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The eleventh annual review provides an inventory of chemical libraries, solid-phase reagents, scavengers, linkers, and polymer-supported chiral ligands reported in 2007. This year there is a new category highlighting molecular probes for chemical biology and a separate inventory of fluorous technology.

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Comprehensive Survey of Chemical Libraries for Drug Discovery and Chemical Biology: 2007

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This is the eleventh installment of the comprehensive survey series in combinatorial chemistry.[1] This year there is a new grouping highlighting molecular probes (Table 6) and a separate inventory of fluorous technology (Table 13). Bioactive libraries are captured in Tables 1−5 under the headings of proteases, nonproteolytic enzymes, GPCRs, nonGPCRs, and oncolytics/antiinfectives. Compound collections without disclosed biological activity are captured in Tables 7−10 under the headings of scaffold derivatization/acyclic synthesis, monocyclic, bicyclic/spirocyclic, and polycyclic/macrocyclic synthesis. Polymer-supported reagents/scavengers/linkers and polymer-supported chiral ligands are presented in Tables 11 and 12, respectively. There are a total of 498 entries this year.[8– 467]

The amalgamation of modern high-throughput chemistry with ultra-high-throughput screening gave birth to 21st century chemical biology, an interdisciplinary field exploring the intersection of chemical space and biological activity. One anticipated outcome of chemical biology research is the discovery and characterization of molecular probes or tool compounds. Such probes serve to investigate fundamental biological function at the molecular, cellular, and whole organism level. A probe compound may be defined as a small molecule that elicits a cellular event or phenotypical result (or responds to a phenotype or event) through the specific interaction with a target protein, pathway or analyte. Probes need not possess the rigorous ADME properties or oral bioavailability of a drug, although drugs generally make superb probes. Currently, academic researchers, research institutions such as the U.S. National Institutes of Health (NIH), and the pharmaceutical sector (by way of drug discovery) are engaged in the search for novel probe compounds. The Molecular Libraries Screening Center Network (MLSCN) that includes the NIH Chemical Genomics Center and the Broad Institute are examples of institutions committed to identifying probe compounds. With this in mind, selected probes reported in the literature in 2007 are presented in Table 6. The listing is not intended to be comprehensive but rather to include molecules that represent first in class reagents or compounds relevant to the goals of chemical biology. Furthermore, the significance of the

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cellular target was considered, and molecules that influence cellular constructs associated with important phenotypes/cellular events were given extra consideration. The degree of characterization, selectivity over ancillary targets, and appropriate physiochemical properties were also criteria for selection.

In addition to the tables there are 26 vignettes. Selected vignettes on biologically active libraries include: metabotropic glutamate receptor-1 (mGluR1) antagonists,[289] cannabinoid-1 receptor antagonists,[363] dual dopamine D3/D2 receptor antagonists,[2] CCR3 chemokine receptor antagoinsts,[299] gonadotropin-releasing hormone receptor antagonists,[194] T-type calcium channel blockers,[163] protein geranylgeranyltransferase type I inhibitors,[52] and the application of "substrate-activity screening" to identify phosphatase[366] and cathepsin B inhibitors.[154] Glutathione sensor H22,[3] spliceostatin A,[164] interleukin-2-inducible T cell kinase inhibitor,[365] and heat shock protein inhibitor PU-H71[323] are the molecular probe selections. Methodology selections include a new method for converting alcohols to primary amines,[380] mild hydrolysis of resin-bound ester with Me_3SnOH,[252] new application of resin-bound selenyl bromide for heterocyclic synthesis,[147,148] post functionalization of multicomponent reactions (MCRs) yielding polycyclic ring systems, [317,368,369] an MCR leading to highly substituted γ-lactams,[422] and the use of fluorous technology in the synthesis of DOS and natural-product-like libraries.[78,212,243,451]

Related publications and reviews appeared in 2007 on fluorous chemistry and separations,[482−485] multicomponent condensations,[486−489] fragment-based lead discovery,[490−496] high-throughput heterocyclic synthesis,[497,498] applications of click chemistry,[499] dynamic combinatorial chemistry,[500] DNA-encoded chemical libraries,[501] chemical genomics,[502−507] high-throughput microwave synthesis,[508−512] library design,[513−517] combinatorial solid-phase natural product chemistry,[518] heterocyclic synthesis with 1,5-difluoro-2,4-dinitrobenzene,[519] synthesis of flavonoid,[520] medium-sized lactam,[521] and diketopiperazine[522] scaffolds, DNA-binding library,[523] PNA-encoded libraries,[524] polyamine analog libraries,[525] aziridines in parallel synthesis,[526] colorimetric tests for the detection of hydroxyl groups[527] and aromatic amines,[528] catch-and-release techniques,[529] continuous-flow microchemical synthesis,[530] one-bead-one-reactor synthesis,[531] discovery of chemical reactions through multidimensional screening,[532] phase-switch synthesis with boronic acids,[533] image-based screening,[534] and label-free detection of solid-phase-bound compounds via Raman scattering microspectroscopy.[535]

Lastly, Fitzgerald, Sabat, and Geysen published a fascinating analysis of the diversity space coverage by public libraries.[536] All 3-point diversity libraries were culled from the Comprehensive Annual Review of Library Synthesis series covering the literature from 1992−2003.[537] A total of 698 libraries resulting in 1246 unique scaffolds were analyzed using Diversity Space methodology,[538] to assess *inter*library versus *intra*library diversity. In this methodology, the 3-point diversity elements of a library are combined to yield a diversity triangle, which when further translated into diversity space become the means for library-to-library comparison. Among the many observations and nuances, the analysis revealed (a) several apparent scaffold hopping opportunities, (b) one example where ~25% of the all the libraries were complete subsets of a single isoquinolone library, for which no bioactivity had yet been disclosed, and (c) over 50% of the 698 libraries were completely contained in the top 11 ranked libraries, suggesting rather significant overlap in chemical landscape covered by existing pubic domain libraries.

mGluR1 Antagonists.[289] Glutamate is a key neurotransmiter in the central nervous system (CNS). Its receptors include the ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). There are eight subtypes of mGluRs (mGluR1−8). The mGluR1 subtype is directly involved in pain signaling, and it is thought that antagonists of mGluR1 represent potential analgesics. Historically the first mGluR1 antagonists were amino-acid-based derivatives. Because these types of agents generally exhibit poor CNS bioavailability, research is focused on the discovery of non-amino-acid-based antagonists. Screening compounds containing a pyrazine subunit from Pfizer's compound repository in a mGluR1 inhibitory binding assay afforded amide hits **1**−**4** with low micromolar to submicromolar inhibitory potency (Figure 1a).[289] The hits share the same carboxylic acid **5**. To diversify this moiety, Owen and colleagues reacted amines **6**−**9** present in the hits with a set of 125 heterocyclic acids **10** generating a 500-membered library **11** (library 3.24). Care was taken to select heterocyclic acids of molecular weight < 250. Library **11** was prepared via solution phase using HBTU as the coupling reagent in DMA at 50 °C for 12 h. The screening of **11** afforded a few hits with nanomolar potency **12**−**14**. These hits share the quinoxaline-2-carboxylic acid that had been previously identified as an active fragment against mGluR1. Although **14** was the most potent analog in the mGluR1 inhibitory assay, it exhibited low stability in an in vitro human liver microsomal metabolic assay. To optimize the profile of this compound series, further efforts centered on decreasing compound lipophilicity (e.g., lower cLogP, lower LogD). The synthesis and profiling of related analogs **15**−**20** indicated that the benzylic gem dimethyl was optimal with respect to potency (compare **14** to **15/16**), while the introduction of heteroatoms at the benzylic position (**18**, **19**) and in the phenyl ring (**14** → **20**) decreased potency. The most potent analog was **17** (K_i = 2 nM), the 4-fluoro analog of **14**. The next step focused on the SAR of the quinoxaline-2-carboxylic acid group. Removal of either the carbonyl group (**14** → **26**) or the fused ring (**14** → **21**) was detrimental to activity. On the other hand, incorporation of a phenyl ring at either the 5- or 6-postion of the pyrazine ring was somewhat tolerated (**22**, K_i = 315 nM; **24**, K_i = 179 nM). Replacement of the phenyl groups with piperidine led to a 10- to 30-fold increase in potency (**23**, K_i = 11 nM; **25**, K_i = 17 nM). Although replacement of the phenyl fused ring with a cyclohexyl group improved potency greatly (**27**, K_i = 2 nM), it was thought that further derivatization of this site would not lead to viable compounds.

Since incorporation of the piperidine amine showed improvement on potency, two additional targeted libraries **28a** and **28b** were constructed using 5-chloro and 6-chlo-

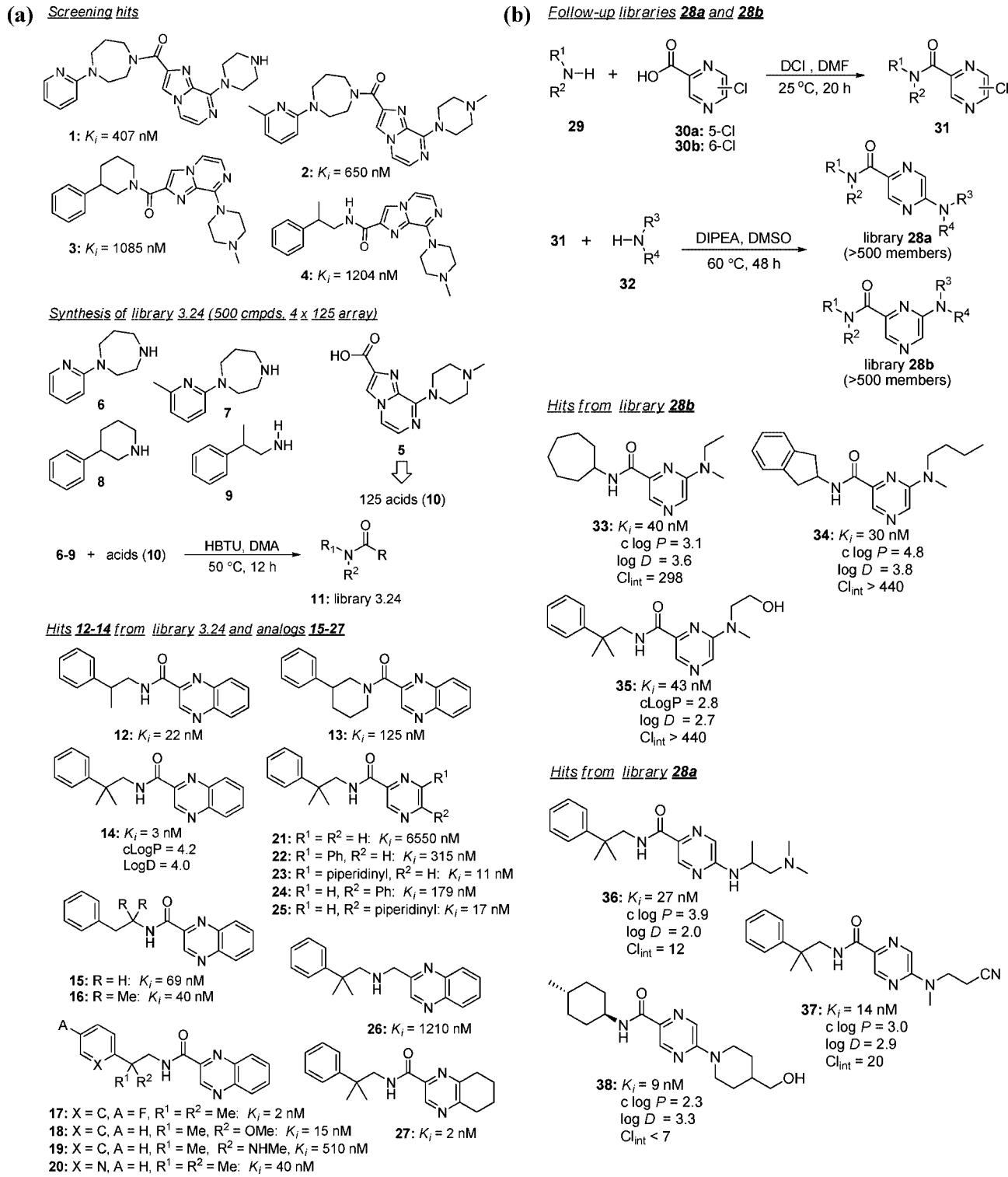


Figure 1. Pfizer's mGluR1 antagonist leads.[289]

ropyrazine 2-carboxylic acids and a set of amines (clog P < 4.8 and molecular weight < 450; Figure 1b). More than 500 compounds were prepared for each regioisomer library. It was observed that although the C-6 regioisomer library **28b** afforded potent compounds, they exhibited low human liver microsomal stability (**33**−**35**, K_i = 30−43 nM, Cl_{int} > 290 μL/min/mg) and were, therefore, not viable. In contrast, compounds from the C-5 regioisomer library **28a** were found not only to be highly potent against mGluR1, but also stable in vitro human liver microsome preparations (**36**−**38**, K_i < 30 nM, Cl_{int} < 20 μL/min/mg). Further analysis showed that compound **38** exhibited a good permeability profile (PAMPA assay, 25.5 × 10^{-6} cm/s) making it an attractive lead for mGluR1 inhibition.

Cannabinoid Receptor Antagonists.[363] Obesity has increased dramatically in the last two decades affecting at least 25% of the adult population in the U.S.A. and about 8% in the rest of the world. Obesity often leads to or exacerbates other diseases, such as type 2 diabetes, hypertension, osteoarthritis, and cardiovascular disease. Based on the

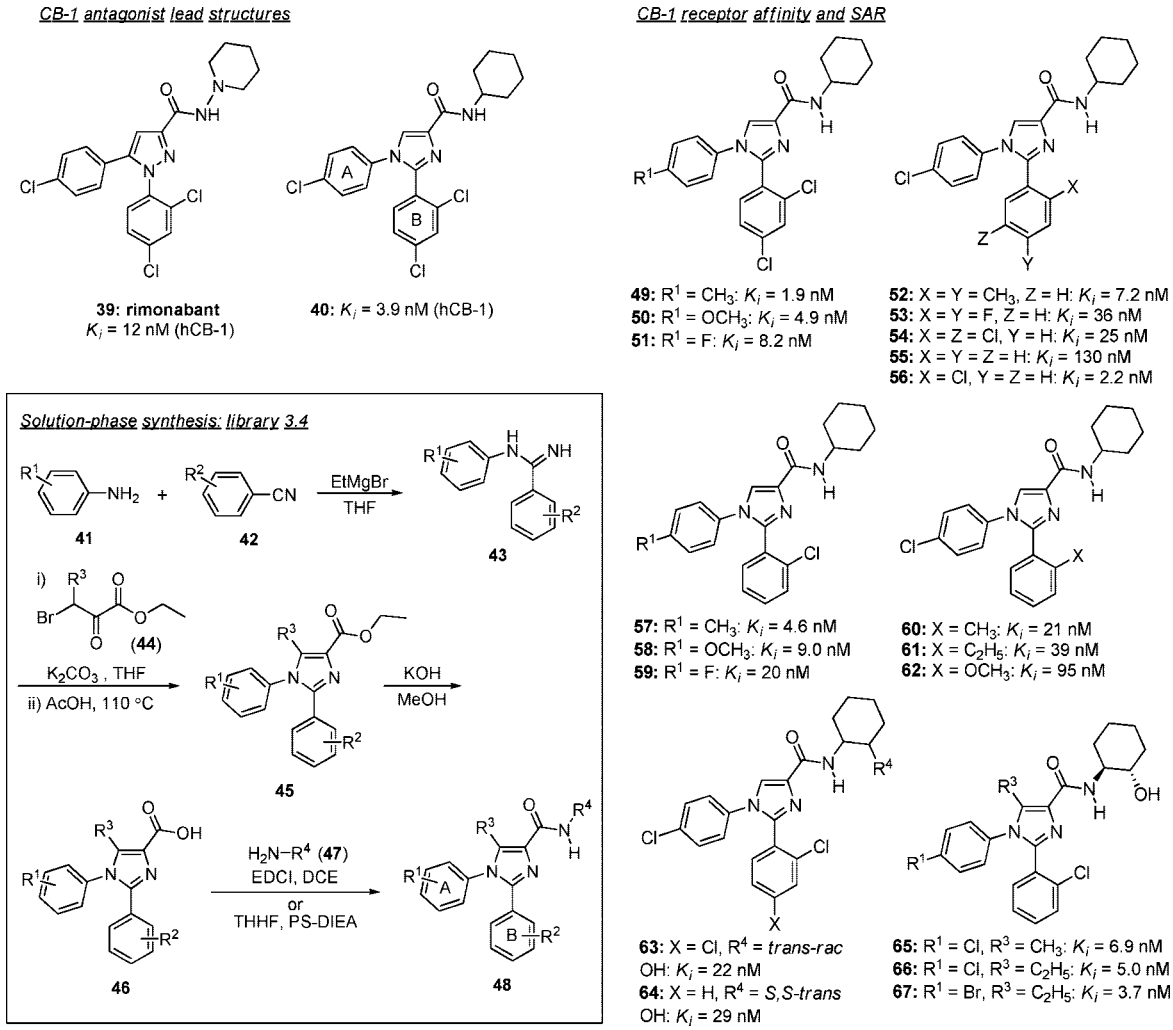


Figure 2. Bayer's CB-1 antagonists.[363]

pioneering work at Sanofi-Aventis, cannabinoid-1 (CB-1) receptor antagonists are a viable option to treat obesity in humans. CB-1 antagonists reported in the literature generally possess a heterocyclic core flanked by two aromatic rings and a H-bond acceptor/donor group, as exemplified by **39** (rimonabant). On the basis of this and other SAR observations, Smith and colleagues explored diaryl imidazoles as potential CB-1 ligands employing **40** as the lead structure (Figure 2).[363] A solution-phase route was developed where anilines **41** were reacted with benzonitriles **42** in the presence of ethylmagnesium bromide to afford diaryl amidine intermediates **43**. These in turn were condensed with bromopyruvates **44** to give diaryl imidazole esters **45**. Following saponification, the corresponding carboxylic acids **46** were coupled with amines **47** in the presence of either EDCI/DCE or THHF and polymer-supported DIEA yielding the desired library **48** (library 3.4). The SAR that emerged upon screening of **48** indicated that small R^1 subsitutents, for example, Me, OMe, F, on the *para* position of the nitrogen-bearing aryl ring A were well tolerated (**49**−**51**, K_i = 1.9 − 8.2 nM) relative to **40**. The methyl group readily substituted for the chloro groups at R^2 on phenyl ring B (**52**, K_i = 7.2 nM); however, fluoro substitution was less successful, resulting in a ∼10-fold loss in activity (**53**, K_i = 36 nM). The *ortho*/*para* pattern of the chlorine atoms in ring B was optimal for activity as the 2,5-substitution pattern resulted in diminished affinity (**54**, K_i = 25 nM). Removal of both chlorine atoms was detrimental for affinity (**55**, K_i = 130 nM), and removal of the 4-chloro was found to increase potency (**56**, K_i = 2.2 nM). To follow up on this latter result, the 2-chloro substituent on ring B was kept constant, while analogs at R^1 in ring A were investigated. The SAR followed the previously observed trend: Me > OMe > F (**57**−**59**, K_i = 4.6, 9.0, and 20 nM, respectively). Variation of the 2-chlorophenyl substituent on R^2 was not productive (**60**−**62**, K_i = 21, 39, and 95 nM, respectively). Because rodent pharmacokinetic (PK) studies of all the potent compounds revealed a trend toward poor plasma levels (**40**, $C_{max} \approx 50$ nM; 10 mg/kg po), an SAR study was therefore conducted on the cyclohexyl group (R^4). Amino, methylamino, and hydroxyl groups were incorporated at the 2 position of the cyclohexyl moiety to decrease lipophilicity. The new analogs displayed superior PK properties. The hydroxy group proved to be the best of the polar substituents as exemplified by **63**, K_i = 22 nM, and **64**, K_i = 29 nM. Although **64** was 10-fold less potent than **40**, plasma exposures increased some 30-fold (**64**, C_{max} = 1.64 μM; 10 mg/kg po). In vivo studies of **64** in a fasted−re-fed rat model (10 mg/kg, p.o) produced a 34−62% reduction in food intake when measured at the 0.5−4.0 h time points. Further SAR studies targeted the

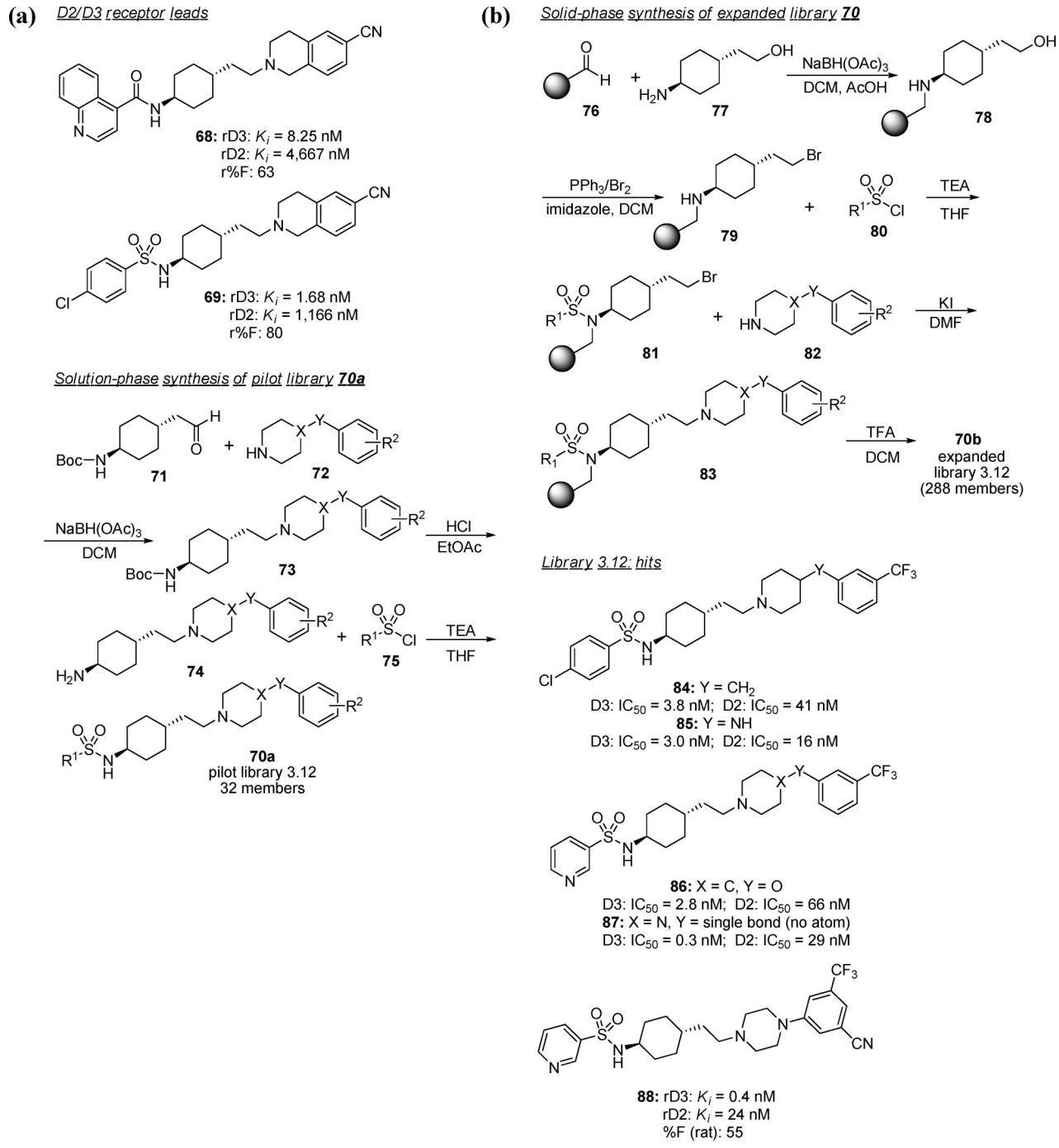


Figure 3. (a) Dual dopamine D3/D2 antagonists: pilot library **70a**.[2] (b) Dual dopamine D3/D2 antagonists: expanded library **70b**.[2]

5-position of the imidazole ring (R^3). Incorporation of small alkyl groups did not affect potency significantly (**65**, **66**, K_i = 6.9 and 5.0 nM, respectively). Replacement of the chloro atom at R^1 with a bromo atom furnished analog **67**. This agent was as potent as the initial lead **40** and exhibited one of the highest plasma exposures of the series (**67**, K_i = 3.7 nM, C_{max} = 2.10 μM; 10 mg/kg po). In vivo studies of **67** in a fasted−re-fed rat model (10 mg/kg, p.o.) also resulted in a 35−64% reduction in food intake when measured at the 0.5−4.0 h time points. These data were comparable to the marketed CB-1 antagonist rimonabant **39**.

