D. M. [110]
- 14 ex; 21-95%
- Nenitzescu indole synthesis



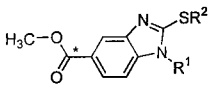
- Scheeren, H. W. [117]
- 5 ex; 29-56%
- high pressure [3+2] cycloaddition of vinyl ether and styrene to resin-bound nitroalkene



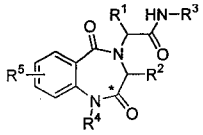
- OAI [13]
- 8 ex; 45-95%
- derived from 4,6-dichloro-5-nitropyrimidine



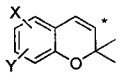
- Pollini, G. P. [8]
- 2 ex; 40-46%
- intramolecular tandem Michael reaction



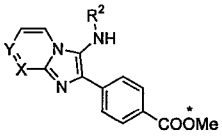
- Sun, C.-M. [247]
- 12 ex; 64-92%
- derived from soluble polymer-bound 4-fluoro-3-nitrobenzoic acid



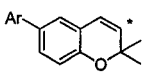
- RPR [100]
- 9750 members
- resin-bound amino acids subjected to Ugi/deBOC/cyclize strategy



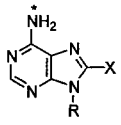
- Nicolaou, K. C. [174]
- >100 members
- use of selenenyl bromide resin



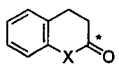
- Mellenium [19]
- 24 ex; 0-95%
- 3-component condensation; X, Y = CH or N



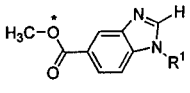
- Nicolaou, K. C. [175]
- >50 members
- use of selenenyl bromide resin



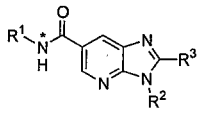
- Gilbert, I. H. [53]
- 10 ex; ca. 10%
- from 4,6-dichloro-5-nitropyrimidine coupled to Rink amide resin



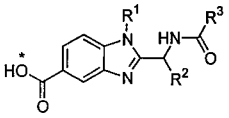
- Kondo, Y. [114]
- 2 ex; 62+66%
- Heck coupling of *o*-iodo aniline and phenol to REM resin then photoinduced cyclorelease



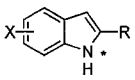
- Sun, C.-M. [43]
- 13 ex; 71-94%
- from 4-fluoro-3-nitro benzoic acid using soluble support



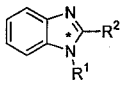
- SKB [66]
- 8 ex; 50-94%
- from resin-bound 2-chloro-3-nitro-pyridine-5-carboxylic acid



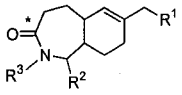
- Novo Nordisk [111]
- 6 ex; 36-86%
- from resin-bound 4-fluoro-3-nitrobenzoic acid



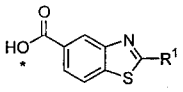
- R. W. Johnson [255]
- 17 ex; 85-100%
- Pd-mediated coupling/ intramolecular indole cyclization of alkynes with resin-bound *o*-iodo anilino sufonamides



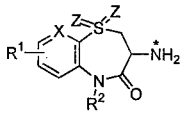
- NanoSyn [146]
- 13 ex; 77-98%
- from 2-fluoro-3-nitrobenzene



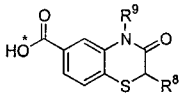
- Blechert, S. [216]
- 9 ex; 14-22%
- yne-ene cross metathesis and Diels-Alder cycloaddition reaction



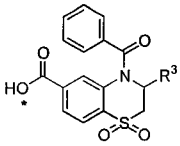
- Barany, G. [248]
- 8 ex; 64-72%
- from resin-bound 3-amino-4-carboxythio-phenol and oxidative cyclocondensation with RCHO



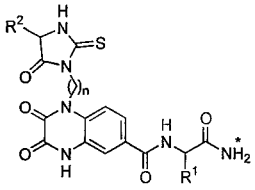
- RPR [157]
- 18 ex; 49-78%
- alkylation of resin-bound cysteine with fluoronitrobenzenes, nitro reduction then lactam formation and cleavage



- Barany, G. [248]
- 16 ex; 44-71%
- from resin-bound 3-amino-4-carboxy-thiophenol



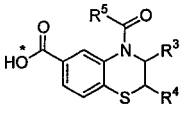
- Barany, G. [248]
- 2 ex; good yield
- from resin-bound 3-amino-4-carboxy-thiophenol



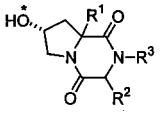
- Houghten, R. A. [162]
- 11 ex; purity >80%
- derived from 4-fluoro-3-nitrobenzoic acid

Table 9. (Continued)

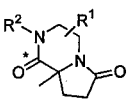
(a) Solid-Phase Bicyclic and Spirocyclic Synthesis (Continued)