Dual Dopamine D3/D2 Antagonists.[2] Dopamine is a key neurotransmitter involved in many neuropsychological events. The dopamine receptors comprise 5 subtypes, D1−D5, where each subtype has a distinct role in the mammalian CNS. Because of the notion that multimodal CNS agents are more efficacious than selective single target agents, researchers at Gedeon Richter pursued dual-acting dopamine D2/D3 receptor antagonists as antipsychotics.[2] The dopamine D3 receptor ligand **68** (SB-277011) (D3 (rat), K_i = 8.25 nM; D2 (rat), K_i = 4,667 nM, $\%F$ = 63 (rat)) and in-house analog **69** (rD3, K_i = 1.68 nM; rD2, K_i = 1,166 nM, $\%F$ = 80 (rat)) were used as a starting point for the design of library 3.12 (**70a/b**) to identify novel potent dual ligands (Figure 3a). For this study, two synthetic approaches were employed. The first approach was a solution-phase route where *trans*-Boc-4-aminocyclohexyl acetaldehyde **71** underwent reductive amination with several piperidine and piperazine analogs **72** to

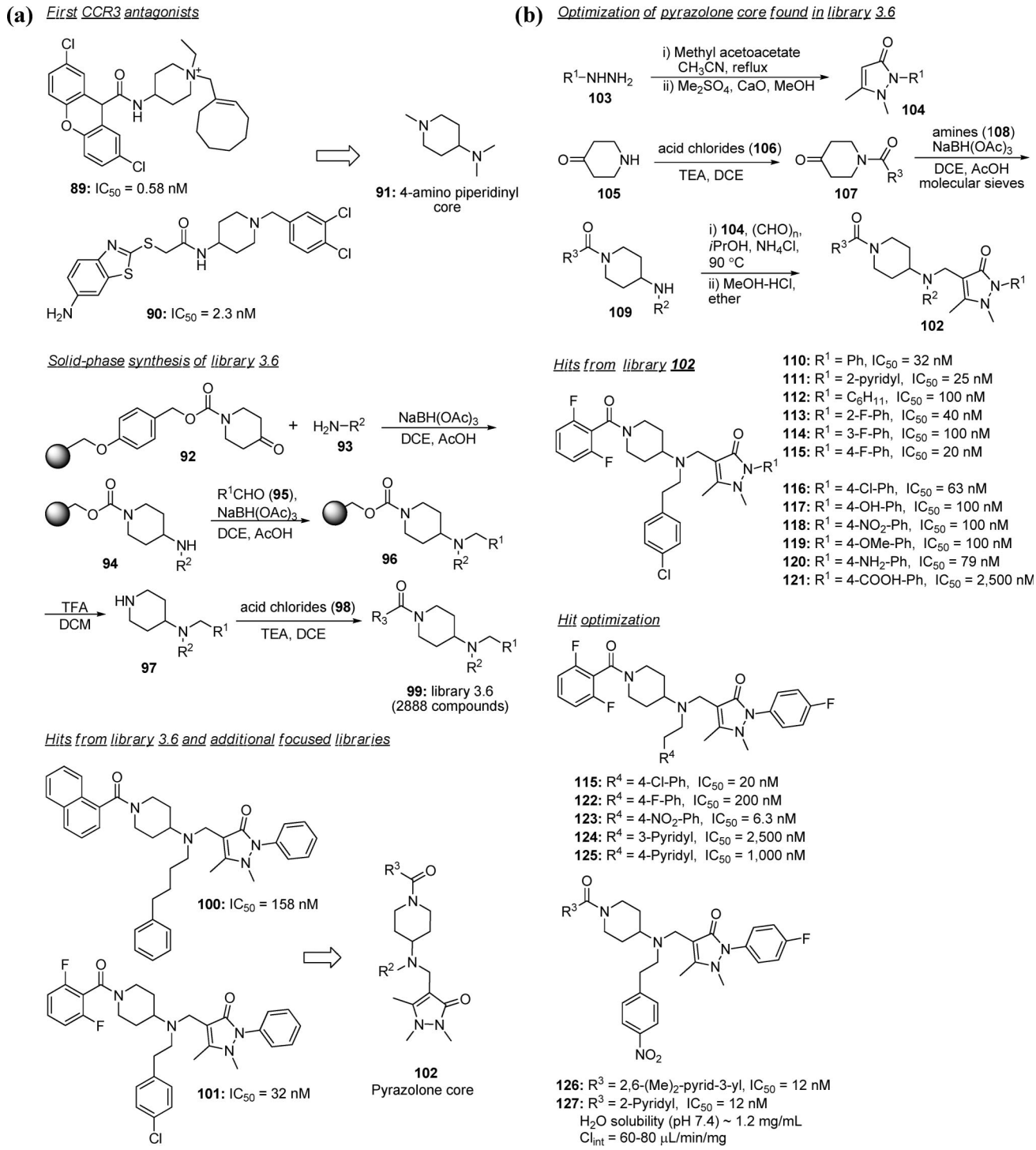


Figure 4. (a) CCR3 antagonists.[299] (b) Optimization of CCR3 antagonists.[299]

give intermediates **73**. Removal of the Boc protecting group with HCl/EtOAc (**73** → **74**), followed by reaction with a set of sulfonyl chlorides **75**, afforded the desired sulfonamide library **70a** (32 members). After the sulfonamide library was profiled at the D3 receptor, a computational model was developed (3D-QSAR study using CoMFA). This model was used to build a 1288-membered virtual library around **70a**. After application of the pharmacophore model and reactivity filtering, 288 candidates in an expanded library 3.12 (**70b**) were targeted for synthesis (Figure 3b). A solid-phase synthetic route was devised. *trans*-4-Aminocyclohexylethanol **77** was immobilized on an aldehyde resin **76** via reductive amination. The resulting amino alcohol resin **78** was treated with PPh_3/Br_2 to convert the primary alcohol to its corresponding bromide **79**. The secondary amine **79** was derivatized with sulfonyl chlorides **80** (**79** → **81**), and then the bromide of **81** was displaced with amines **82** in the presence of KI to afford intermediates **83** (**81** → **83**). Exposure of **83** to TFA/DCM released library **70b**. Of the 288 members so produced, 45 compounds had K_i values of 1−5 nM, and 41 compounds possessed a K_i < 1 nM. Compounds with a K_i < 10 nM were also assayed against the D2 receptor. Many of the hits exhibited a D3/D2 inhibition ratio ranging from 5 to 100. A broad range of substituents was tolerated on the

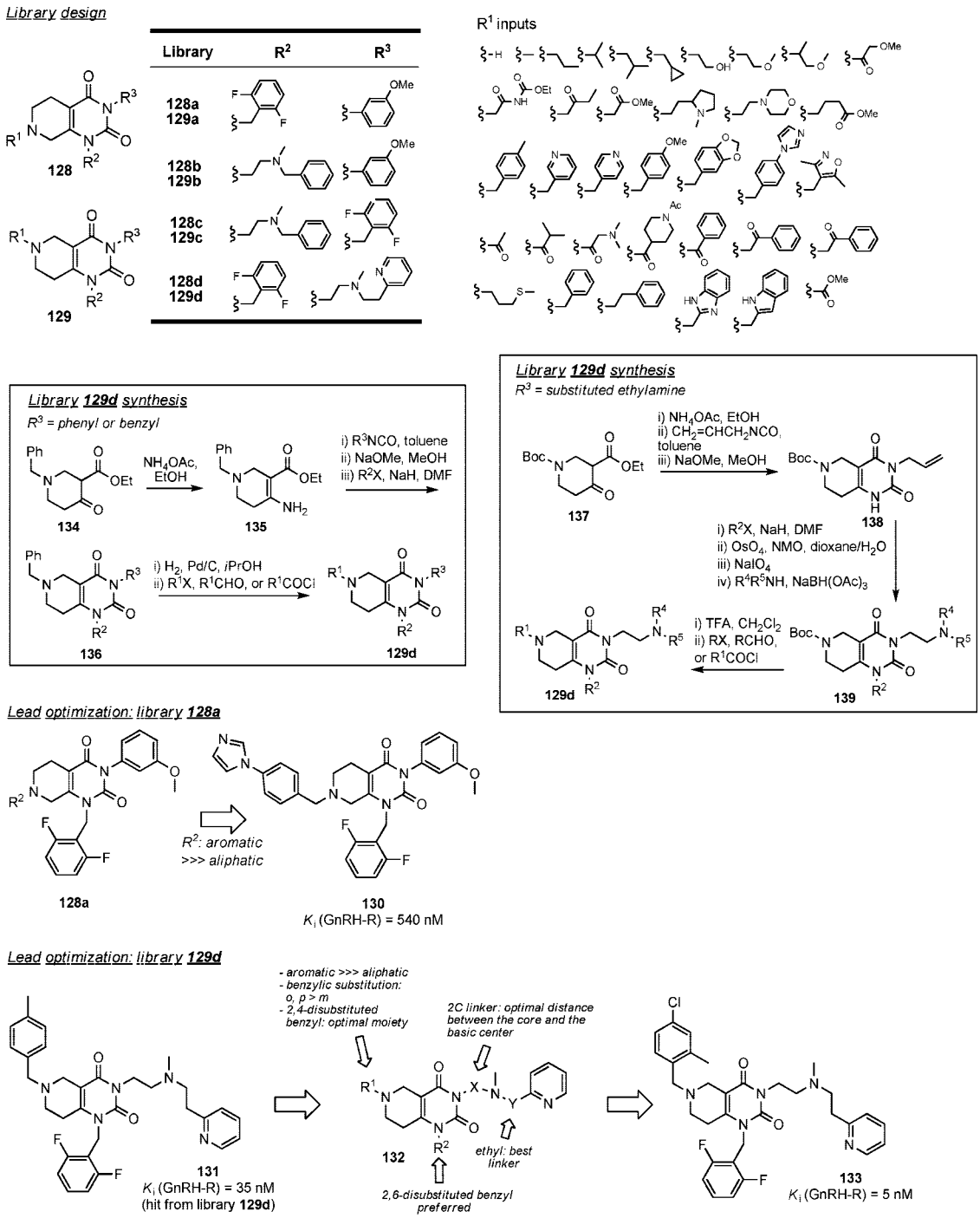


Figure 5. hGnRH receptor antagonists.[194]

aryl sulfonamide group, particularly at the *meta* and *para* positions. On the amino substitution site, *meta*-CF_3−Ph was the preferred group (**84**−**87**). Selected hits were subjected to PK evaluation, and those with acceptable oral bioavailability were tested in vivo for antipsychotic activity. Compound **88** was identified as a desirable lead (rD3, $K_i = 0.4$ nM; rD2, $K_i = 24$ nM; r%$F = 55$ (rat); brain $t_{max} = 1$ h; $C_{max} = 921$ ng/mL, 10 mg/kg po). Interestingly, advanced lead **88** contains the CF_3 group observed in the actives from the 288-compound library, as well as the CN group from the original leads **68** and **69**.

CCR3 Antagonists.[299] Chemokines are chemoattractant cytokines organized into four groups, CXC, CC, C, and CX3C, based on the position of the cysteines in the *N*-terminal region. Chemokines bind to a family of GPCRs referred to as chemokine receptors. CCR3 is the predominant chemokine receptor found on eosinophils that are directly involved in pulmonary inflammation. Consequently CCR3 antagonists could lead to the inhibition of pulmonary eosinophilia offering a therapeutic avenue for asthma treatment. Pégurier and colleagues[299] considered agents **89** ($IC_{50} = 0.58$ nM) and **90** ($IC_{50} = 2.3$ nM), the first CCR3 antagonists originally disclosed by Banyu Pharmaceuticals, as starting points for the design of novel CCR3 antagonists (Figure 4a). The two inhibitors share a 4-aminopiperidin-1-yl amino core (**91**), which the researchers chose to explore.

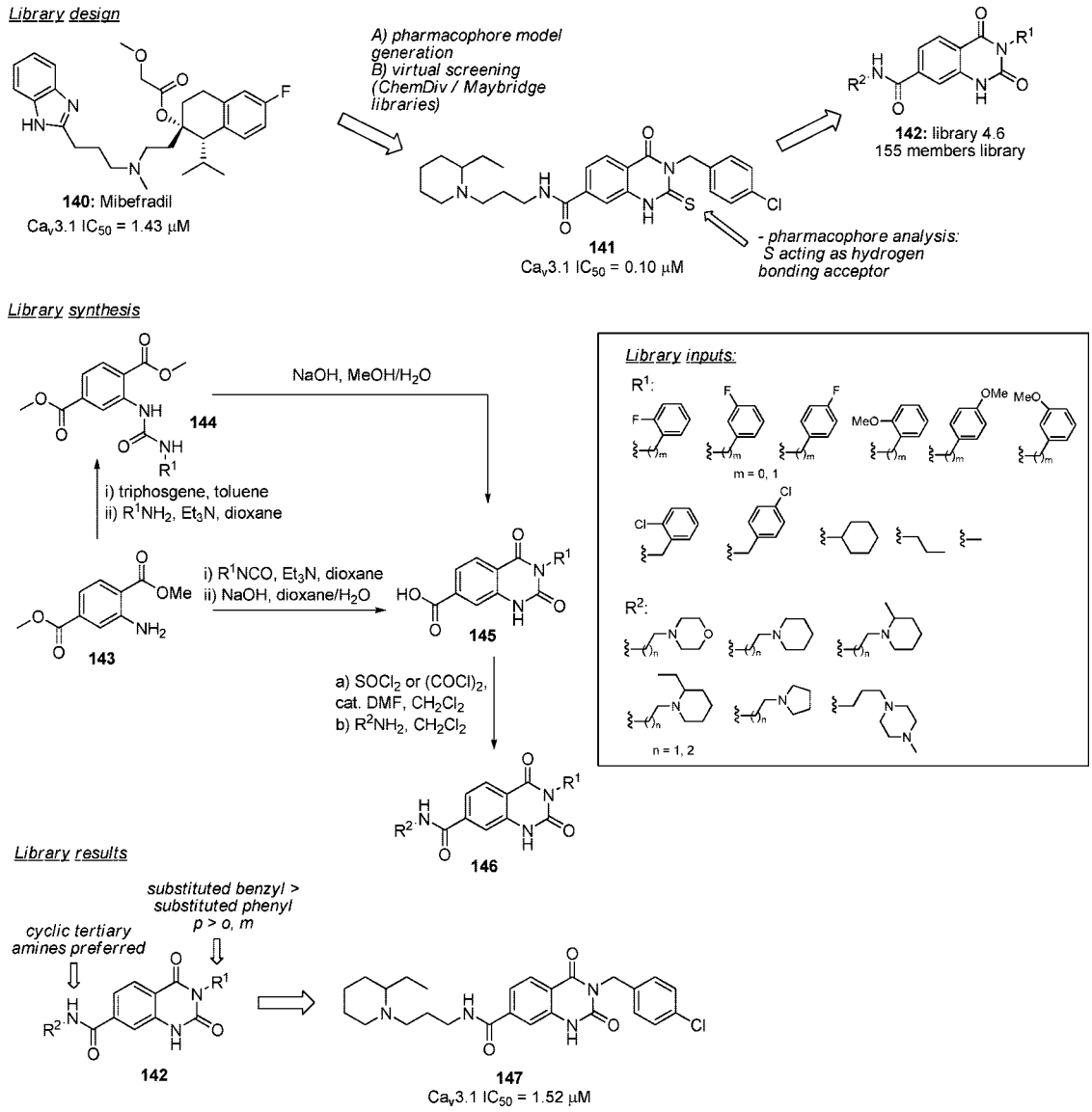


Figure 6. T-type calcium channel blockers.[161]

A solid-phase synthesis approach using Wang resin was developed, and inputs were selected on the basis of commercial availability and physicochemical properties. The solid-phase strategy began with immobilization of 4-piperidone via a carmabate linkage (**92**). Two sequential reductive aminations afforded resin-bound dialkylamine intermediates **96**. TFA treatment released dialkylamino piperidines **97**, which were acylated in solution phase to afford the 2888-member library 3.6 (**99**). From this library, compound **100** was identified as a CCR3 receptor antagonist (IC_{50} = 158 nM), an analog containing a phenyl pyrazolone moiety that had been previously reported as CCR3 receptor recognition element. Using the same solid-phase synthesis approach, several focused libraries were prepared to explore its R^2 and R^3 diversity points producing a total of 790 additional analogs. The observed SAR indicated that at the R^3 position, *ortho*-mono- and *ortho*-disubstituted phenyl substituents were favored, while at the R^2 position, *para*-substituted phenylethyl group was optimal as exemplified by compound **101** (IC_{50} = 32 nM).

The next campaign centered on the optimization of the phenyl ring linked to the pyrazolone group, and a solution-phase hydrazine approach was developed (Figure 4b). Custom hydrazines **103** were condensed with methyl acetoacetate in acetonitrile under reflux conditions to afford pyrazolone intermediates that were methylated with methyl sulfate in the presence of CaO in methanol to give pyrazolones **104**. 4-Piperidone **105** was acylated providing amides **107**. Intermediates **107** underwent reductive amination to afford monoalkyl amino amides **109**. Amides **109** were treated with pyrazolones **104** and paraformaldehyde in the presence of ammonium chloride at 90 °C, thereby incorporating pyrazolones via a Mannich reaction, ultimately yielding library **102**. The initially observed SAR on the pyrazolone unit indicated that the phenyl group of **110** could be successfully exchanged with either a heteroaryl group (2-pyridyl; **111**, IC_{50} = 25 nM) or a saturated cycloalkyl group (cyclohexyl; **112**, IC_{50} = 100 nM). When a fluorine atom was introduced on the phenyl ring, it was clear that preferred placement was *para* > *ortho* > *meta* (**115** > **113** > **114**,

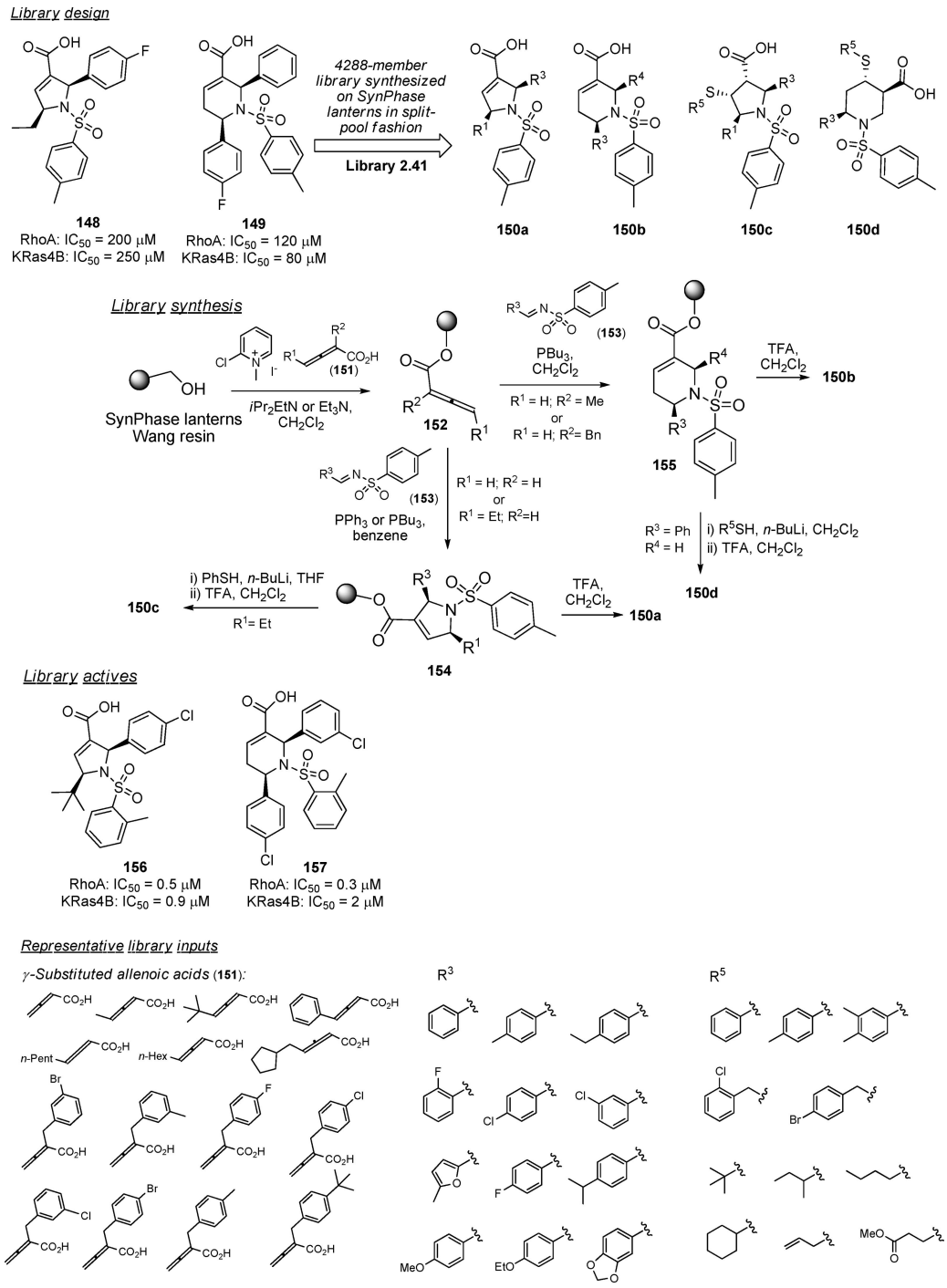


Figure 7. PGGT-1 inhibitors.[52]

IC_{50} = 20, 40, and 100 nM, respectively). Electron-withdrawing or -donating functional groups at the *para* position were for the most part well tolerated (**116**−**120**, $IC_{50} \leq 100$ nM), except for the negatively charged carboxylic acid (**121**, IC_{50} = 2500 nM). Although **115** was the most potent analog identified at this stage, absorption/distribution/metabolism/excretion (ADME) profiling showed that this compound had both low water solubility and poor metabolic stability (**155**, water solubility = 0.001 mg/mL at pH 7.4, Cl_{int} rat microsomes = 472 μL/min/mg protein). Further efforts to optimize the ADME properties and water solubility profile of the series focused on the aromatic site of the phenethyl group (R^4). 4-Fluoro analog **122** was 10-fold less potent than **115**; substitution with a nitro group in this position was well tolerated (**123**, IC_{50} = 6.3 nM). Although **123** exhibited high potency and better water solubility (0.1 mg/mL at pH 7.4), this compound was still prone to significant microsomal degradation (Cl_{int} on rat microsomes = 235 μL/min/mg protein). Additional studies replacing the 2,6-difluorophenyl amide group (R^3) with more water soluble groups (3-(2,6-dimethylpyridyl) **126** or 2-pyridyl **127**) indicated that increasing water solubility resulted in higher microsomal stability while still retaining potency against CCR3. Compound **127** (IC_{50} = 12 nM; water solubility $\approx$ 1.2 mg/mL at pH 7.4, Cl_{int} on rat microsomes = 79 μL/min/mg protein) was one of the more optimal antagonists.

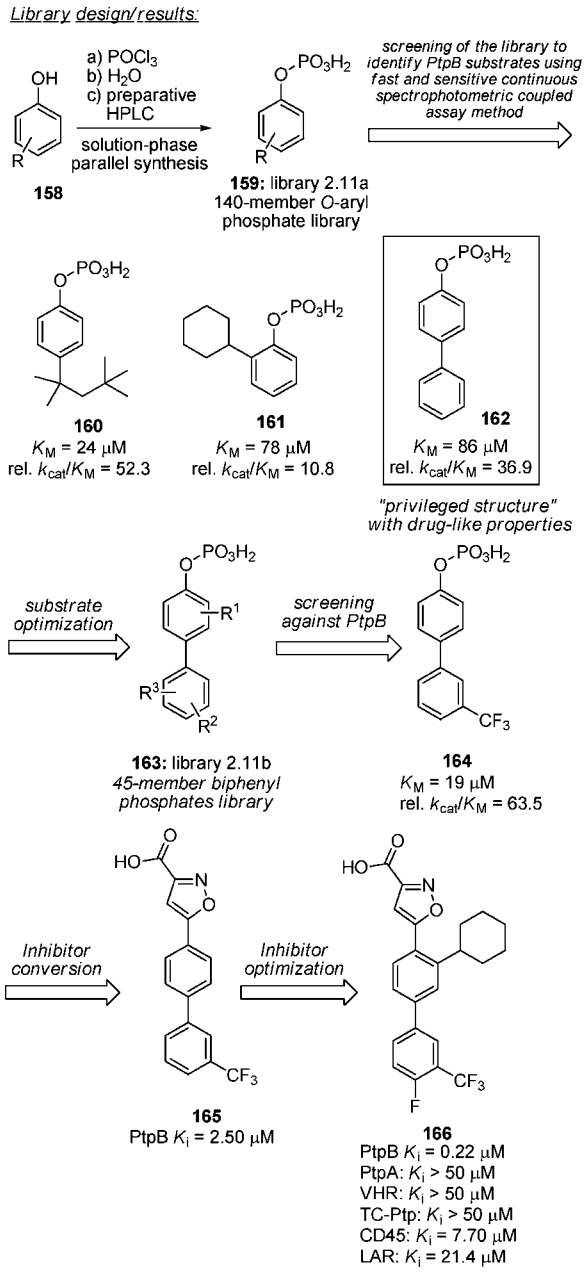


Figure 8. *M. tuberculosis* phosphatase PtpB inhibitors.[366]

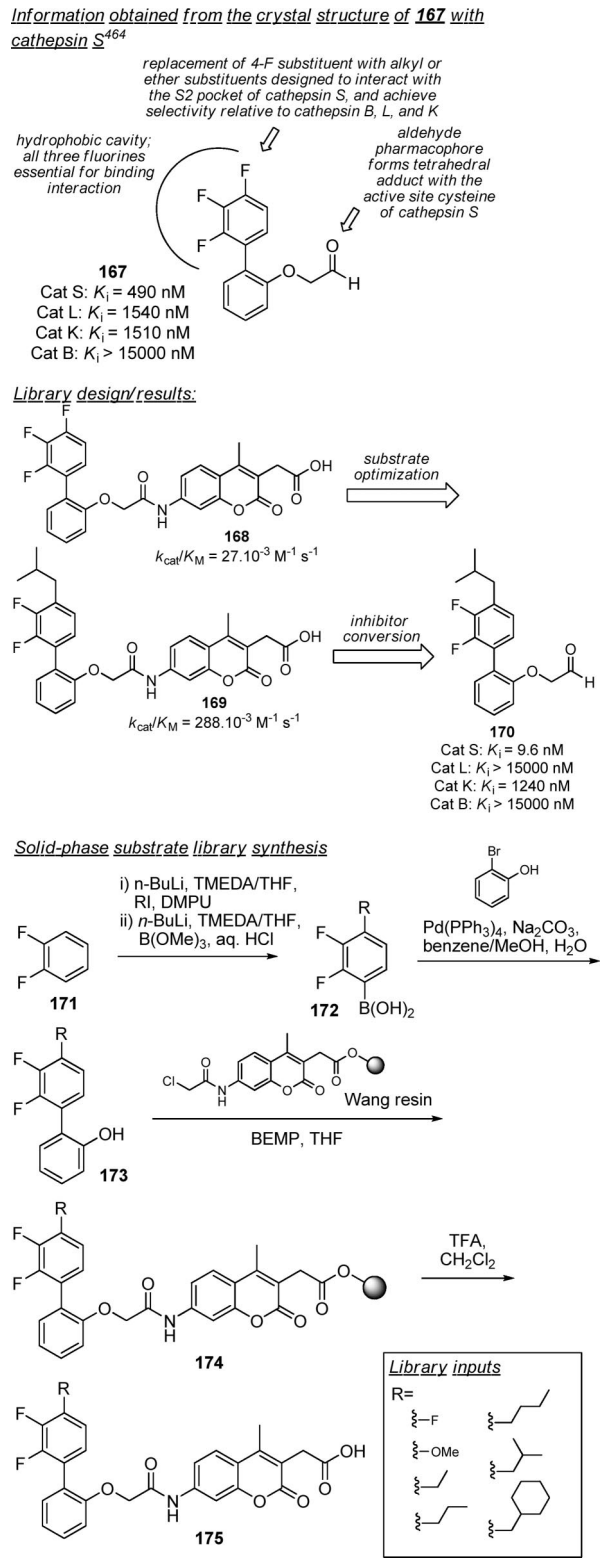


Figure 9. Cathepsin S inhibitors.[154]

hGnRH Receptor Antagonists.[194] Gonadotropin-releasing hormone (GnRH) plays an important role in the biology of reproduction. The GnRH decapeptide (pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2), produced in the hypothalamus, is released into the pituitary, where it interacts with GnRH receptors that belong to the GPCR superfamily. In the pituitary, GnRH triggers the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). GnRH is consequently the primary regulator of the sex hormones testosterone and estrogen. GnRH and its analogs have stimulated much interest because of their potential therapeutic utility in treating sex-hormone-dependent diseases such as prostate, ovarian, and breast cancer as well as endometriosis, uterine fibroids, benign prostate hyperplasia, and fertility disorders. After a transient elevation in hormone production (also referred as the flare effect), the administration of GnRH receptor agonists results in a down-regulation of GnRH receptors leading to a decrease in circulating levels of LH, testosterone, and estrogen. In contrast, GnRH antagonists, which have been recently available for clinical evaluation, directly lower the hormone levels without the observed flare effects associated with the agonists. Since most of the GnRH antagonists evaluated clinically are peptides, intense effort is currently underway in several laboratories to identify orally bioavailable, potent, small molecule GnRH antagonists. Researchers at Neurocrine Biosciences used computational tools to identify a new class of small

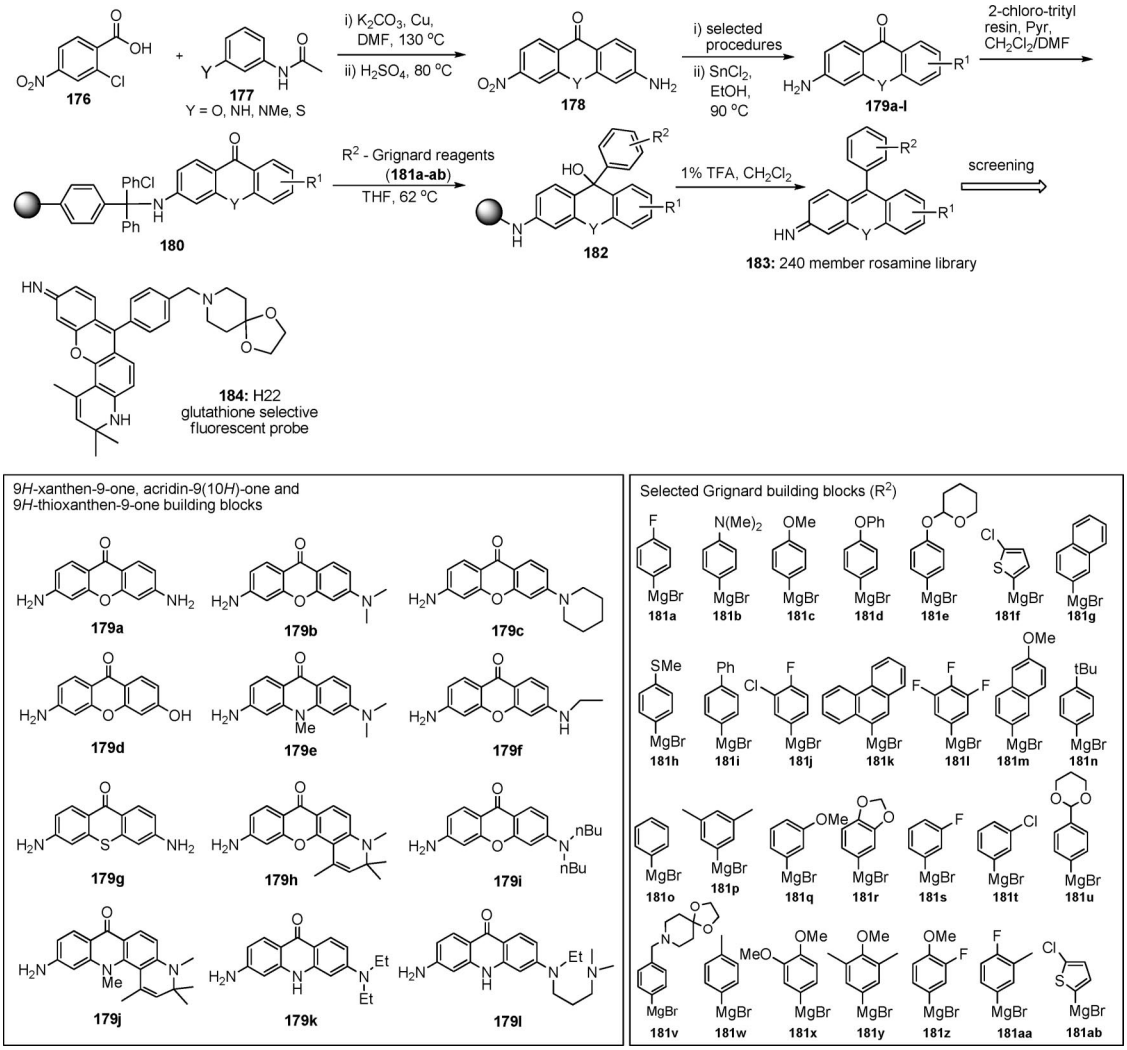


Figure 10. Fluorescent rosamine library design.[3]

molecules GnRH antagonists with a unique template and distinct structure activity relationships (SAR).[194] Using the consensus scoring method, about one hundred different templates were evaluated via computational analysis as potential core structures for the generation of GnRH antagonists. As selection criteria, these templates, designed using a knowledge-based approach, had to contain three points of diversity and the synthesis needed to be amenable to combinatorial chemistry. For each of the templates, virtual libraries were generated, and the products were scored. The top scoring templates were then chosen for further evaluation. On the basis of additional considerations including intellectual property and synthetic accessibility, templates **128** and **129** were selected for library synthesis (library 3.15; Figure 5). The library compounds **128a**−**d** and **129a**−**d** prepared via parallel solution phase synthesis were evaluated for their ability to inhibit [^{125}I](His^5, D-Tyr^6)-GnRH agonist binding to the cloned human GnRH receptor. Of the 8 libraries synthesized, only libraries **128a** and **129d** generated active compounds. The best compound identified from library **128a** was derivative **130**, which binds to the cloned human GnRH receptor with an affinity of 540 nM. Replacement of the [4-(*1H*-imidazol-1-yl)benzyl] group of **130** with other benzylic moieties did not result in an improvement in GnRH binding. Because of the potent hGnRH receptor affinity of compound **131** identified from the library **129d**, a SAR campaign was conducted at the R^1, R^2, X, and Y positions of general structure **132**. Over one hundred analogs of **131** were prepared during this SAR study. From this effort, compound **133** was identified as a very potent hGnRH receptor ligand (K_i = 5 nM).

T-Type Calcium Channel Blockers.[161] Calcium channel blockers (CCBs) have been used since the early 1960s for the treatment of a variety of cardiovascular diseases. CCBs are a heterogeneous group of drugs that inhibit inward calcium channel current to a variable degree in different tissues including the vascular smooth muscle, myocardium, and sinus and atrioventricular nodes. The different subtypes of voltage-dependent Ca^{2+} channels are classified into two main classes, high voltage activated (HVA) channels and low voltage activated (LVA) channels. On the basis of pharmacological studies, HVA Ca^{2+} channels are further divided into L-, N-, P-, Q-, and R-types, and the LVA Ca^{2+} channel is also called T-type. The distribution and properties of T-type Ca^{2+} channels have been reported to be altered in pathophysiological conditions such as ventricular hypertrophy and cardiomyopathy. Thus, T-type Ca^{2+} channels may have utility for the treatment of cardiovascular disorders such as heart failure, arrhythmia, and hypertension. In addition, many reports have shown that T-type Ca^{2+} channels are involved

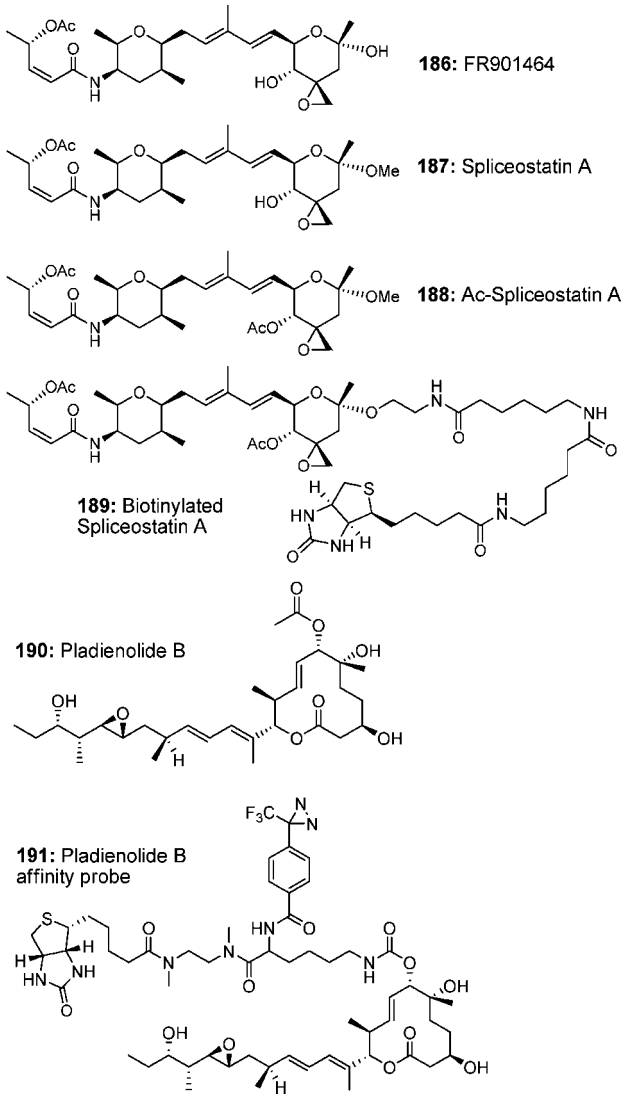


Figure 11. Natural products targeting splicing factor SF3b[164]

in the pathogenesis of neuropathic pain. Mibefradil (**140**), one of the most important examples of T-type calcium channel blockers, appeared to be a promising drug for the treatment of hypertension and angina pectoris. However, this drug was later withdrawn from the market because of serious CYP450 related drug−drug interactions. Currently, the main problem with elucidating the exact role of T-type calcium channels is the relative paucity of potent and selective T-type Ca^{2+} channel blockers. Using a T-type CCBs pharmacophore generated by using internal T-CCB hits and **140**, scientists at the Korea Institute of Technology in Seoul (Republic of Korea) conducted a virtual screening of a small molecule library from ChemDiv and Maybridge to identify novel T-CCBs scaffolds.[161] Among the hits, the thioxoquinazolinone **141** was confirmed as a potent T-type Ca^{2+} channel blocker ($IC_{50} = 0.10\ \mu M$). From the pharmacophore analysis, the sulfur atom of **141** was found to act as a hydrogen bond acceptor. Since oxygen is a stronger hydrogen bond acceptor than sulfur, a 155-member library of dioxoquinazoline carboxamides was designed and constructed using parallel synthesis (**142**, library 4.6; Figure 6). The library compounds were initially screened against HEK293 cells stably expressing T-type Ca^{2+} channel $Ca_V3.1$ with α_{1G} subunit and K^+

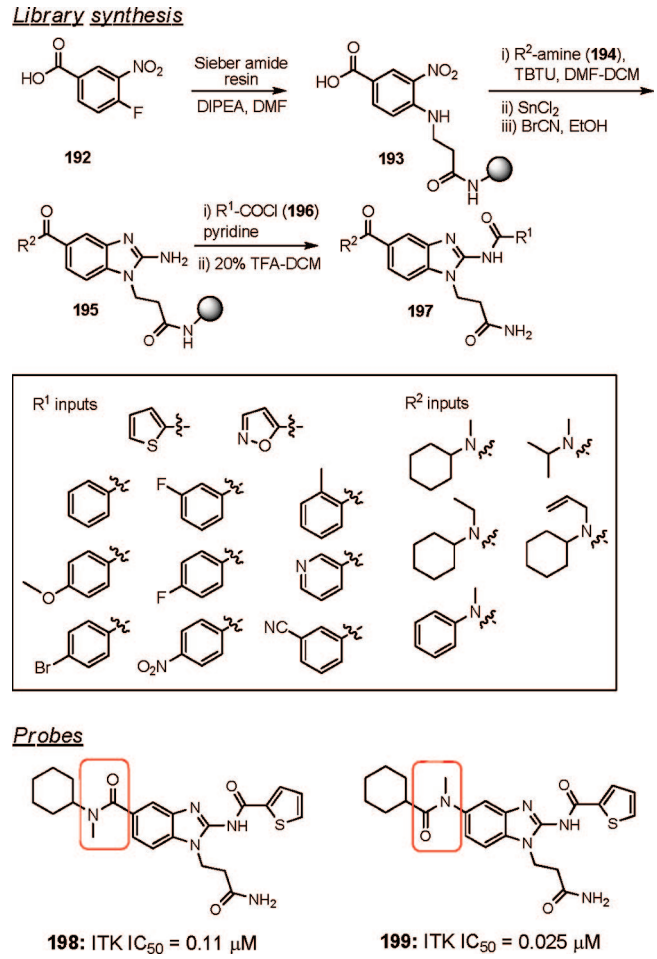


Figure 12. ITK probes.[365]

channel Kir2.1. From this initial screen, 15 compounds with the most T-type current blocking activity were selected and evaluated in the electrophysiological (patch clamp) assay. From this confirmatory test, compound **147** was identified as a novel T-type Ca^{2+} channel blocker with inhibitory activity in the patch clamp assay ($IC_{50} = 1.52\ \mu M$) comparable to the inhibitory activity of mibefradil **140** ($IC_{50} = 1.43\ \mu M$) under the same assay conditions.

Protein Geranylgeranyltransferase Type I (PGGT-1) Inhibitors.[52] Protein isoprenylation or the posttranslational modification of specific cysteine residues in nascent proteins with either a farnesyl group or a geranylgeranyl group is a key event in the regulation of many biological processes. Of particular interest is the finding that isoprenylation of pro-Ras proteins is a prerequisite for their functioning. Oncogenic Ras, with the intrinsic GTPase impaired, are found in 40% of human tumors. For this reason, many research laboratories are focusing on the development of compounds that can interfere with Ras isoprenylation. The natural isoprenyl group found on Ras proteins is the farnesyl lipid, transferred from farnesyl pyrophosphate (FPP) to consensus cysteine residues through the action of the enzyme protein/farnesyl transferase (PFT). As a consequence, most research activities to date have focused on the development of PFT inhibitors. However, the enzyme protein/geranylgeranyl transferase-1 (PGGT-1) has emerged as an important alternative target for several reasons. First, there is the observation that upon blocking PFT, *N*-Ras and the most abundant human oncogenic Ras

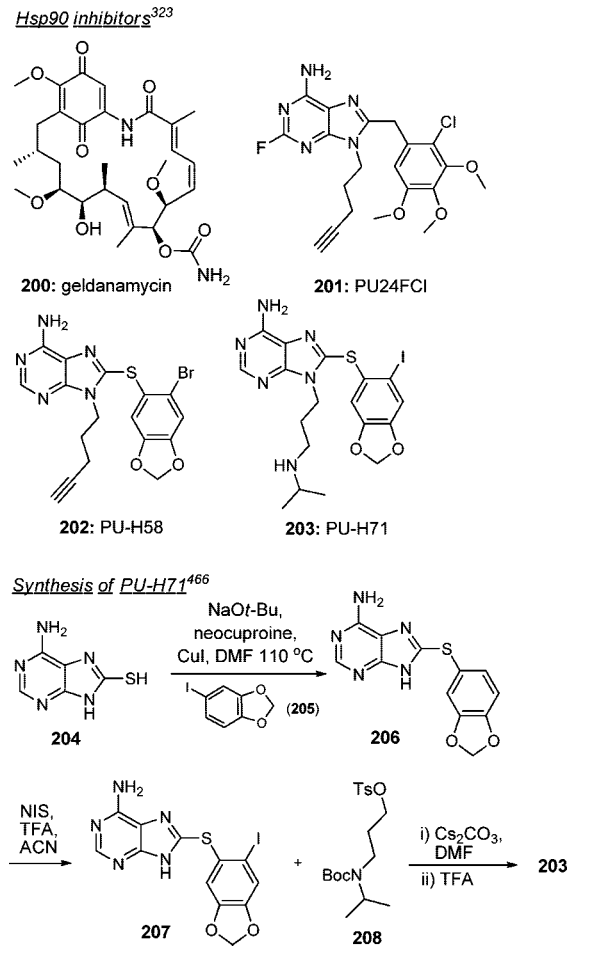


Figure 13. Substituted purine-based probes as selective Hsp90 inhibitors.[323,466]