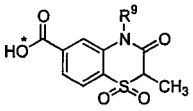
- Barany, G. [248]
- 15 ex; 51-70%
- from resin-bound 3-amino-4-carboxy-thiophenol



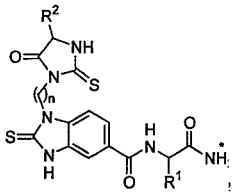
- Bianco, A. [18]
- 30 ex; >50% purity
- from Fmoc-protected hydroxyproline methyl ester



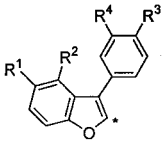
- RPR [99]
- 3 ex; good purity
- Ugi reaction using resin-bound isocyanate



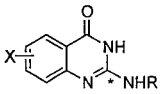
- Barany, G. [248]
- 3 ex; ca. 50%
- from resin-bound 3-amino-4-carboxy-thiophenol



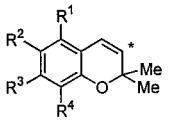
- Houghten, R. A. [162]
- 11 ex; purity >80%
- derived from 4-fluoro-3-nitrobenzoic acid



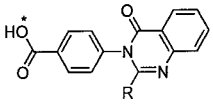
- Nicolaou, K. C. [173]
- 15 ex; 6-29%
- cyclofragmentation of resin-bound epoxy sulfones



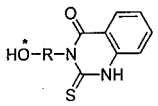
- ArQule [246]
- 10 ex; 53-88%
- reaction of resin-bound isothiourea and isatoic acid



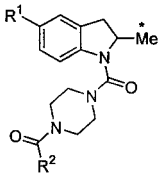
- Nicolaou, K. C. [170]
- six libraries
- cycloaddition of *o*-prenylated phenols with selenenyl bromide resin and further elaboration of benzopyrans



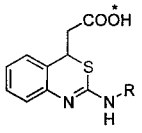
- Ajinomoto [137]
- 7 ex; good yield
- cyclocondensation of anthranilamides with orthoformates



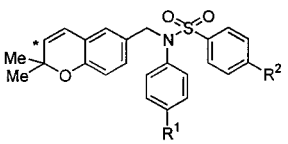
- Ajinomoto [138]
- 5 ex; 35-90%
- condensation of resin-bound nitrobenzenes with 2-methoxycarboxyl phenylisothiocyanate



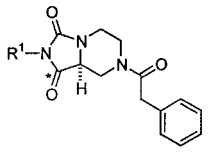
- Nicolaou, K. C. [173]
- ca. 10 ex; good purity
- Se-mediated loading of O-alkyl anilines, acylation and reductive cleavage



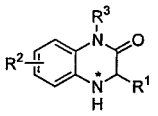
- Miller, B. L. [87]
- 14 ex; 0-78%
- conversion of resin-bound *o*-nitrocinnamic acid to thiourea and treatment with TFA



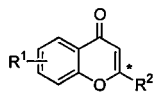
- Nicolaou, K. C. [169]
- 12 members
- cyclo-loading of 4-hydroxy-3-prenylbenz-aldehyde with selenenyl bromide resin, reductive amination, sulfoxylation, oxidative elimination



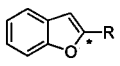
- Ibis [152]
- 8 ex; 59-98%
- reaction of resin-bound N-phenacyl piperazine carboxylic acid with isocyanate, intracyclative cleavage with iPr_2NH



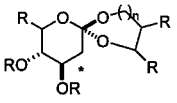
- SIDDCO [116]
- 10 ex; 53-91%
- arylation of resin-bound amino acid esters with 2-fluoro-nitrobenzene, reduction then cyclization



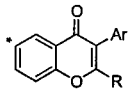
- Brueggemeier, R. W. [17]
- 3 ex; 70-76%
- resin-capture of TMS-protected *o*-hydroxy alkynyl aryl ketones with piperazinyl resin then intracyclative cleavage



- Hartley, R. C. [84]
- 4 ex; 38-83%
- from resin-bound enol ethers

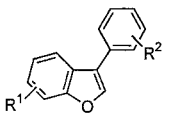


- Nicolaou, K. C. [167]
- 12 ex; good yield
- from resin-bound selenides

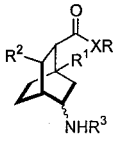


- Park-Davis [88]
- 9 ex; 32-74%
- traceless silyloxy linker

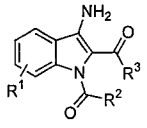
(b) Solution-Phase Bicyclic and Spirocyclic Synthesis



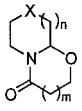
- Nicolaou, K. C. [173]
- ca. 6 ex; 4-13%
- novel cyclofragmentation of epoxy sulfones