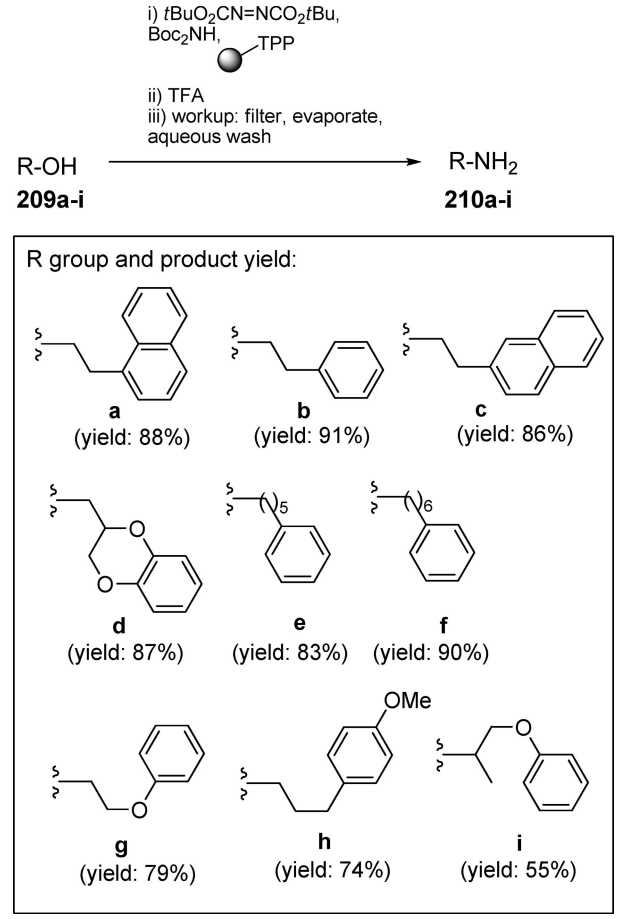


Figure 14. Conversion of primary and secondary alcohols to primary amines.[380]

protein *K*-RasB are geranylgeranylated through the action of PGGT-1. This indicates that blocking the action of PGGT-1, next to PFT, may prove equally important in the development of antitumor agents aimed at disabling Ras functioning. In addition, PGGT-1 inhibitors have been shown to be potential valuable agents for the treatment of smooth muscle hyperplasia, multiple sclerosis, parasitic infections, osteoporosis, atherosclerosis/restenosis, and hepatitis C virus infection. With the aim of identifying selective PGGT-1 inhibitors, researchers at the UCLA's Jonsson Comprehensive Cancer Center and Molecular Biology Institute initially screened a collection of 138 heterocycles for their ability to inhibit the activity of human PGGT-1 to geranylgeranylate K-Ras4B or RhoA.[52] From this screen, compounds **148** and **149** were identified as weak PGGT-1 inhibitors (Figure 7). To further improve the efficacy of these compounds and to explore structure activity relationships (SAR), 4288 PGGT-1 analogues of **148** and **149** were synthesized on SynPhase lanterns in a split−pool fashion (**150a-d**, library 2.41). The unprecedented loading of allenoic acids (**151**) onto solid support (SynPhase-PS lanterns grafted with Wang resin) was performed using Mukaiyama's reagent and Hünig's base or Et_3N in dichloromethane. The phosphine-catalyzed (PPh_3 or PBu_3) annulation between the polymer-supported allenoates **152** and *N*-tosylimines **153** proceeded smoothly. This represents the first example of solid-phase phosphine catalysis of resin-bound allenoates. Heterocycles **154** and **155** were then cleaved from the resin using TFA to provide, in high yield (91−94% based on a theoretical loading of 15 μmol/lantern), the carboxylic acids **150a** and **150c**, respectively. The compounds **150a** and **150c** were isolated with high diastereoselectivities (dr = 99:1 for **150a**; 93:7 for **150c**) after chromatographic purification. The 1,4-conjugate addition of thiols to **154** and **155** using *n*-butyllithium as base, followed by TFA-mediated cleavage of the resin, provided the pentasubstituted pyrrolidines **150b** and the tetrasubstituted piperidines **150d**, respectively. These derivatives were isolated as single diastereoisomeric products in 77−95% yield (Figure 7). From the 4288 member library tested for activity against PGGT-1, compounds **156** and **157** were identified as potent PGGT-1 inhibitors. Further in vivo experiments demonstrated that compounds **156** and **157** inhibit geranylgeranylation in cells.

***Mycobacterium tuberculosis* Phosphatase PtpB Inhibitors.**[366] Tyrosine phosphorylation broadly regulates the physiology of eukaryotic cells. While pharmaceuticals targeting tyrosine kinases are already on the market, development of drugs that target any of the 85 human protein tyrosine phosphatases (PTPs) is at an earlier stage. The central roles of PTPs in eukaryotic signaling are exploited by some pathogenic bacteria, which produce and secrete PTPs to attenuate host immune defenses. Tuberculosis (TB) is a major cause of worldwide mortality from infectious disease, prompting a search for innovative targets for therapeutics. New targets are needed not only

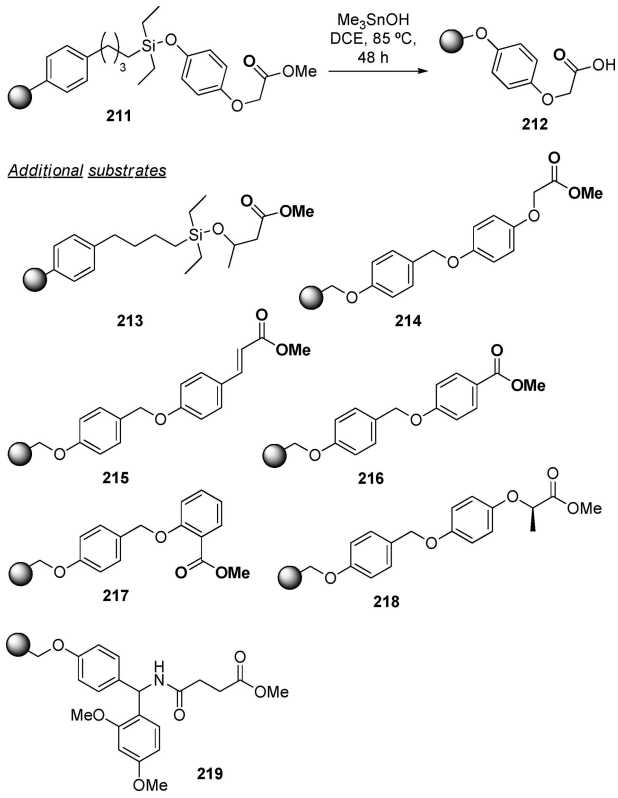


Figure 15. Trimethyltin hydroxide-mediated ester hydrolysis on solid support.[252]

to speed the course of treatment, but also to attack emerging multi-drug-resistant *Mycobacterium tuberculosis (Mtb)* strains and to treat tuberculosis in AIDS patients. Among the proteins secreted into the host cell by *Mtb* are PtpA and PtpB, which are thought to interfere with host signaling pathways. The attenuated growth and virulence of a *ptpB* gene knockout strain of *Mtb* in IFNγ-stimulated macrophages and in guinea pigs afforded a compelling rationale to target PtpB to develop new drugs to treat TB. In addition, PtpB also provides an attractive target because the enzyme functions outside the bacterium in the host cells, eliminating the need for inhibitors to traverse the relatively impermeable bacterial envelope. Jonathan Ellman's group at the University of California Berkeley developed a new substrate-based fragment approach for the identification of *Mtb* PtpB inhibitors.[366] In the first step of this method called "substrate activity screening" (SAS), a library of 140 *O*-aryl phosphates (**159**, library 2.11a) was screened against PtpB to identify phosphate substrates using a fast and sensitive continuous spectrophotometric coupled assay method (Figure 8). Screening this library provided several promising fragment substrates exemplified by compounds **160**, **161**, and **162**. The biphenyl fragment **162** was selected for further substrate optimization. A small focused 45-member biphenyl library (**163**, library 2.11b) was then prepared and screened against PtpB. From this work, compound **164** was identified as the optimal substrate. To convert the PtpB substrate **164** to a potential inhibitor, the phosphate group of **164** was replaced by an isoxazole carboxylic acid moiety, previously used as monoacidic phosphate isostere. Compound **165** was identified as a micromolar PtpB inhibitor (K_i = 2.50 μM). Further optimization of this lead was conducted to improve PtpB inhibitory activity. This resulted in the identification of compound **166**, the most potent PtpB inhibitor known in the literature (K_i = 220 nM). Additional experiments demonstrated that **166** displays good selectivity against a panel of mycobacterial (PtpA) and human PTPs.

Nonpeptidic Cathepsin S Inhibitors with Unprecedented Binding Mode.[154] Cathepsin S is a cysteine protease expressed in antigen-presenting cells, such as B cells, dendritic cells, and macrophages. This protease, belonging to the papain superfamily, mediates the proteolysis of the invariant chain that is associated with the major histocompatibility class II (MHC-II) complex. This proteolytic event is a prerequisite to productive loading of antigen onto the MHC-II complex, rendering cathepsin S an attractive therapeutic target for immunosuppression. The development of selective cathepsin S inhibitors for the modulation and regulation of immune hyper-responsiveness may provide a novel treatment for chronic conditions such as asthma, allergies, and rheumatoid arthritis. Ellman's group previously used the substrate activity screening (SAS) method, a substrate-based fragment identification and optimization method for the development of enzyme inhibitors, to identify compound **167**, a novel cathepsin S inhibitor with a K_i value of 0.49 μM (Figure 9).[468] The crystal structure of cathepsin S with **167** demonstrated that this novel inhibitor which lacks nitrogen functionality, common to many cathepsin S inhibitors, has an unprecedented binding mode. On the basis of this X-ray information, additional 2-biaryloxy ligands were designed. In particular, it was envisioned that replacement of the 4-fluoro group of **167** with alkyl or ether substituent would add additional interaction of the ligands with the S2 binding pocket of cathepsin S. This modification would provide the opportunity to improve the affinity toward cathepsin S and potentially improve the selectivity of the ligands relative to cathepsins B, L, and K. The substrate **168** containing a fluorogenic *N*-acyl-7-amino-4-methylcoumarin acetic acid group[154] was designed on the basis of the structure of the inhibitor **167**. On the basis of the structure of **168**, additional biaryloxy substrates were prepared by either solution or solid-phase synthesis. This substrate optimization resulted in the identification of compound **169** displaying greater cleavage efficiency relative to the initial substrate **168**. The inhibitor **170** was then designed on the basis of the structure of the substrate **169** by replacement of the aminocoumarin functionality of **169** with a hydrogen atom to introduce the aldehyde mechanism-based pharmacophore. Compound **170** was identified as a potent and selective cathepsin S inhibitor (K_i = 9.6 nM).

H22: In Vivo Glutathione Sensor.[3] Recently, several innovative researchers used combinatorial chemistry and high-throughput screening in the search for novel compounds that possess fluorescent properties associated with a cellular phenotype. Molecules with innate fluorescence have found utility in the various disciplines of biological chemistry. There are few generalities that enable scientists

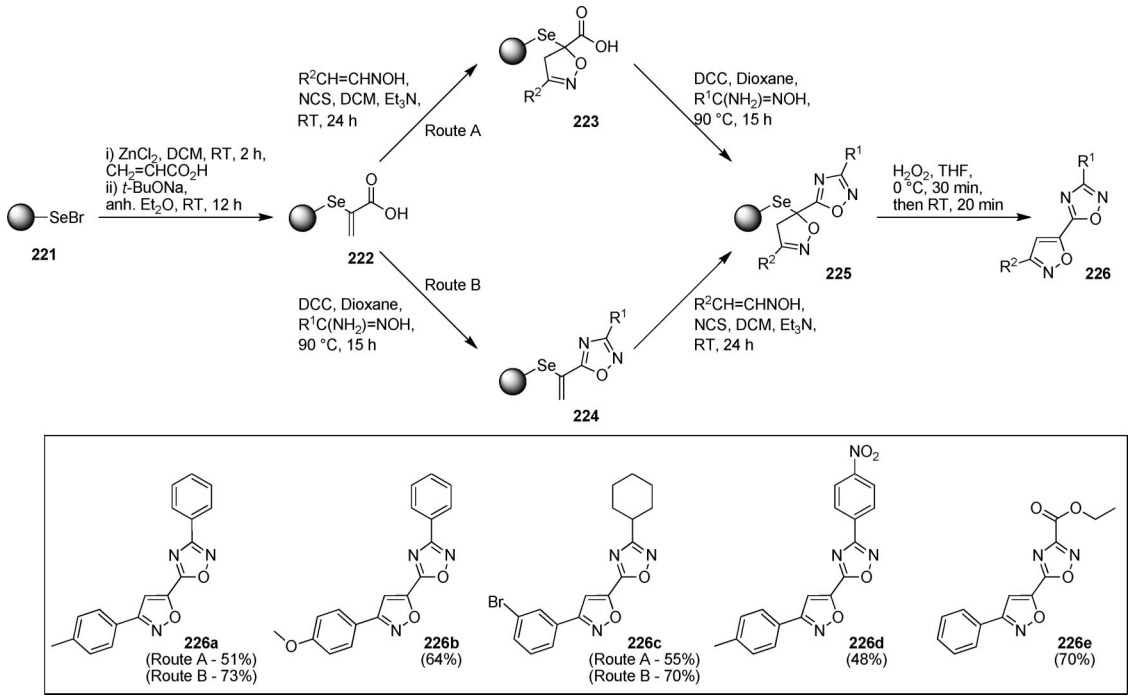


Figure 16. Solid-phase isoxazolyl-oxadiazole synthesis.[148]

to accurately predict or understand the fluorescent nature of a given chemotype in a given situation. Researchers like Tsien[469] have brought great insight into the rational design of fluorophores aimed at probing specific cellular phenomenon. In addition, several recent efforts by Blackwell and co-workers[470] and Bäuerle and co-workers[471] have been reported surrounding the synthesis of compound libraries aimed at identification of novel fluorescent materials. In a communication by Chang and co-workers, a combinatorial library was designed and synthesized, based on the core structure of rosamine (Figure 10).[3] The synthesis relied upon the loading of 12 divergent xanthone derivatives **179a**−**l** on 2-chlorotrityl chloride resin. The subsequent reaction with a variety of phenyl Grignard reagents **181a**−**ab** and the concomitant acid catalyzed dehydration and removal from the resin provided the core rosamine structures **183**. A collection of 240 novel rosamine analogues was created and assayed against a variety of biochemically relevant analytes. One agent, **H22** (**184**), was noted to exhibit a selective fluorescence response to glutathione (GSH). This effect was found to be specific to reduced glutathione rather than GSSG and other prevalent biological thiols only produced modest effects. A further investigation of this effect in a cell based system found that α-lipoic acid enhanced GSH levels in 3T3 cells, which could easily be tracked utilizing this novel fluorophore. Thus, **H22** represents a novel tool for the tracking of the redox state of various cell types under different external stresses. This work is exceptional in the interesting use of combinatorial chemistry in the search for novel fluorescent materials and the subsequent investigation of these novel fluorophores for specific structures that react to a precise biochemical circumstance. To date, several publications have utilized this strategy to find novel probes of cellular events and phenotype.

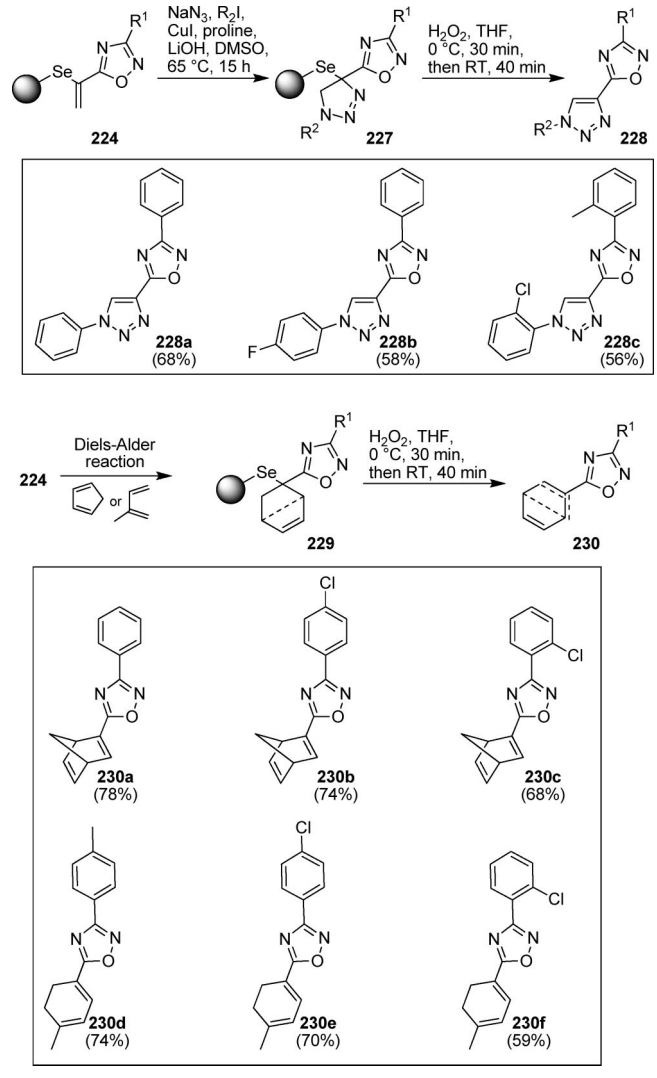


Figure 17. Solid-phase triazole-oxadiazole synthesis.[148]

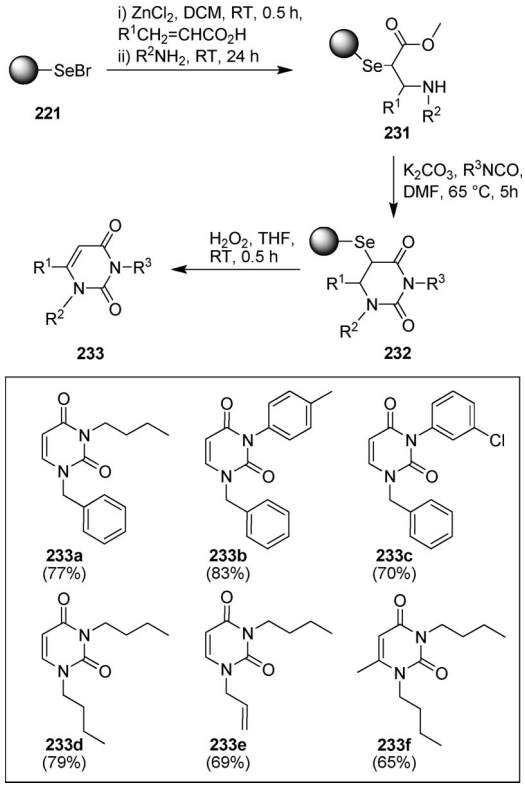


Figure 18. Solid-phase uracil synthesis.[147]

Spliceostatin A: SF3b Inhibitor and Splicing Regulator.[164,472] The splicesome comprises an important, yet difficult, group of protein targets thought to represent a new frontier in therapeutics for several disease states. To date, a limited number of reports have emerged that detail methods providing researchers the pharmacological means for controlling the cellular capacity to correctly remove introns during transcription. Control of selected signal pathways have given researchers using known kinase inhibitors the ability to manipulate selected splicing abnormalities, in lieu of direct control. In back-to-back manuscripts, Mizui and co-workers[472] and Yoshida and co-workers[164] reported two natural products (pladienolide B (**190**) and FR901464 (**186**), respectively) that target splicing factor SF3b (Figure 11). Both reports detail the synthetic elaboration of biotinylated versions of pladienolide **191** and FR901464 **189** that allowed protein enrichment and LC-MS/MS analysis of peptide fragments. Splicesome-associated protein (SAP) 145 was found as a target for pladienolide B, and SAP 130 was found as a target for both pladienolide and FR901464. Both agents were capable of inhibiting splicing in a dose dependent manner in vivo. Mizui and co-workers further demonstrated that the binding affinities of pladienolide B for SF3b correlated with its inhibitory capacity in a cell proliferation assay, thus using the natural product to validate SF3b as a pharmacological target for antineoplastic activity. Yoshida and co-workers demonstrated that treatment of various cell lines with FR901464 produced a C-terminally truncated form of the CDK inhibitor proteins p27 and IκBα and provided an assortment of evidence that these aberrant forms of p27 and IκBα are directly related to alternate splicing. The authors further

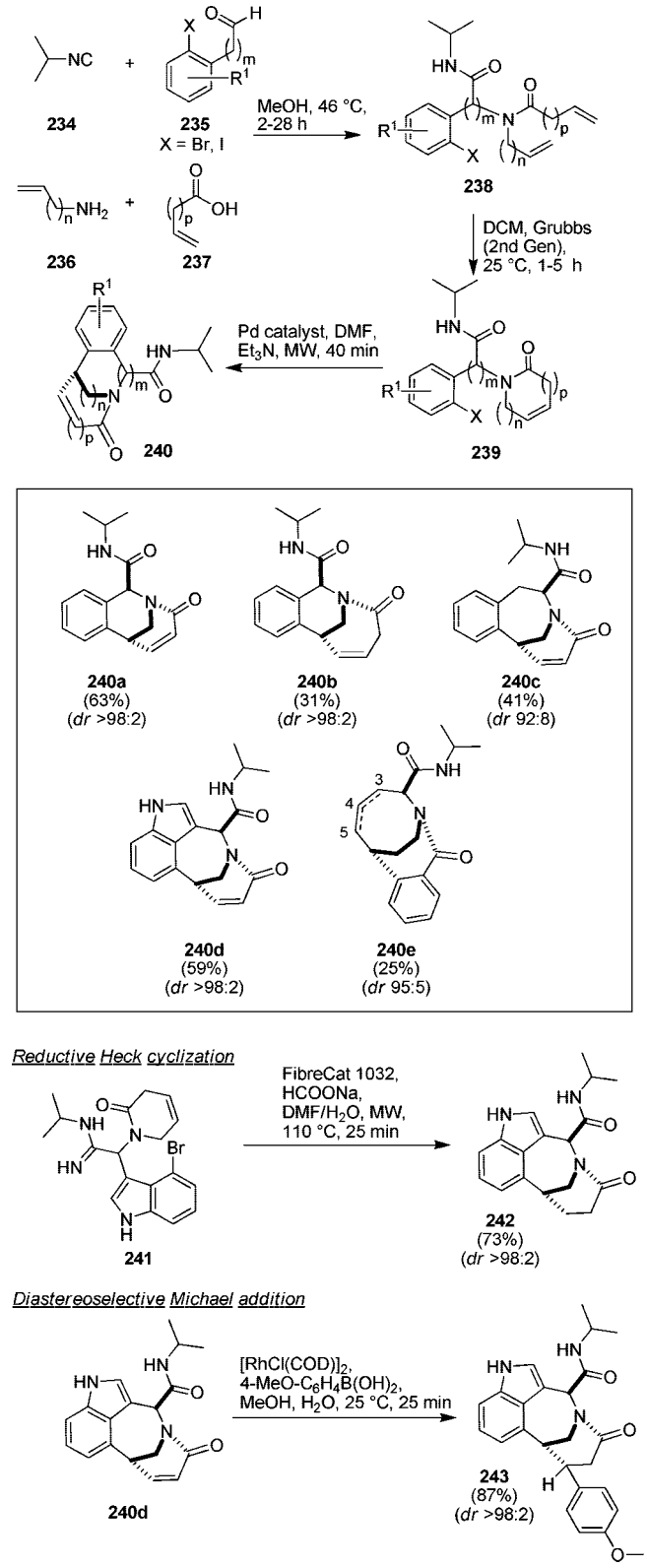


Figure 19. Bridged bicyclic lactam formation.[317]

produced a methylketal derivative of FR901464, named spliceostatin A (**187**), and showed extensive leakage of pre-mRNA into the cytoplasm upon treatment of cells with these agents. While agents that provide a therapeutic result based on inhibition or control of splicing events are not likely to emerge any time soon, the disclosures of pladienolide B and FR901464 provide the first molecules

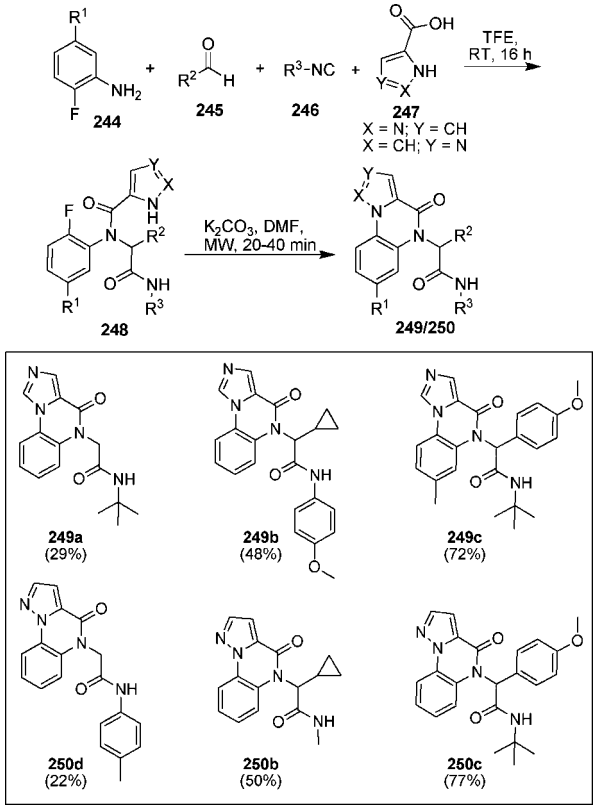


Figure 20. Synthesis of imidazoquinoxalines and pyrazoloquinoxalines.[369]

capable of probing the splicesome and will undoubtedly prove to be useful tools.

Interleukin-2-Inducible T Cell Kinase (ITK) Inhibitor.[365] This contribution by researchers at Boehringer Ingelheim resulted in an important, accessible reagent for the down-regulation of interleukin-2-inducible T cell kinase (ITK). This kinase is quickly gaining appreciation on therapeutic fronts from cancer to HIV. Researchers from Bristol-Myers Squibb had previously released another chemotype that equally qualifies as a probe molecule targeting ITK.[473] Substituted benzimidazoles **197** reported in the Boehringer Ingelheim contribution are synthetially accessible via solid-phase or solution phase methodologies (Figure 12). The solid-phase library was carried out using the Sieber amide resin functionalized with β-alanine. To this reagent was added 4-fluoro-3-nitrobenzoic acid (**192**) via an aromatic nucleophilic substitution at the 4-fluoro position. Coupling of the resin-bound aromatic acid (**193**) to specified amines (**194**) and reduction of the nitro function allowed direct access to the 2-aminobenzimidazole intermediate (**195**) via treatment with cyanogen bromide. Finally, addition of various aromatic acid chlorides (**196**) and release from the resin provides the relevant library compounds for analysis. The investigators used homologous targets BTK and LYN as counterscreens to aid in their choices of chemotypes for follow-up studies. The original lead structure **198** maintained a carboxamide linkage at the 5-position of the benzimidazole and reversal of this amide linkage led to a 5-fold improvement in potency, probe **199**. The report further denotes a proposed binding mechanism for the compound and supplies

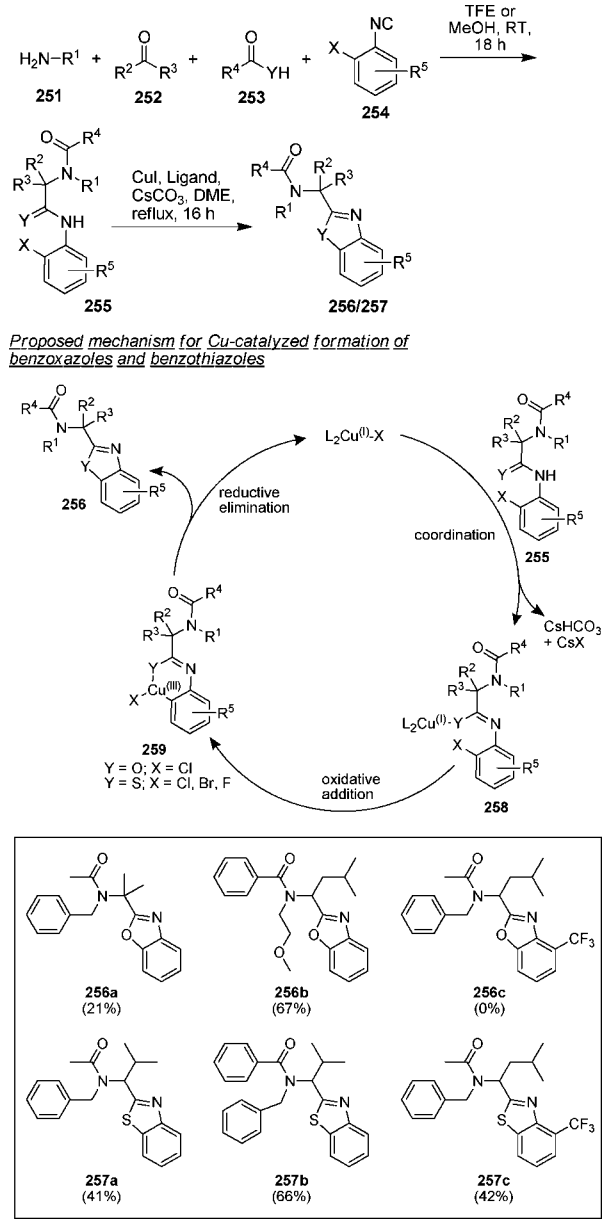


Figure 21. Synthesis of benzoxazoles and benzothiazoles.[368]

selectivity data for over 100 kinases. Finally, favorable cell based results with **199** were reported via measurement of calcium influx within a stimulated B cell receptor deficient in BTK via FLIPR analysis. Given the burgeoning understanding of the relevance of ITK, these tool compounds contributed in reports from Boehringer Ingleheim and Bristol-Myers Squibb[473] will undoubtedly be put to work in advanced interrogations of this important target.

PU-H71: Selective Hsp90 Inhibitor.[323] Heat shock protein 90 (Hsp90) is a fascinating protein and as a molecular chaperone regulates numerous signal transduction pathways and assists several oncogenetic processes. Geldanamycin **200** has served an important role as the primary molecular probe of Hsp90 activity. As a singular agent, geldanamycin has several liabilities, particularly in its realization as a therapeutic candidate. Many of these liabilities are overcome by synthetic derivations of the carbon scaffold of geldanamycin. However, shortcomings

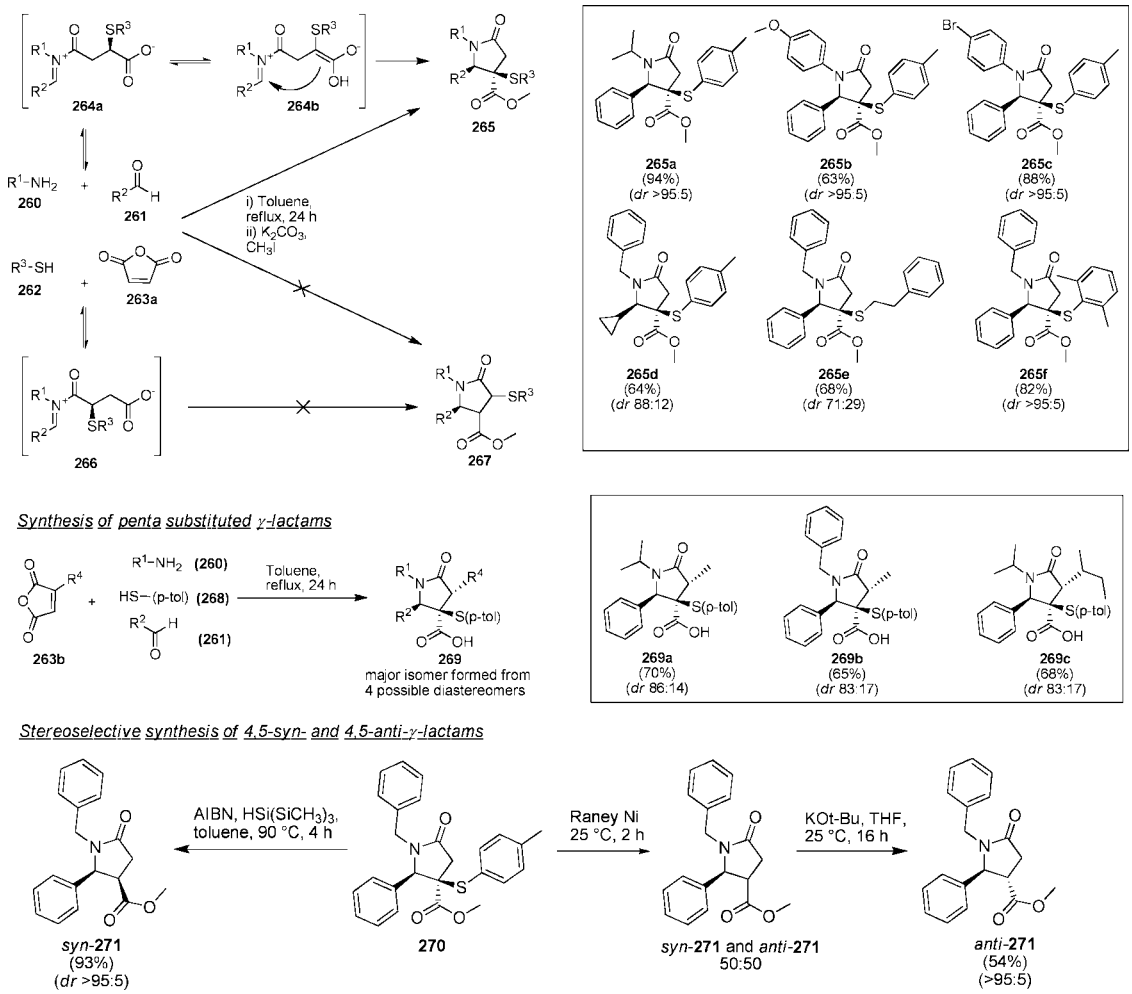


Figure 22. Synthesis of tetra-substituted γ-lactams.[422]

with this class of Hsp90 inhibitors continue to limit its full potential as both a molecular probe of Hsp90 and a potential treatment option for cancer. Chiosis and co-workers introduced a novel class of selective Hsp90 inhibitors based on a substituted purine scaffold[474] and utilized these agents to identify Hsp90 as a principal regulator of apoptosis within small-cell lung cancer (Figure 13).[323] Utilizing three representatives from this class of compounds with divergent potencies [(least potent) PU24FCl (**201**), 2−6 μM < PU-H58 (**202**), high nanomolar < PU-H71 (**203**), 10−20 nM (most potent)], the investigators found that both binding and growth inhibition tracked in accordance to the known Hsp90 affinities across a collection of small-cell lung cancer cell lines. Utilizing other known Hsp90 inhibitors, the researchers demonstrate similar findings, suggesting that the cellular activities of **201**−**203** are directly related to their inhibition of Hsp90. The researchers further demonstrated that proapopotic proteins caspase-3 and caspase-7 are activated in dose correlation with the affinities of **201**−**203** for Hsp90. It is further shown that Hsp90 regulates apoptosis by the dual facilitation of an Apaf-1-caspase 9 complex and down-regulation of Akt. The use of **201**−**203** provided evidence that regulation of apoptosis by Hsp90 is both a cell-specific and transformation-specific event. The utility of these agents against chemotherapy resistant cell lines and in small-cell lung cancer animal models further demonstrate the importance of this novel class of Hsp90 inhibitors. This report highlights the power of highly specific small molecule probes in delineating protein function and, in the best of cases, translating probes into potentially useful frontline therapies.

Efficient Conversion of Primary and Secondary Alcohols to Primary Amines.[380] Numerous methods have been used to convert hydroxyl groups into amino groups in the synthesis of amines and amino acids. For the synthesis of primary amines, standard procedures involve a 2−3 step process including (a) conversion of the alcohol to an alkyl halide or sulfonate, (b) nucleophilic displacement of the halide or sulfonate with a metal azide, and (c) reduction of the azide to the primary amine. As an improvement to this 3-step process, alkyl bromides can also be converted directly to the primary amines. Each of these methods has narrow scope, and the purification of the crude products contaminated with triphenylphosphine oxide or other byproducts could be challenging. The Department of Chemical and Screening Sciences at Wyeth developed a new methodology to convert primary and secondary alcohols to primary amines using a one-step process easily amenable to parallel synthesis (Figure 14).[380] In the optimized reaction conditions, a mixture of the alcohol **209**, bis-*tert*-butyliminodicarboxylate (4 equiv),

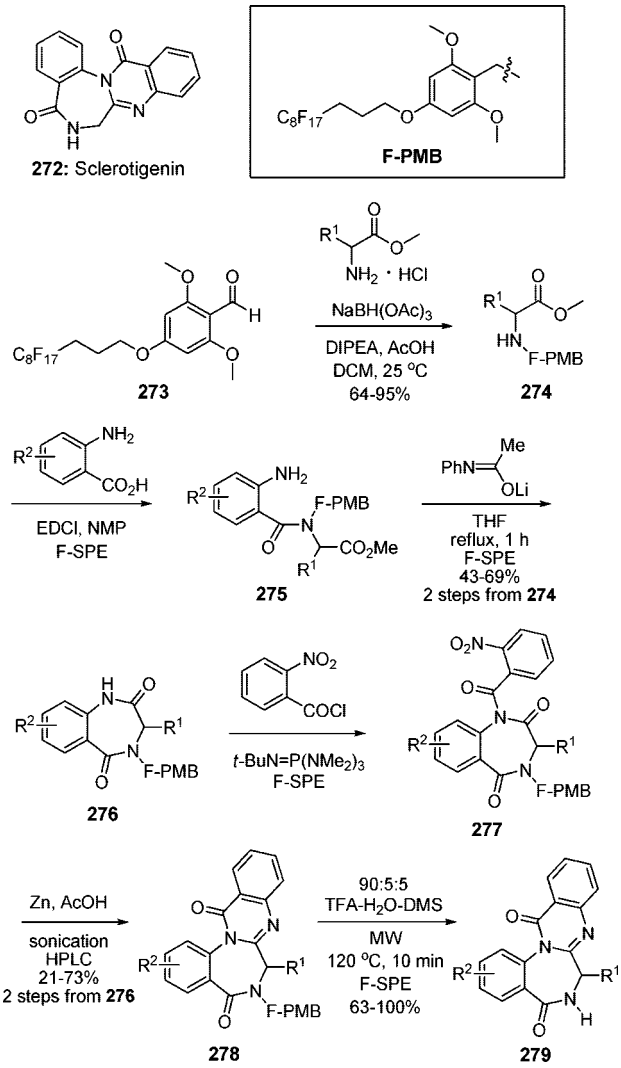


Figure 23. F-PMB tag-facilitated synthesis of sclerotigenin analogs.[451]

and PS-bound triphenylphosphine (3 equiv) in dichloromethane was treated with di-*tert*-butylazodicarboxylate (3 equiv), and the mixture was stirred for 30 min at room temperature. After treatment with TFA, filtration, evaporation, and typical aqueous work up, the crude product was isolated in high purity. The yields of purified amines **210** ranged from 55% to 91%.

Mild, Efficient, and Selective Hydrolysis of Polymer-Supported Methyl Esters Using Trimethyltin Hydroxide (TMTOH).[252] Selective deprotection of particular functional groups in the presence of others is still one of the most important strategies in solution- and solid-phase organic synthesis. In this regard, studies directed to the selective hydrolysis of esters on solid support have received relatively little attention. Researchers at the Instituto de Química Orgánica de Síntesis in Argentina developed a non-acidolytic, non-nucleophilic reagent for the selective hydrolysis of methyl esters on solid support (Figure 15).[252] Using the ester **211** as model substrate, they first investigated the use of trimethylsilanolate to convert the methyl ester functionality of **211** to the corresponding solid-supported carboxylic acid **212**. However, treatment of **211** with trimethysilanolate (10 equiv) in dichloromethane at room temperature for 12 h resulted in the cleavage of the Si−O bond of **211**. Treatment of the methyl ester **211** with a solution of sodium hydroxide in THF−H_2O also failed to produce the desired resin **212**. In this case, no reaction occurred. The utility of trimethyltin hydroxide (TMTOH) has previously been documented as a non-acidic reagent for the selective cleavage of carboxylic esters. In this case, treatment of resin **211** with TMTOH (10 equiv) in 1,2-dichloroethane at 85 °C for 48 h (with an additional 5 equiv of TMTOH added after 24 h) provided the desired carboxylic acid **212** as indicated by gel-phase ^{13}C NMR analysis (disappearance of the OMe carbon signal peak at 51.98 ppm). This method proved to be versatile because hydrolysis of the various methyl ester supported resins **213**−**219** was performed cleanly using this methodology. In addition, as exemplified in the case of resin **218**, this mild hydrolysis method does not result in epimerization of chiral centers positioned α to the methyl ester functionality.

Selenium-Based Resins for Heterocyclic Synthesis.[148] Using resin-supported selenium, Huang and co-workers reported a highly efficient five-step sequence for the production of bis-heterocyclic compounds (Figure 16).[148] Reaction of polystyrene-supported selenium bromide **221** with acrylic acid, followed by treatment with potassium *tert*-butoxide, gave resin **222.** Two choices then faced the authors for the production of the bis-heterocyclic products. Route A utilized a 1,3-dipolar cycloaddition to give the resin bound 4,5-dihydroisoxazole **223**. Condensation of **223** with various amidoximes gave compounds of type **225**. In route B, the synthetic steps of route A were reversed: condensation of resin **222** with various amidoximes to give intermediate **224** was followed by the 1,3-dipolar cyclization to give **225**. Treatment of **225** with hydrogen peroxide in THF afforded the desired products **226** (23 compound library) in high purity (87−95%) with moderate to good yields. The authors report significantly improved yields when route B was employed (e.g., compounds **226a** and **226c**). The purities of the final compounds, however, were similar using either route.

After the plausibility of the reaction sequence was established, its utility was expanded.[148] As shown in Figure 17, replacement of the nitrile oxide dipole with an azide dipole, during the 1,3-cycloaddition step involving **224**, gave the polymer-supported triazole intermediates **227**. After treatment with hydrogen peroxide, a 14-compound oxadiazolyl−triazole library was generated (**224** → **227** → **228**). Representative examples include **228a**−**c**. The compounds were obtained in high purity (88−93%) and moderate yield (56−68%). The chemistry was extended using either cyclopentadiene or isoprene in a Diels−Alder reaction generating two 8-member libraries (**224** → **229** → **230**). Yields for the two libraries ranged from 68−78% (89−92% purities) for the cyclopentadiene library (e.g., **230a**−**c**) and 59−74% (89−94% purities) when isoprene was employed (e.g., **230d**−**f**).

Huang and co-workers also prepared an eleven-member library of uracils in three steps (Figure 18).[147] In a one-pot, two-step procedure, resin-bound selenium bromide

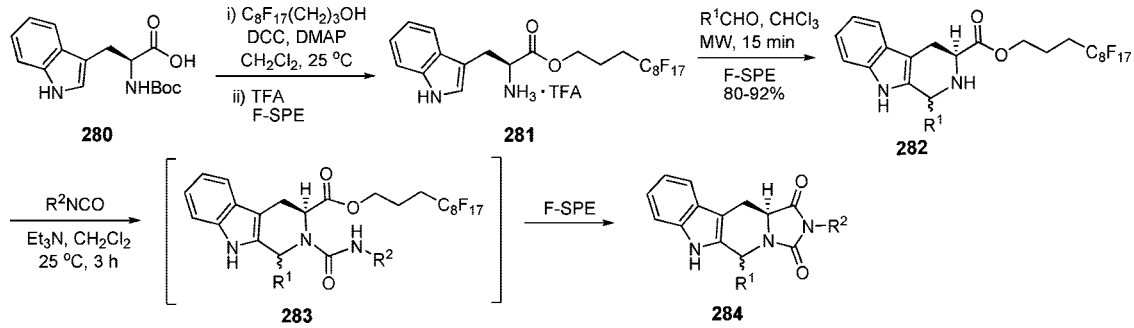


Figure 24. Fluorous alcohol-facilitated synthesis of tetrahydro-β-carboline hydantoins.[212]

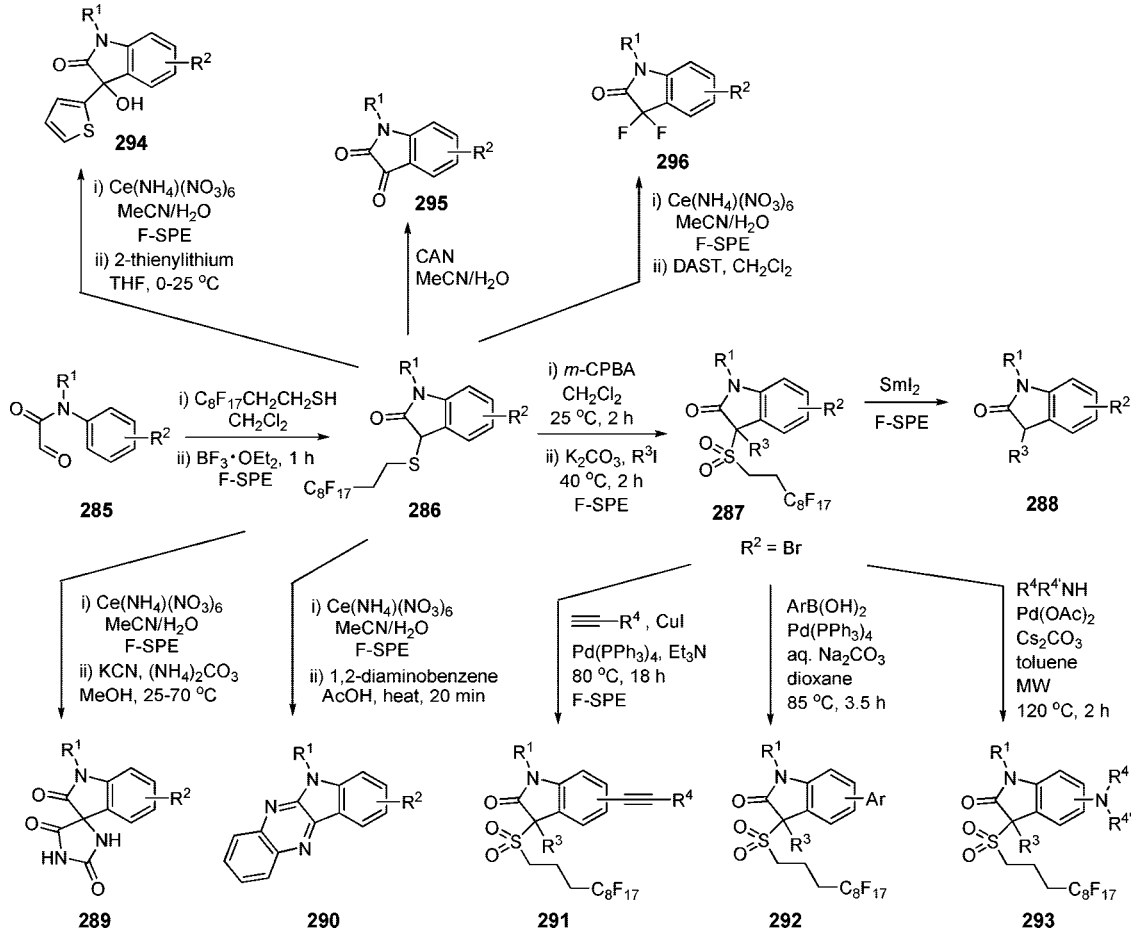


Figure 25. Thiol tag for catch and release of Pummerer cyclization products and DOS of heterocyclic compounds.[243]

221 was reacted sequentially with α,β-unsaturated esters and primary amines to afford the substituted amino ester resins **231**. Reaction of **231** with various isocyanates in the presence of potassium carbonate afforded the polymer supported 1,3,6-trisubstituted 5,6-dihydrouracils (**232**). Release of the target compounds **233** was achieved using hydrogen peroxide. Representative compounds **233a**−**f** were obtained in high purity (88−96%) and good yield (65−83%).