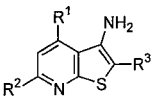
- Ley, S. V. [124, 125]
- ca. 50 ex; 71-98%
- tandem Michael addition of enolates from 2-cyclo hexenones and acrylates then reductive amination and derivatization; X = O, NH



- Hoffmann-La Roche [165]
- 205 members
- N-alkylation of N-acylbenzonitriles then cyclization



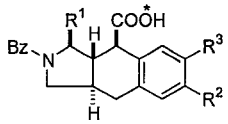
- Yudin, A. K. [219]
- 6 ex; 80-95%
- intramolecular cyclization via electrolysis



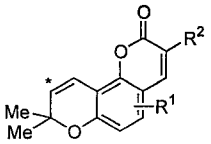
- Semenov, V. V. [218]
- 14 ex; 68-95%
- S-alkylation then hetero-cyclization of CF_3-3-cyano-2(1H)-pyridinethiones

Table 10. Polycyclic and Macrocyclic Synthesis (∗ Represents Point of Attachment to the Resin)

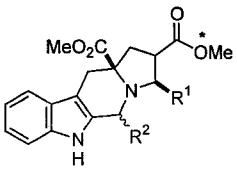
(a) Solid-Phase Polycyclic and Macrocyclic Synthesis



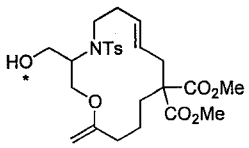
• R. W. Johnson [226]
• 8 ex; 0-98%
• intramolecular Diels-Alder reaction using vinyl benzenes as diene component



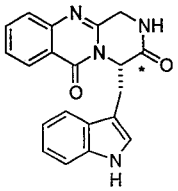
• Nicolaou, K. C. [169]
• 10 members
• synthesis via cycloloading of σ-prenylated phenols with selenenyl bromide resin and coumarin annulation



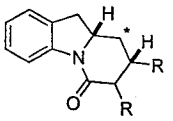
• Grigg, R. [58]
• 20 members
• Ag-mediated imine cycloaddition to Wang resin acrylate then Pictet-Spengler cyclization



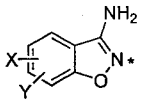
• Deslongchamps, P. [199]
• 2 ex; 8 + 45%
• on resin macrocyclization of malonate anion and alkylic chloride



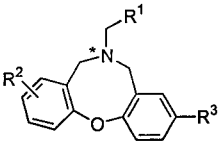
• Ganesan, A. [239]
• ca. 20 ex; 17-90%
• resin-bound tripeptides containing a central anthranilate subjected to dehydration and intracyclative cleavage



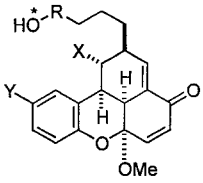
• Nicolaou, K. C. [172]
• 5 ex; 13-26%
• radical-based cyclo-release of resin-bound Se-loaded indolines



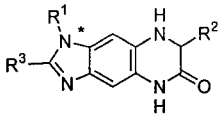
• Eli Lilly [123]
• ca. 15 ex; good yield
• O-arylation of Kaizer oxime with fluoro benzonitriles, hydrolysis and intramolecular cyclization



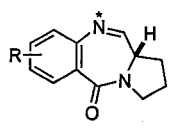
• Amgen [183]
• 17 ex; 12-69%
• S_NAr of fluoride with phenolic OH



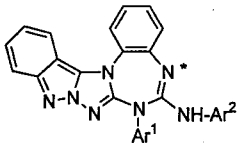
• Shair, M. D. [128]
• 5 ex; 77-81%
• intermolecular oxidative heterodimerization of *o*-hydroxystyrenes



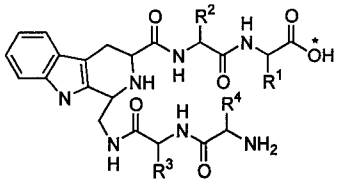
• Nanosyn [147]
• 7 ex; 72-92%
• from 1,5-difluoro-2,4-dinitrobenzene



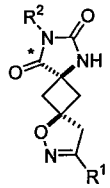
• Thurston, D. E. [15]
• 4 ex; 37-68%
• derived from resin-bound anthranilic acid and pyrrolidinemethano



• Molina, P. [130]
• 17 ex; 72-81%
• aza Wittig/carbodiimide-mediated annulation

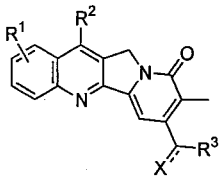


• Sphinx [126]
• 15 ex; high purity
• Picket-Spemgler condensation of resin-bound tryptophan fragments with Fmoc-amino aldelyde



• Kurth, M. J. [185]
• 4 ex; 35-40%
• nitrile oxide cycloaddition

(b) Solution-Phase Polycyclic and Macrocyclic Synthesis



• Curran, D. P. [52]
• 64 members
• cascade radical annulation reaction; X = OH, O

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