Post Modification of Multicomponent Reaction (MCR) Products. Using sequential Ugi 4-component (U-4CR), ring-closing metathesis (RCM), and Heck reactions, Ribelin and co-workers generated a series of novel bridged bicyclic lactams with a high degree of diastereoselectivity.[317] As illustrated in Figure 19, condensation of various olefinic amines, olefinic acids, and aryl aldehydes with isopropylisocyanide gave the U-4CR products **238** in good to excellent yields. The lactams **239** were then obtained in almost quantitative yields from the ring-closing metathesis of the acyclic diolefins using the second generation Grubb's catalyst. Finally, an intramolecular Heck cyclization gave the desired compounds **240a**−**e** in good to excellent yields, with a high degree of diastereoselectivity. Initially the Heck reactions were performed with a soluble palladium catalyst. In an effort to develop a procedure more suited for automation, the authors repeated the Heck reactions using FiberCat 1032, an immobilized palladium catalyst. With the exception of compound **240e**, use of the resin-bound palladium afforded the desired compounds in comparable yields and diastereoselectivities to those seen with the soluble catalyst, with the added benefit of easier purification. In the case of compound **240e**,

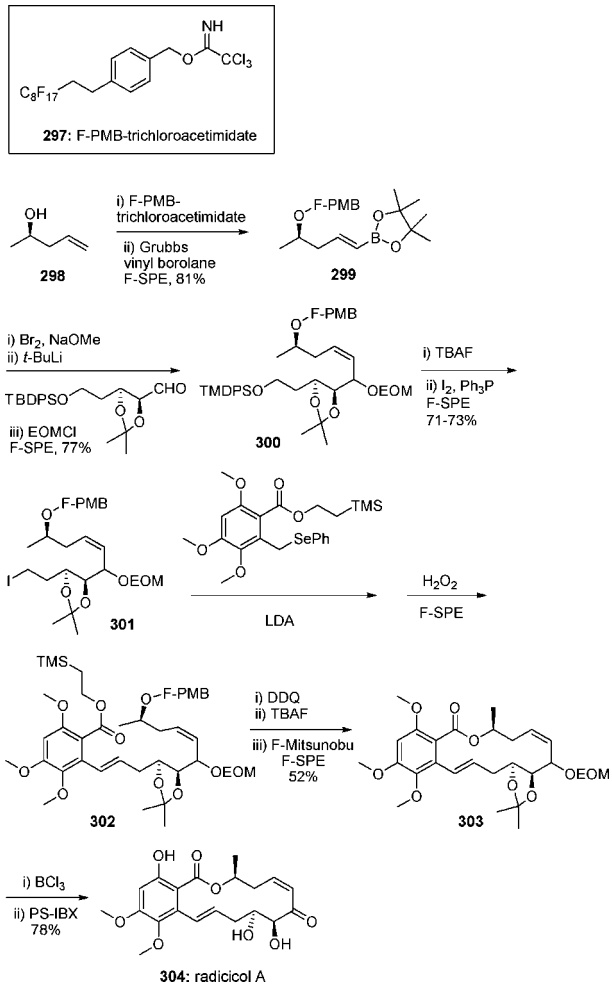


Figure 26. F-PMB-facilitated synthesis of radicicol A.[78]

however, the use of the immobilized catalyst eroded the regioselectivity of the 4,5-alkenyl:3,4-alkenyl products from 95:5, observed with the soluble catalyst, to a ratio of 74:26. The authors propose that this is the result of a palladium hydride-mediated isomerization of the initial 4,5-alkenyl product. From X-ray crystallographic studies of the compounds, the authors observed a high level of bridgehead amide bond distortion in compound **240a**. Homologation of the lactam ring systems (e.g., **240b** and **240c**) attenuated the bond distortion. The least distortion was seen in the bicycloundecene analog **240e**. Concerned that the twisted nature of the bridgehead amide could lead to enhanced reactivity toward biological nucleophiles (e.g., hetero-Michael addition), the authors pursued the possibility of performing the ring closure-step under reductive Heck conditions. Following optimization of the reaction conditions, the authors were able to perform a highly diastereoselective reductive Heck reaction in excellent yield (**241** → **242**). Conversely, the increased reactivity of the α,β-unsaturated lactam could be exploited to provide further diversification via Michael reaction. Therefore, rhodium-catalyzed Michael addition was conducted using 4-methoxyphenylboronic acid with compound **240d** to give **243**. The reaction was found to be highly efficient and was determined, by ROESY correlation, to have occurred with complete diastereoselectivity from the exo face of the indole.

Spatz and collaborators reported the synthesis of a series of 4-oxo-imidazoquinoxalines **249** and 4-oxo-pyrazoloquinoxalines **250** through the post functionalization of Ugi-four component reaction (U-4CR) products (Figure 20).[369] Introduction of the imidazole or pyrazole component was achieved through the use of their respective acids **247** during the standard U-4CR condensation procedure. A series of bases was then profiled to determine the most suitable for the S_NAr cyclization. From their studies, the authors found cesium or potassium carbonate to be the bases of preference for optimal yields. Using microwave irradiation, the authors obtained the target imidazoquinoxalines (**249a**−**c**) and pyrazoloquinoxalines (**250a**−**c**) in moderate to good yields. With three points of diversity, this two-step procedure was found to be robust and tolerated a broad range of starting materials.

Using an Ugi-four component reaction (U-4CR) followed by a Cu-catalyzed intramolecular cyclization, Spatz and coworkers prepared a series of highly substituted benzoxazoles **256** and benzothiazoles **257** (Figure 21).[368] Variation of the amine, carbonyl, acid, or isocyanate component of the U-4CR step allows for potential diversification at 5 different points. A mechanism for the Cu-mediated generation of the benzoxazoles and benzothiazoles was proposed by the authors. Coordination of the Cu-complex to the carbonyl or thiocarbonyl group of the U-4CR condensate (**255**) gives intermediate **258**. Oxidative addition to the arylhalide, followed by reductive elimination, affords the desired benzoxazoles (**256a**−**c**) or benzothiazoles (**257a**−**c**) with regeneration of the copper catalyst. Yields for the benzothiazoles were generally better than those seen for the equivalent benzoxazole analog (e.g., **257c** vs **256c**). As illustrated by the ability of an aryl fluoride to undergo cyclization, the authors attribute the higher yields for the benzothiazoles to a higher reactivity of the thioamide intermediates.

MCR Leading to Highly Substituted γ-Lactams.[422] The highly diastereoselective synthesis of tetra- (**265**) and pentasubstituted γ-lactams (**269**) in a one pot, four-component reaction (4-CR) using amines, maleic anhydrides, aldehydes, and thiols is reported by Wei and Shaw (Figure 22).[422] Only one regioisomer was produced during the course of the reaction (**265**). This was a particular surprise. The addition to the anhydride by the imine, following thiol conjugate addition, to give intermediates **264a** or **266** is known to be non-selective. The authors postulate that the imine−anhydride addition is reversible and that only the α-thioaryl isomer (**264a**) is able to undergo enolization (**264b**) and proceed to product. Using this strategy, a series of γ-lactams **265a**−**f** were prepared in good to excellent yield. Limited to nonenolizable aldehydes because of the enamide formation, the reaction was successfully performed with cyclopropane carboxaldehyde (**265d**) demonstrating the need for energetic suppression of enolization. While the use of alkylthiols led to a reduction in stereoselectivity (**265e**), *ortho*-substituted

aryl thiols were well tolerated (**265f**). In an extension of this research, Wei and Shaw used 3-substituted maleic anhydrides to prepare a series of pentasubstituted γ-lactams **269**. Compared to reactions performed with the unsubstituted maleic anhydride (**263a**), the use of a substituted anhydride (**263b**) led to a slight decrease in the yields of the final compounds (**269a**−**c**). However, the reaction still proceeded with a high degree of diastereoselectivity. This was somewhat surprising because this requires the maleic amide regioisomers, formed in the initial step, to converge to a single iminium ion regioisomer capable of proceeding to the lactam product. The mechanism for this reaction is not fully understood and is currently under investigation by the authors. Finally, the removal of the thioether group to yield highly diastereochemically defined trisubstituted lactams **271** was described. Under a radical reductive procedure using AIBN, the lactam **270** was converted to the *syn*-**271** product in high yield and stereoselectivity. Reduction of the thioether with Raney nickel gave a 1:1 mixture of the syn and anti products, which were epimerized with potassium *tert*-butoxide to give the *anti*-**271** product as a single epimer.

Synthesis of Natural Alkaloid Sclerotigenin Analogs.[451] Sclerotigenin (**272**) was isolated from the sclerotia of *Penicillium sclerotigenum* (Figure 23). It is the simplest member of the natural alkaloid benzodiazepine−quinazolinone family and has shown promising antiinsectan activity.[475] Many other members in this family, such as circumdatins A−G and benzomalvins A−C, also possess interesting biological activities.[476] 1,4-Benzodiazepine-2,5-dione is a privileged ring system that can be prepared by conventional solution-phase, as well as solid-phase, methods.[477] The Zhang group employed a fluorous PMB-type tag for the parallel synthesis of 1,4-benzodiazepine-2,5-diones and further converted them to sclerotigenin analogs.[451] The fluorous PMB-type tag **273** was attached to amino esters through reductive amination under a general solution-phase condition. The attached amines **274** underwent amide couplings to form amides **275**. Base-promoted cyclizations of **275** afforded the 1,4-benzodiazepine-2,5-dione ring. Sequential *N*-acylation of **276** and nitro group reduction of **277**, followed by cyclization, afforded **278**. Nine benzodiazepine-quinazolinone analogs **279** were obtained after microwave-assisted TFA-mediated cleavage of the fluorous PMB tag. Except for compounds **278,** all the other intermediates and the final products were purified by fluorous solid-phase extraction (F-SPE). The fluorous PMB tag was found stable under sonication and microwave conditions. The synthesis of this small library successfully demonstrated the utility of fluorous tags for solution-phase synthesis of natural product analogs.

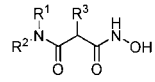
Synthesis of Hydantion-Fused Tetrahydro-β-Carboline Library.[212] The Sun group employed a fluorous alcohol as a tag in the synthesis of hydantion-fused tetrahydro-β-carboline analogs (Figure 24).[212] The skeleton of the products contains hydantoin and tetrahydro-β-carboline rings. Because these two moieties are known pharmacophores, the combined tetracyclic scaffold could contain appealing drug-like molecules for drug-discovery screening. The synthesis of tetrahydro-β-carboline hydantoins was accomplished by conventional solution-phase synthesis[478] and also on the soluble-polymer support.[479] The same research group extended the synthetic scope and developed a microwave-assisted fluorous method. The fluorous alcohol was attached to Boc-L-tryptophan **280** using DCC and DMAP as the coupling agents. After Boc deprotection with TFA, fluorous aminoester **281** was employed for the Pictet−Spengler reaction with aldehydes to form tetrahydro-β-carboline derivatives **282**. This step was conducted under microwave conditions, and the reactions were completed in 15 min. Treatment of **282** with isocyanates led to the formation of ureas **283** that spontaneously underwent cyclizations to afford hydantoin-fused tetrahydro-β-carbolines **284** as the major products. A demonstration library containing fifteen products was prepared by using different aldehydes and isocyanates as the building blocks. This project combined the tag cleavage and hydantoin ring-formation in one reaction step to achieve a high synthetic efficiency. Purifications of reaction intermediates and products were facilitated by F-SPE.

Pummerer Cyclization Product for DOS.[243] The Procter group introduced a fluorous Pummerer cyclative-capture strategy for the synthesis of nitrogen-containing heterocycles.[243] This work was initially attempted to improve a solid-phase approach that was difficult in monitoring intermediate transformations. Fluorous thiol tag allowed in-process analysis in a solution-phase environment and also enabled F-SPE for purification of reaction mixtures. A wide range of post-Pummerer reaction modifications and tag cleavage methods have been developed for diversity-oriented synthesis (DOS) of heterocyclic frameworks (Figure 25). The post-Pummerer reactions include the oxidation of sulfides **286** to sulfones followed by alkylation to form **287**. Other modifications include Pd-catalyzed coupling reactions of arylhalides **287** (R^2 = Br) to form propargylated products **291**, arylated products **292**, and aminated products **293**, respectively. The tag cleavage reactions include reductive (traceless) reactions to form **288**, oxidative reactions to form **294** or 1,2-diketones **295**, and fluorination reactions to form **296**. The cyclative tag cleavage strategy has been developed to form spiro- or fused-heterocyclic compounds **289** and **290**.

Synthesis of Radicicol A.[78] Radicicol A (**304**) is a member of resorcylic acid lactone family (Figure 26). This biologically interesting compound is able to accelerate the degradation of specific mRNA sequences.[480] Other related resorcylic acid lactones were reported to be potent irreversible yet selective kinase inhibitors.[481] Winssinger and coworkers developed a fluorous PMB-trichloroacetimidate tag **297** and applied it for the total synthesis of radicicol A.[78] A fluorous PMB-attached alkene underwent cross-metathesis

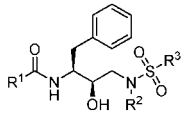
Table 1. Chemical Libraries Targeting Proteases[a]

Metallo proteases

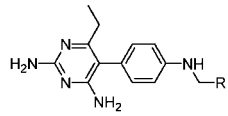


- Library 1.1
- Flipo [104, 105]
- neutral aminopeptidase inhibitors and zinc plasmodial aminopeptidase PfA-M1 inhibitors

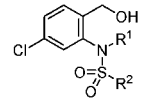
Aspartyl proteases



- Library 1.2
- Chellappan [58]
- HIV protease (mutation-resistant) inhibitors

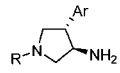


- Library 1.3
- Holsworth [142]
- renin inhibitors

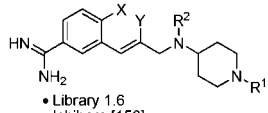


- Library 1.4
- Parker [295]
- γ-secretase inhibitors

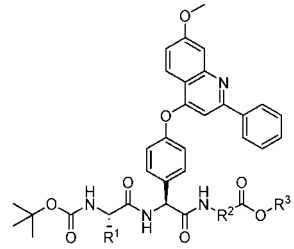
Serine proteases



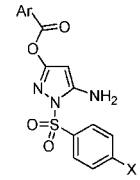
- Library 1.5
- Backes [18]
- dipeptidyl peptidase IV (DPP4) inhibitors



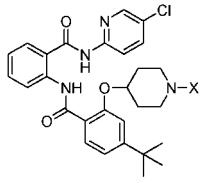
- Library 1.6
- Ishihara [156]
- factor Xa inhibitors; X, Y = H or taken together to form naphthyl ring



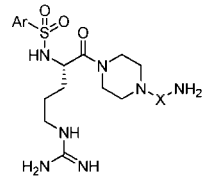
- Library 1.7
- Ortqvist [287]
- hepatitis C virus NS3 protease inhibitors



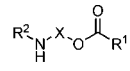
- Library 1.8
- Johnston [162]
- NS_2B-NS_3 proteinase of West Nile virus



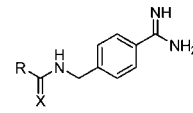
- Library 1.9
- Mendel [248]
- factor Xa inhibitors



- Library 1.10
- Salvagnini [332]
- thrombin inhibitors

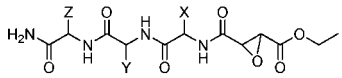


- Library 1.11
- Gertach [117]
- thrombin inhibitors

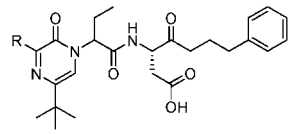


- Library 1.12
- Melkko [250]
- trypsin inhibitors

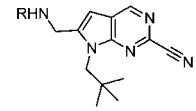
Cysteine proteases



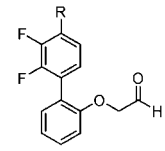
- Library 1.13
- Cuerrier [72]
- calpain inhibitors



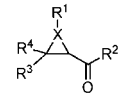
- Library 1.14
- Isabel [155]
- caspase-3 inhibitors



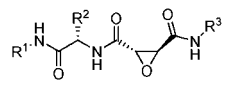
- Library 1.15
- Teno [386]
- cathepsin K inhibitors



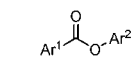
- Library 1.16
- Inagaki [154]
- cathepsin S inhibitors



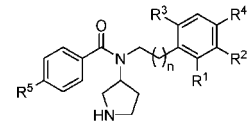
- Library 1.17
- Schulz [337]
- falcipain-2 and falcipain-3 protease inhibitors



- Library 1.18
- Sadaghiani [330]
- papain-family cysteine protease inhibitors



- Library 1.19
- Zhang [456]
- 3C-like protease ($3CL^{pro}$) inhibitors

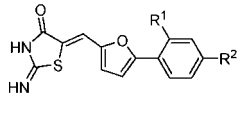


- Library 1.20
- Hay [402]
- protein site-1 inhibitors

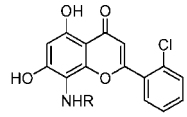
[a] Asterisk is the point of attachment to resin.

Table 2. Chemical Libraries Targeting Nonproteolytic Enzymes[a]

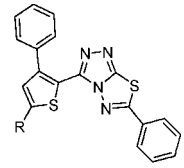
Kinases



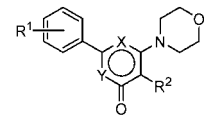
- Library 2.1
- Richardson [318]
- CDK2 inhibitors



- Library 2.2
- Ahn [4]
- CDK2-cyclin A inhibitors

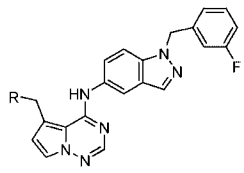


- Library 2.3
- Shiradkar [355]
- cyclin-dependent kinase 5/p25 inhibitors
- one of several structurally related libraries

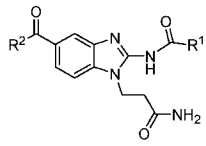


- Library 2.4
- Hollick [140]
- DNA-dependent protein kinase inhibitors

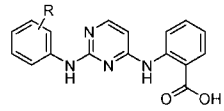
Table 2. Continued



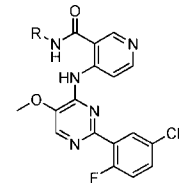
- Library 2.5
- Mastalerz [241]
- dual EGFR and HER2 protein tyrosine kinase inhibitors



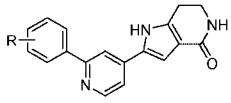
- Library 2.6
- Snow [365]
- interleukin-2-inducible T cell kinase (ITK) inhibitors



- Library 2.7
- Liu [215]
- c-Jun *N*-terminal kinase inhibitors

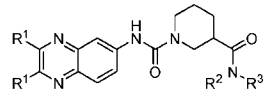


- Library 2.8
- Raboisson [310]
- JNK and VEGFR kinase inhibitors

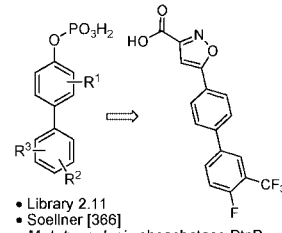


- Library 2.9
- Anderson [10]
- mitogen-activated protein kinase-activated protein kinase 2 (MK-2) inhibitors

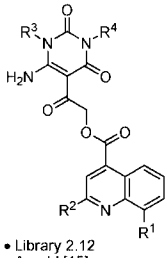
Phosphatases



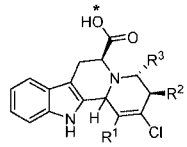
- Library 2.10
- Zhang [458]
- Jnk Stimulatory Phosphatase-1 (JSP-1) inhibitors



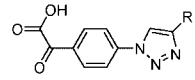
- Library 2.11
- Soellner [366]
- *M. tuberculosis* phosphatase PtpB
- selective inhibitor derived from an *O*-aryl phosphate substrate library



- Library 2.12
- Arnold [15]
- mitogen-activated protein kinase phosphatase inhibitors

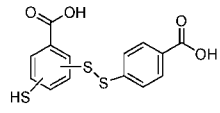


- Library 2.13
- Correa Jr. [71]
- mycobacterial protein tyrosine phosphatase B (MptpB) inhibitors

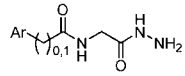


- Library 2.14
- Xie [432]
- protein tyrosine phosphatase inhibitors

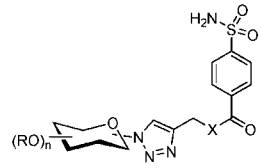
Alphebetical order



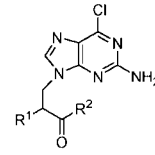
- Library 2.15
- Lienard [211]
- *Bacillus cereus* metallo-β-lactamase (BcII) inhibitors



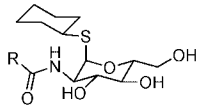
- Library 2.16
- Ejim [91]
- bacterial cystathionine β-lyase inhibitors



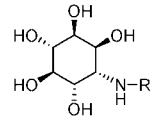
- Library 2.17
- Wilkinson [425]
- carbonic anhydrase isozymes IX, XII and XIV inhibitors



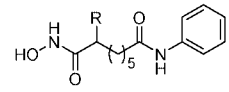
- Library 2.18
- Paradis-Bleau [293]
- FtsZ GTPase inhibitors (*P. aeruginosa*)



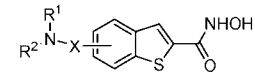
- Library 2.19
- Metaferia [260]
- dual inhibitors of the mycothiol biosynthesis enzyme GlcNAc-Ins deactylase (MshB) and the mycothiol-dependent detoxification enzyme mycothiol-S-conjugate amidase (MCA) from *M. tuberculosis*



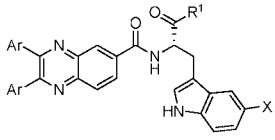
- Library 2.20
- Serrano [345]
- glucocerebrosidase inhibitors



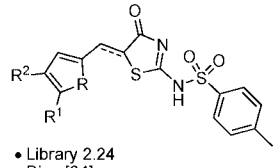
- Library 2.21
- Bieliauskas [31]
- histone deacetylase (HDAC) inhibitors



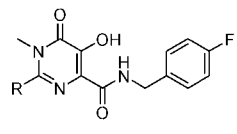
- Library 2.22
- Witter [427]
- histone deacetylase inhibitors



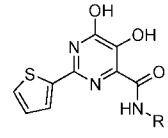
- Library 2.23
- Rong [327]
- HCV NS5B RNA-dependent RNA polymerase inhibitors



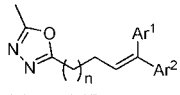
- Library 2.24
- Ding [84]
- HCV NS5B polymerase inhibitors



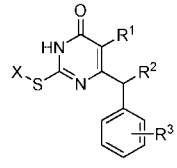
- Library 2.25
- Gardelli [113]
- HIV integrase inhibitors



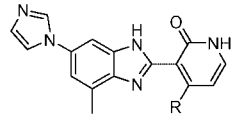
- Library 2.26
- Pace [290]
- HIV integrase inhibitors



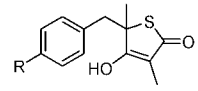
- Library 2.27
- Cullen [74]
- HIV-1 non-nucleoside reverse transcriptase inhibitors



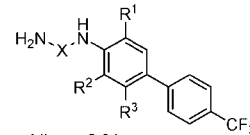
- Library 2.28
- Mugnaini [268]
- HIV-1 reverse transcriptase inhibitors



- Library 2.29
- Velaparthi [403]
- insulin-like growth factor 1-receptor (IGF-1R) inhibitors

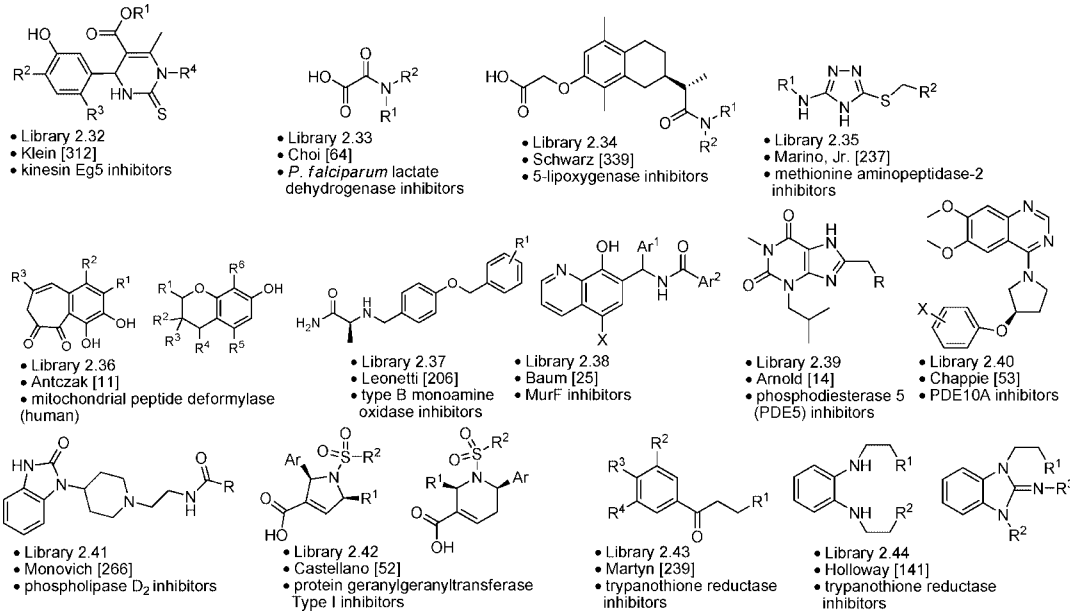


- Library 2.30
- Bhowruth [30]
- β-ketoacyl-ACP synthase III inhibitors



- Library 2.31
- Parrish [296]
- kinesin spindle protein inhibitors

Table 2. Continued



[a] Asterisk is the point of attachment to resin.

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

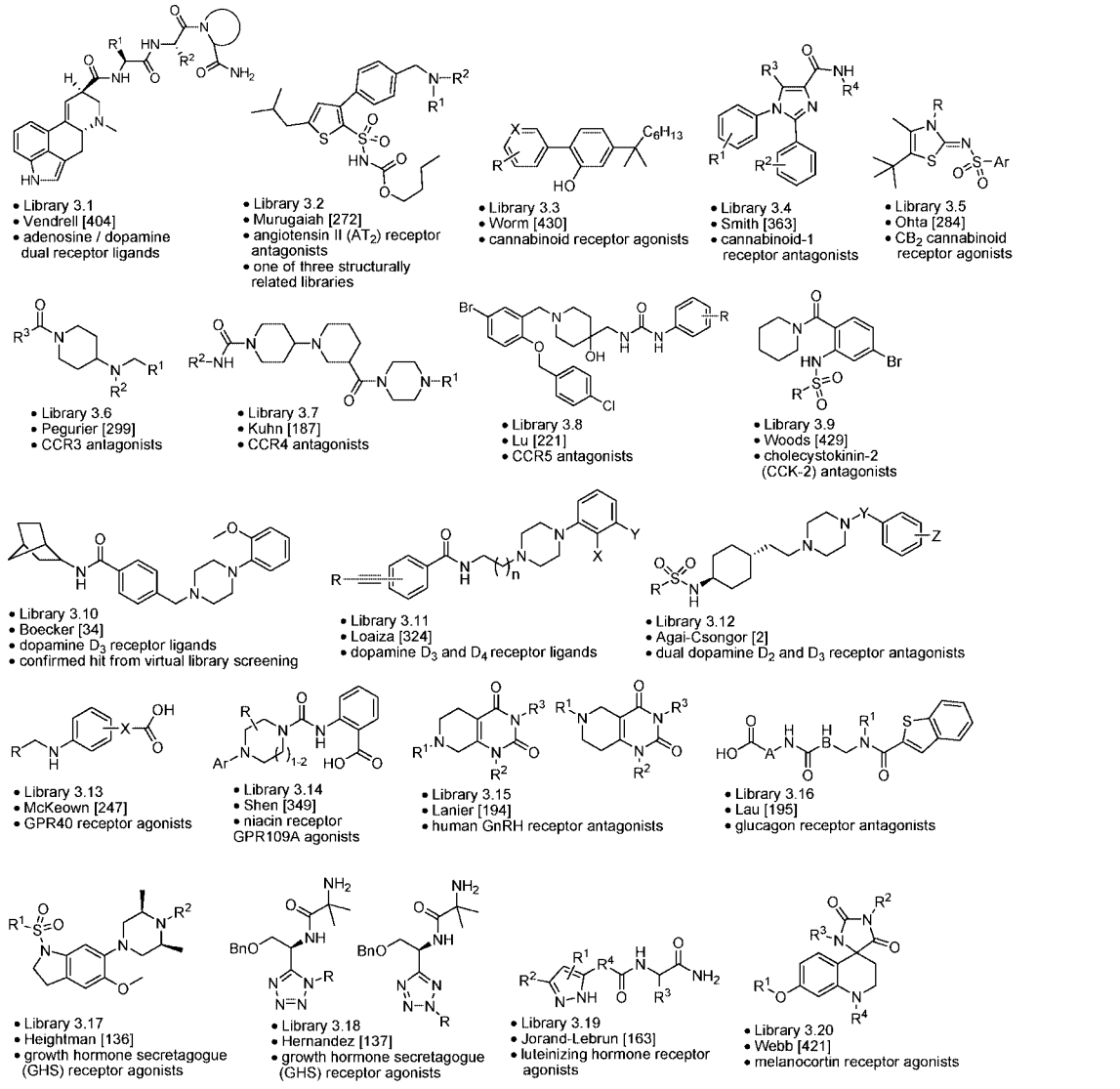
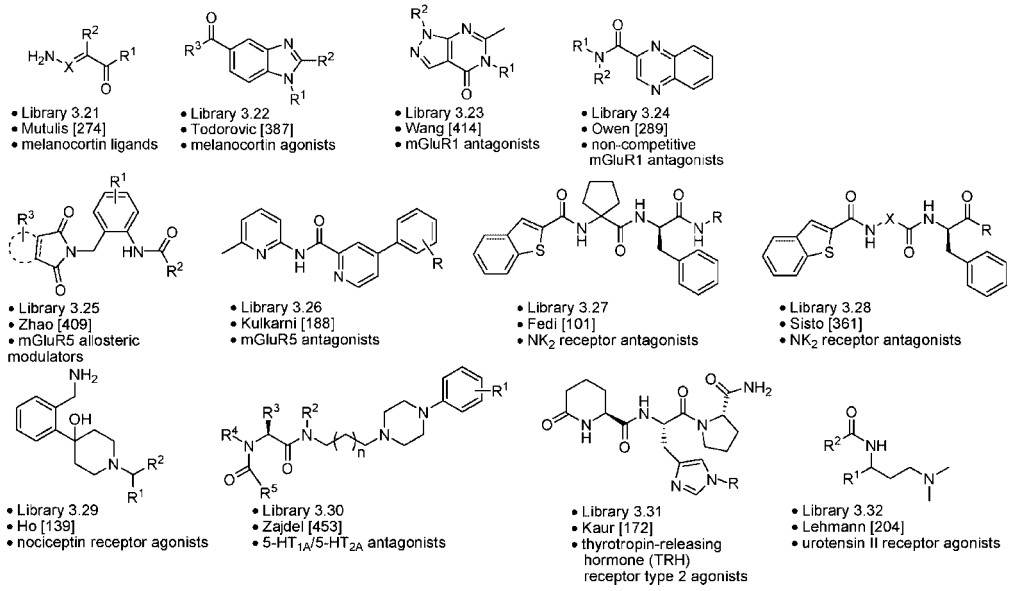


Table 3. Continued



[a] Asterisk is the point of attachment to resin.

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

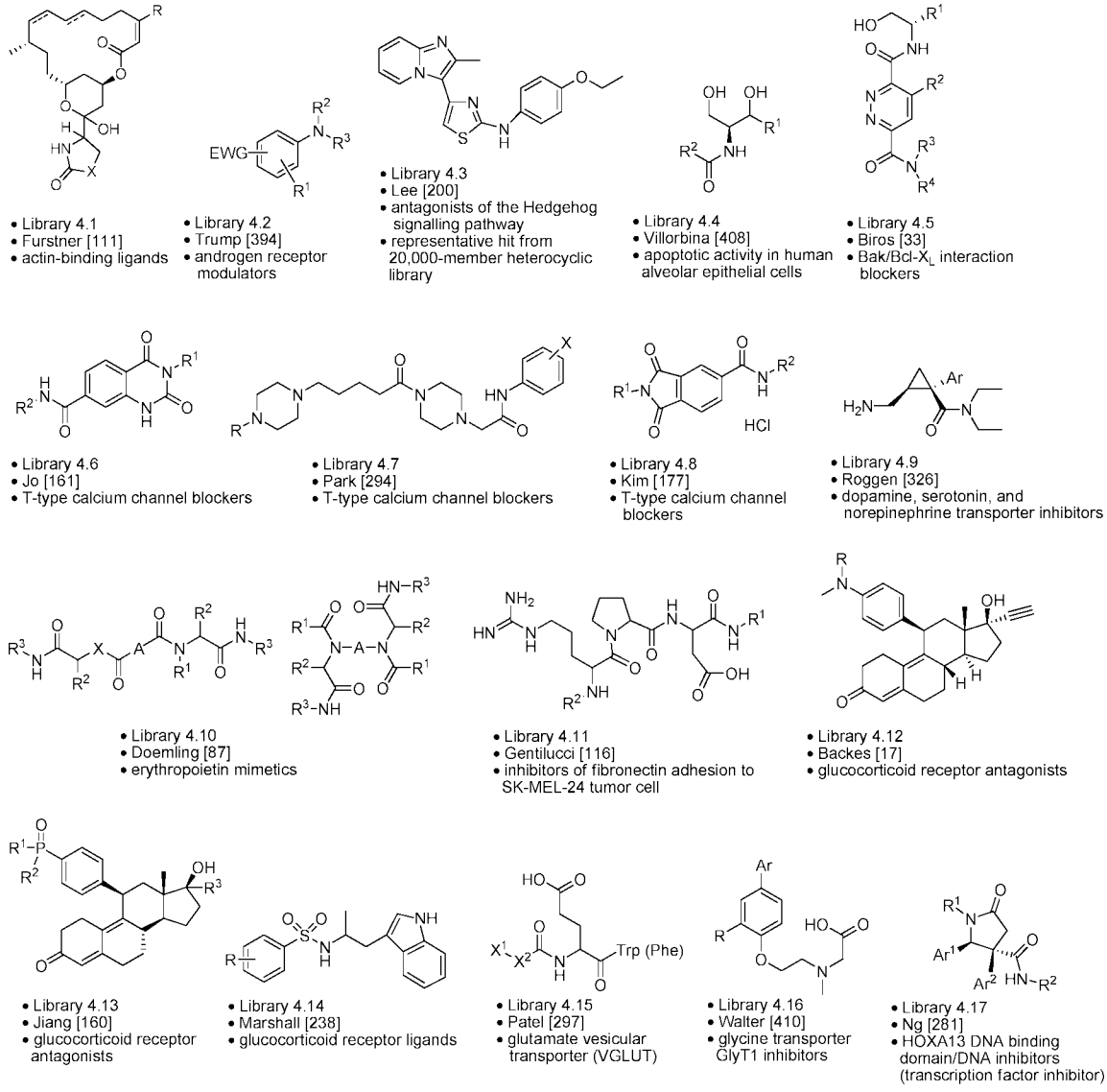
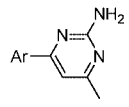
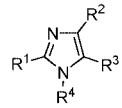


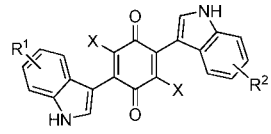
Table 4. Continued



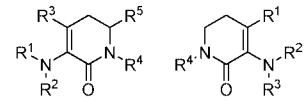
- Library 4.18
- Huth [152]
- HSP90 inhibitors



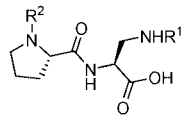
- Library 4.19
- Williams [426]
- induction of neurogenesis in skeletal muscle



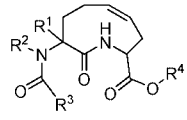
- Library 4.20
- Pirrung [304]
- insulin receptor activators



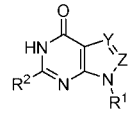
- Library 4.21
- Benfatti [27]
- dual integrin $\alpha_v\beta_3/\alpha_5\beta_1$ antagonists



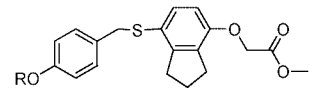
- Library 4.22
- Choi [63]
- integrin $\alpha_2\beta_1$ inhibitors



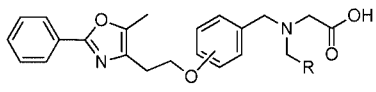
- Library 4.23
- Banfi [20]
- integrin $\alpha_v\beta_3$ inhibitors



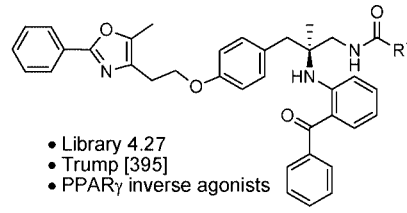
- Library 4.24
- Tan [384]
- multidrug resistance protein 4 inhibitors



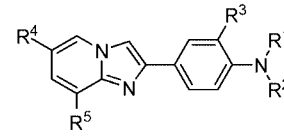
- Library 4.25
- Bratton [44]
- peroxisome proliferator-activator receptor (PPAR) δ agonists



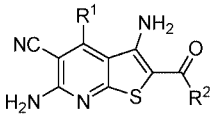
- Library 4.26
- Devasthale [82]
- dual PPARα/γ agonists-I



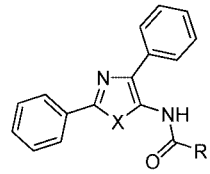
- Library 4.27
- Trump [395]
- PPARγ inverse agonists



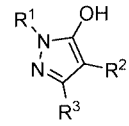
- Library 4.28
- Cai [49]
- ligands for human β-amyloid plaques



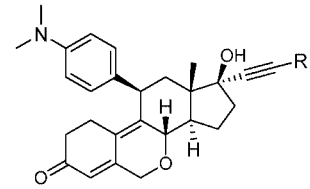
- Library 4.29
- May [245]
- oligomeric prion protein (PrP^{Sc}) inhibitors



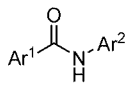
- Library 4.30
- Heal [134]
- binding to prion protein (PrP^{C}) and inhibition of PrP^{Sc} formation



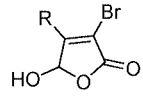
- Library 4.31
- Kimata [178]
- protease-resistant prion protein accumulation inhibitors



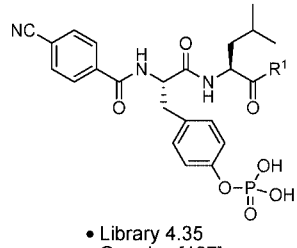
- Library 4.32
- Kang [169]
- progesterone receptor antagonists



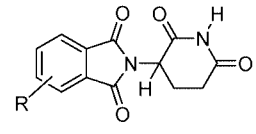
- Library 4.33
- Dahlgren [75]
- type III secretion in *Yersinia* inhibitors



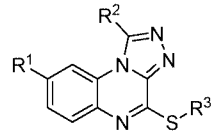
- Library 4.34
- Guerrero [125]
- inhibitors of prostanoid production



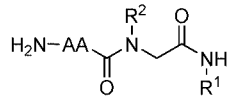
- Library 4.35
- Gunning [127]
- STAT1 or STAT3 homo-dimerization inhibitors



- Library 4.36
- Stewart [374]
- TNF expression inhibitors



- Library 4.37
- Gururaja [128]
- inhibitors of TNFα-induced survival and death pathways

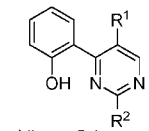


- Library 4.38
- Quintanar-Audelo [309]
- transient receptor potential vallinoid 1 (TRPV1) noncompetitive antagonists

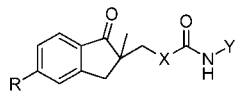
[a] Asterisk is the point of attachment to resin.

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

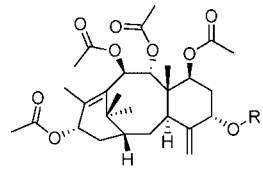
Cytotoxic agents



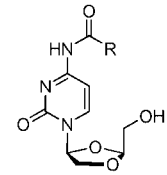
- Library 5.1
- Xie [431]
- BEL-7402 growth inhibition



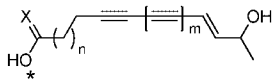
- Library 5.2
- Charrier [54]
- H661 cell proliferation inhibitors



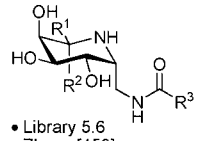
- Library 5.3
- Botta [40]
- reversal activity in human mammary carcinoma MDR cell line MCF7-R



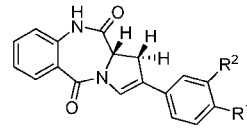
- Library 5.4
- Radi [311]
- cytotoxic activity on two non-small cell lung cancer cell lines (A549 and SW 1573)



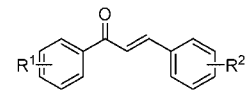
- Library 5.5
- Lee [201]
- HTC116 human colon cancer cell growth inhibitors



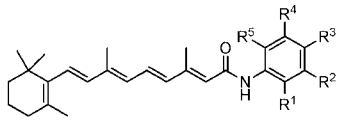
- Library 5.6
- Zhang [459]
- human cervical carcinoma cell line Hela and leukemia cell line HL-60 inhibitors



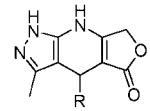
- Library 5.7
- Antonow [13]
- cytotoxic agents



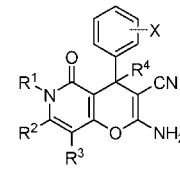
- Library 5.8
- Liu [216]
- cell cycle progression inhibitors



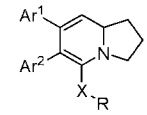
- Library 5.9
- Mershon [257]
- human mammary tumor cells (MCF-7) growth inhibitors



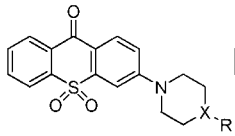
- Library 5.10
- Magedov [225]
- Hela growth inhibitors



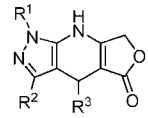
- Library 5.11
- Magedov [224]
- antiproliferative activity in Hela and induce apoptosis in Jurkat cell lines



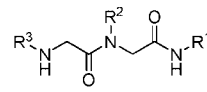
- Library 5.12
- Kimball [179]
- HCT-116 growth inhibitors



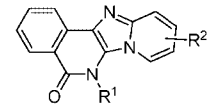
- Library 5.13
- Lory [218]
- BRCT domain inhibitors of breast cancer gene 1



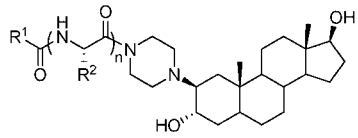
- Library 5.14
- Magedov [226]
- antiproliferative and apoptosis-inducing agents



- Library 5.15
- Mas-Moruno [240]
- antiproliferative activity on human neoplastic cells

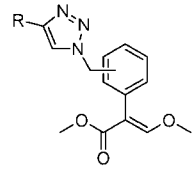


- Library 5.16
- Meng [254]
- A549 cell growth inhibitors

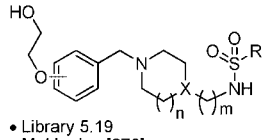


- Library 5.17
- Roy [328]
- antiproliferative activity on human leukemia HL-60 cells

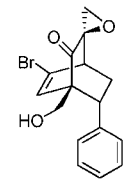
Antiinfective agents



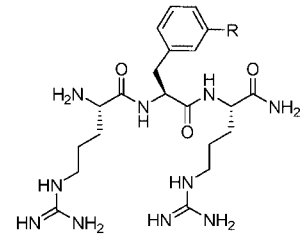
- Library 5.18
- Chen [60]
- *A. Brassiceae* growth inhibitors



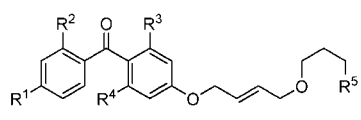
- Library 5.19
- Mukherjee [270]
- *E. coli* cell division inhibitors



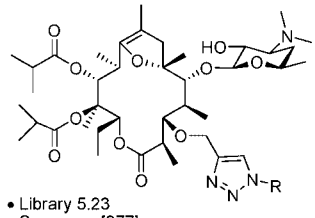
- Library 5.20
- Peng [302]
- hepatitis C virus replication inhibitors
- representative hit from DOS library set:



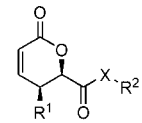
- Library 5.21
- Haug [132]
- methicillin-resistant *S. auveus* (MRSA) growth inhibitors



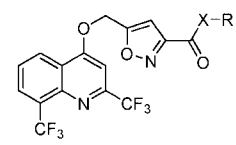
- Library 5.22
- Kurosu [191]
- MRSA growth inhibitors



- Library 5.23
- Sugawara [377]
- MRSA and vancomycin-resistant *Enterococcus* (VRE) strains

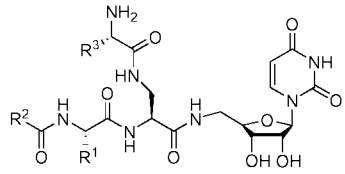


- Library 5.24
- Lessmann [207]
- modulators of cell cycle progression and viral entry

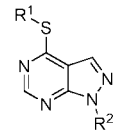


- Library 5.25
- Mao [235]
- *M. tuberculosis* growth inhibitors

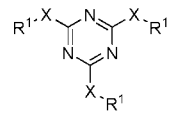
Table 5. Continued



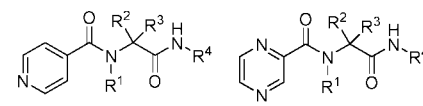
- Library 5.26
- Sun [378]
- *M. tuberculosis*



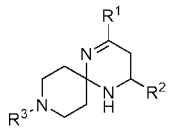
- Library 5.27
- Ballell [19]
- *M. tuberculosis* growth inhibitors



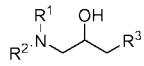
- Library 5.28
- Arya [16]
- *M. tuberculosis* growth inhibitors



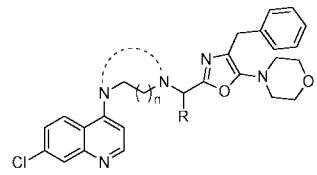
- Library 5.29
- Domling [86]
- *M. tuberculosis* growth inhibitors



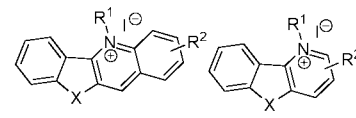
- Library 5.30
- Muravyova [271]
- *M. tuberculosis* growth inhibitors



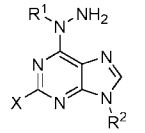
- Library 5.31
- Robin [321]
- *P. falciparum* growth inhibitors



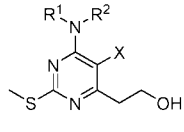
- Library 5.32
- Musonda [273]
- *P. falciparum* growth inhibitors



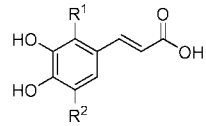
- Library 5.33
- Zhu [357]
- *P. falciparum* growth inhibitors



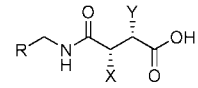
- Library 5.34
- Too [388]
- *P. falciparum* growth inhibitors



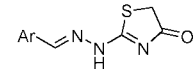
- Library 5.35
- Mugnaini [269]
- rubella virus inhibitors



- Library 5.36
- Srivastava [372]
- *S. auveus* growth inhibition



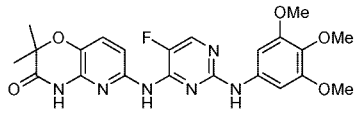
- Library 5.37
- Serrano [344]
- *Saccharomyces cerevisiae* growth inhibitors



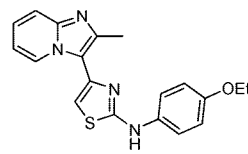
- Library 5.38
- Leite [205]
- *Trypanosoma cruzi* growth inhibitors

[a] Asterisk is the point of attachment to resin.

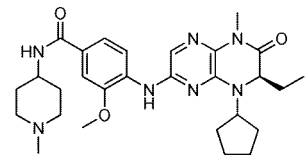
Table 6. Selected Molecular Probes



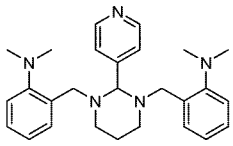
- R406
- Rigel Pharmaceuticals
- Braselmann [43]
- spleen tyrosine kinase inhibitor



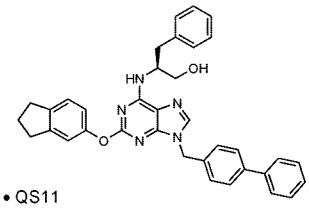
- JK184
- The Scripps Research Institute
- Lee [200]
- Hedgehog signaling pathway (Adh7 inhibition)



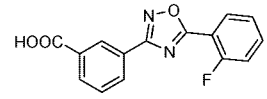
- BI 2536
- Boehringer Ingelheim Austria GmbH
- Steegmaier [373]
- polo-like kinase 1



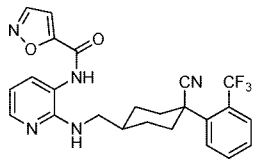
- GANT61
- Karolinska Institut
- Lauth [198]
- GLI-mediated transcription



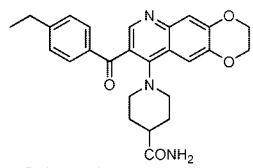
- QS11
- The Scripps Research Institute
- Zhang [452]
- GTPase activating protein of ADP-ribosylation factor 1 (ARFGAP1)



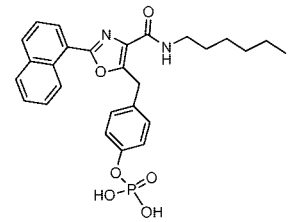
- PTC 124
- PTC Therapeutics
- Welch [423]
- readthrough Induction of premature, mutationally induced translational termination



- 4–substituted phenyl cyclohexanes
- Merck Research Laboratories
- Su [375]
- bradykinin B1 receptor antagonist

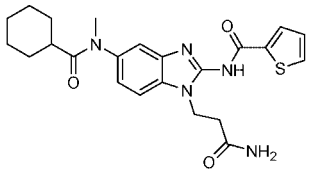


- Quinostatin
- Broad Institute of Harvard and MIT
- Yang [439]
- catalytic subunits of class Ia phosphoinositide 3-kinases

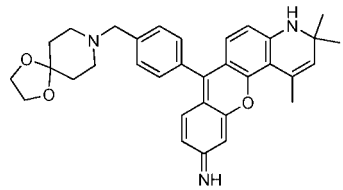


- S31-M2001
- University of Central Florida
- Siddiquee [359]
- Stat3

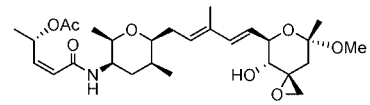
Table 6. Continued



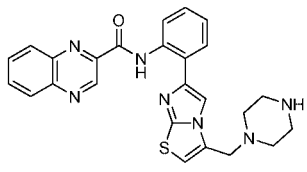
- 2-substituted benzimidazoles
- Boehringer Ingelheim Pharmaceuticals
- Snow [365]
- interleukin-2-inducible T cell kinases (ITK)



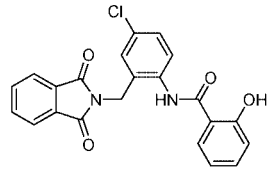
- H22
- New York University
- Ahn [3]
- *in vivo* glutathione probe



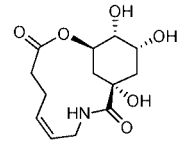
- Spliceostatin A
- Chemical Genetic Laboratory, RIKEN
- Kaida [164]
- splicing factor SF3b



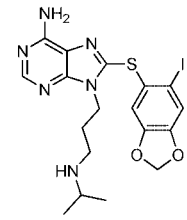
- SRT1720
- Sirtris Pharmaceuticals
- Milne [264]
- sirtuin 1 (SIRT1) activator



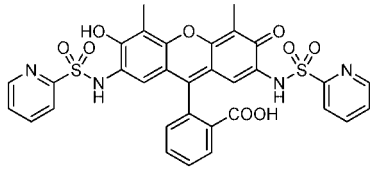
- CPPHA
- Vanderbilt Medical Center and Merck & Co.
- Zhao [409]
- positive allosteric modulator of mGluR5



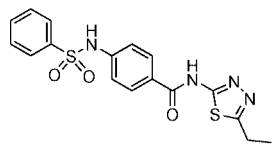
- Macrolide 1
- National Institute of Diabetes and Digestive and Kidney Diseases
- Metaferia [259]
- breast cancer cell migration



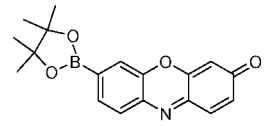
- PU-H71
- Memorial Sloan-Kettering Cancer Center
- Rodina [323]
- HSP90



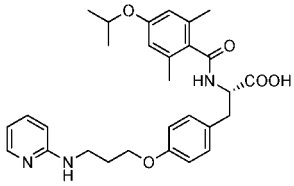
- HisZiFiT
- University of California, San Diego
- Hauser [133]
- Membrane surface protein sensor



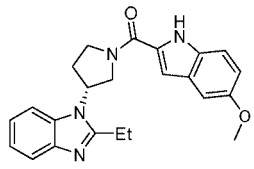
- NCGC2261
- NIH Chemical Genomics Center
- Zheng [393]
- Glucocerebrosidase



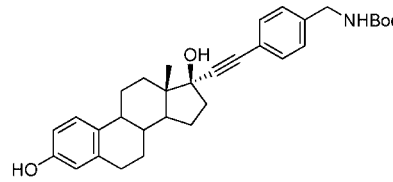
- PC1
- University of California, Berkeley
- Miller [258]
- Cellular H_2O_2 sensor



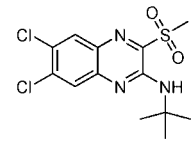
- cmpd 3f
- Dept. Chemie TU München
- Heckmann [135]
- $\alpha 5\beta 1$ and $\alpha v\beta 3$ integrin receptor inhibitor



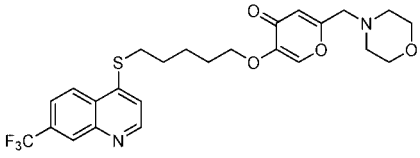
- cmpd 11
- Amgen Inc.
- Frohn [109]
- hFPRL1 agonist



- E2-NB
- UNM Health Sciences Center
- Revankar [316]
- GPR30 and ERα agonist



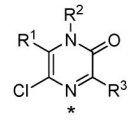
- cmpd 2
- Novo Nordisk AIs
- Knudsen [181]
- glucagon-like peptide 1 receptor agonist



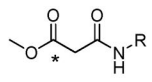
- ETH 1864
- University of North Carolina
- Shutes [358]
- Rac1

Table 7. Scaffold Derivatization and Acyclic Synthesis[a]

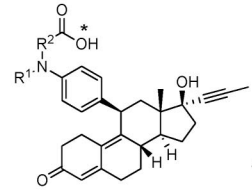
Solid-phase



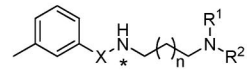
- Kaval [173]
- Liebeskind-Srogl cross-coupling reaction of resin-bound pyrazinones



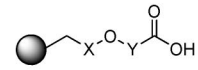
- Yan [438]
- from PEG-bound malonic acid (derived from Meldrum's acid) and amines



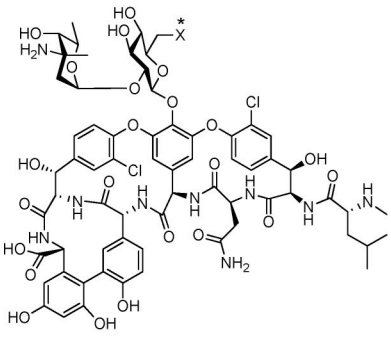
- Hamilton [129]
- C-11 modified mifepristone analogs



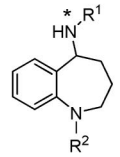
- Zajdel [454]
- multistep sequence



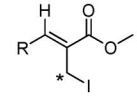
- Mendez [252]
- selective hydrolysis of polymer-supported methyl ester using Me_3SnOH



- Doi [88]
- bidirectional solid-phase semisynthesis of vancomycin derivatives

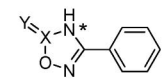


- Boeglin [35]
- derivatization of resin-bound benzazepines

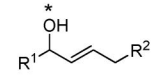


- Sheng [352]
- from PS-selenyl-linked 3-acetoxy-2-methylene-alkanoates

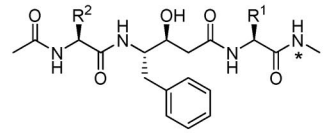
- Kurosu [192]
- regioselective alkylation of resin-bound hydrazines



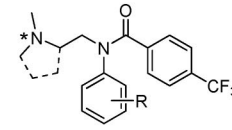
- Charton [55]
- diversification of resin-bound heterocycles coupled to HMPB -BHA resin *via* Mitsunobu



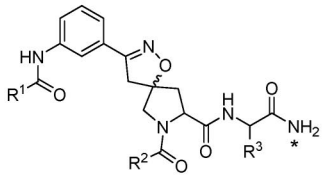
- Garner [114]
- solid-phase olefin cross-metathesis



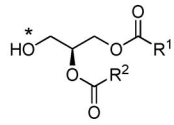
- Taboada [383]
- standard peptide synthesis



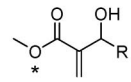
- Gillman [118]
- multistep sequence using REM resin



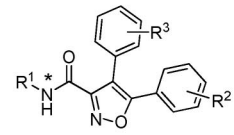
- Dixon [85]
- derivatization of spiroisoxazolinoproline



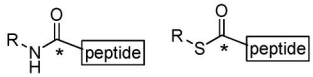
- Seo [343]
- carboxylic acid-promoted epoxide ring-opening reactions of glycidyl-bound resin



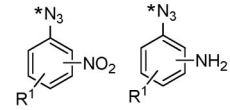
- Sheng [353]
- reaction of resin-bound 2-(phenylseleno)propanoate with RCHO then oxidative elimination and cleavage



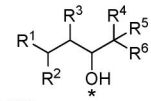
- Letourneau [208]
- Suzuki coupling of resin-bound 5-aryl-4-bromo-3-carboxyisoxazoles



- Merkx [256]
- using safety-catch linker and RNH_2 or RSH C-terminal leavage

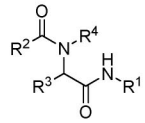


- Zimmermann [466]
- chemoselective reduction of resin-bound nitroarenes in the presence of acid-sensitive functional groups

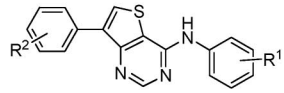


- Buszek [48]
- diimide reduction of multiple bonds on solid-supported substrates

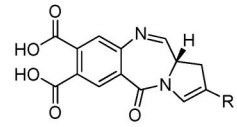
Solution-phase



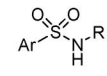
- Ngouansavanh [282]
- IBX-mediated oxidation Ugi-type 3-CR



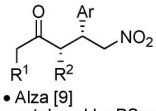
- Peng [301]
- elaboration of thieno-pyrimidine core



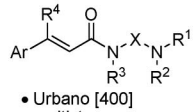
- Antonow [12]
- Suzuki coupling using PS-PPh_3Pd (catalyst) and PS-DEAM (scavenger) under microwave radiation



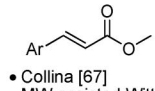
- Griffiths-Jones [124]
- primary sulfonamides monoalkylated using a two-step "catch and release" protocol using a binary reactor system



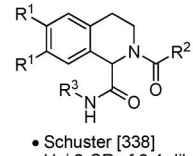
- Alza [9]
- catalyzed by PS-pyrrolidine



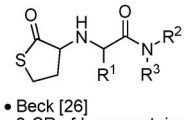
- Urbano [400]
- multistep sequence



- Collina [67]
- MW-assisted Wittig reaction using PS-TPP

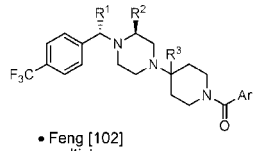


- Schuster [338]
- Ugi 3-CR of 3,4-dihydroisoquinolines, isocyanides and acids

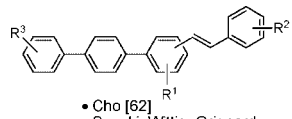


- Beck [26]
- 3-CR of homocysteine, RCHO, and RCNO

Table 7. Continued

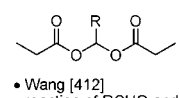


• Feng [102]
• multistep sequence

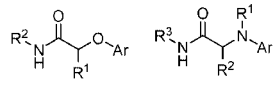


• Cho [62]
• Suzuki, Wittig, Grignard cross-coupling

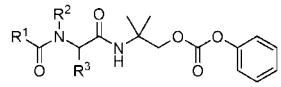
• Yamamoto [435]
• poly(4-iodostyrene)-catalyzed α-tosyloxylation of ketones with *m*CPBA and PTSA



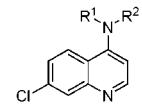
• Wang [412]
• reaction of RCHO and Ac_2O catalyzed by PS-SO_3H



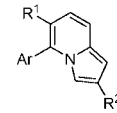
• Dai [77]
• phenol-P-3CR products and phenol-U-4CR products controlled by different solvents and catalytic Ti(O-*i*-Pr)$_4$



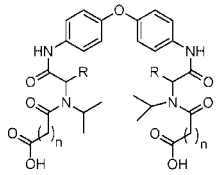
• Rikimaru [319]
• Ugi 4-CC with the carbonate-type isonitrile



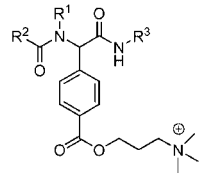
• Melato [249]
• MW-assisted S_NAr reaction of amines and chloroquinolines



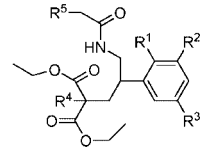
• Kuznetsov [193]
• parallel cross-coupling reactions of 5-Br(I)-indolizines



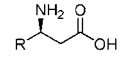
• Michalik [262]
• double Ugi multiple-component reactions of bifunctional building blocks



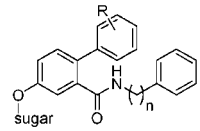
• Ouach [288]
• Ugi 4-CR in water



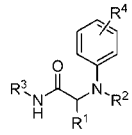
• El Kaim [97]
• Mn(III)-induced radical cascades as Ugi post-condensation reactions



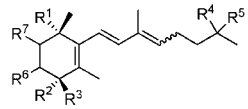
• Davies [79]
• multistep sequence using the conjugate addition of homochiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide as the key step



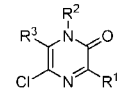
• Huang [149]
• multistep sequence



• El Kaim [92]
• Smiles rearrangements in Ugi- and Passerini-type couplings

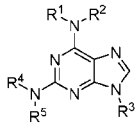


• Schachtschabel [335]
• trisporoid library by combination of synthesis and biotransformation

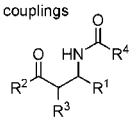


• Kaval [173]
• Chan-Lam arylation and Liebeskind-Srogl cross-coupling reactions

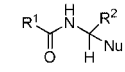
• Srivastava [371]
• MW-assisted Pd-catalyzed cross-coupling of aryl triflates using PS-TPP



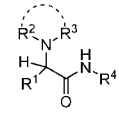
• Huang [146]
• MW-assisted synthesis from 2,6-dichloropurine and amines



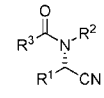
• Salama [331]
• 3-CR of R^1CHO, R^2COR^3 and R^4CN catalyzed by $TMSCl/ZnCl_2$



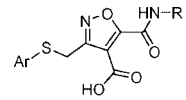
• Wan [411]
• nitrile hydrozirconation and acylation



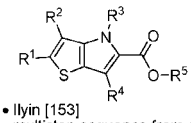
• Tanaka [385]
• acid-free aminoborane-mediated Ugi-type reaction of R^1CHO, R^2R^3NH and R^4NC



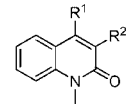
• Pan [292]
• catalytic asymmetric three-component acyl-Strecker reaction



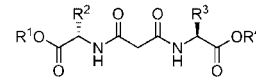
• Robins [322]
• derivatization of dimethyl 3-chloromethylisoxazole -4,5-dicarboxylate



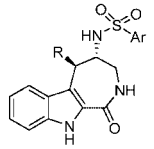
• Ilyin [153]
• multistep sequence from alkyl thienopyrrole-5-carboxylates



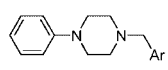
• Wang [419]
• from 4-aryl-3-bromoquinolin-2(1*H*)-one



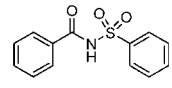
• Fioravanti [103]
• nucelophilc addition of amino acid esters to Meldrum's acid then coupling to second amino acid ester



• Kaiser [165]
• reaction of indole aziridines with *H*-, *N*-, and *O*-nucleophiles



• Zhang [460]
• *N*-benzylation via ROMP benzylsulfonium salts

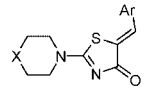


• Wang [415]
• application of polymer -supported reagents

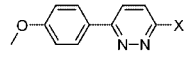
• Chung [81]
• multipolymer reaction system for selective aerobic alcohol oxidation

• Sun [380]
• reaction of 1° and 2° alcohols with $^tBuO_2CN{=}NCO_2{}^tBu$, $(BOC)_2NH$, PS-TPP then TFA gives clean conversion to amines

• Vickerstaffe [407]
• chromatography-free Suzuki reaction using a polymer-assisted solution-phase (PASP) approach

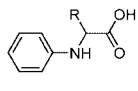


• Bourahla [42]
• MW-assisted sulfur/nitrogen displacement reaction of 5-arylidene rhodamine derivatives with amines

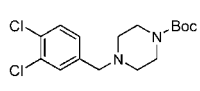


• Lin [213]
• amination of 3-chloro-6 -(4-methoxyphenyl)-pyridazine under MW irradiation

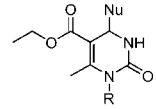
• Kunst [189]
• oxidation using tagged hypervalent iodine reagents



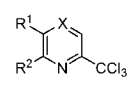
• Rottger [325]
• MW-enhanced Cu-catalyzed *N*-arylation of free and protected amino acids in water



• Ruhland [151]
• Mitsunobu and other reactions using nanoporous Magnesium aluminometasilicate tablets



• Singh [360]
• reaction of ethyl 6-methyl -pyrimidine-2-one-5-carboxylates with C-nucleophiles

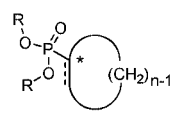


• Goswami [119]
• from methyl-substituted heterocycles, NCS and PPh_3

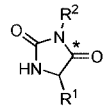
[a] Asterisk is the point of attachment to resin.

Table 8. Monocyclic Synthesis[a]

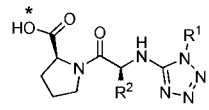
Solid-phase



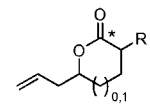
- Liu [217]
- polystyrene-supported phenylsulfonylmethylphosphonates with traceless sulfone linker strategy



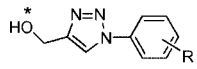
- Colacino [66]
- MW-assisted treatment of resin-bound amino acids with $OCNR^2$ then intramolecular cyclization



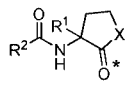
- Gavrilyuk [115]
- electrocyclization of resin-bound peptidic imidoylazides



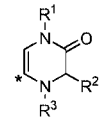
- Mamane [230]
- allylation of resin-bound aldehydes and intramolecular cyclative cleavage



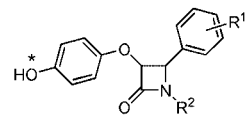
- Shang [347]
- 3-CR 1,3-dipolar cycloaddition reaction using PEG-supported succinate



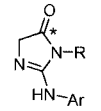
- Scott [341]
- derived from resin-bound amino acid aldehydes



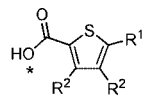
- Lee [203]
- amino acid acylation of resin-bound amino acetals then tandem acidolytic cleavage *in situ* iminium formation then enamide transformation



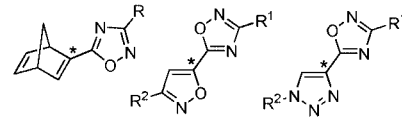
- Mendez [251]
- Staudinger reaction of resin-bound ketones and imines



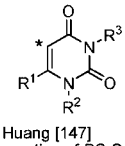
- Li [209]
- reaction of PEG-bound carbodiimides with amines



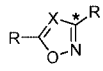
- Traversone [391]
- Hinsberg thiophene synthesis using resin-bound thioglycolic acid derived synthons



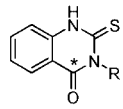
- Huang [148]
- electrophilic additions, 1,3-dipolar cycloaddition, amidoxime and carboxylate condensation, and Diels-Alder reaction to resin-bound α-seleno acrylic acid



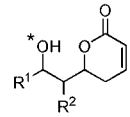
- Huang [147]
- reaction of PS-SeBr with $R^1CH{=}CHCOOMe$, R^2NH_2 and $ZnCl_2$, then R^3NCO and oxidative cleavage



- Wang [417, 418]
- hydrazinolysis, acylation, cyclocondensation, and elimination of selenium safety-catch linker

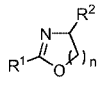


- Peng [300]
- Staudinger-Aza-Wittig reaction of PEG-supported azide, amine addition and intramolecular cyclization and simultaneous cleavage

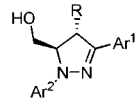


- Umarye [399]
- iterative allylations then RCM on a solid support

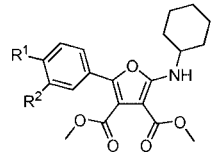
Solution-phase



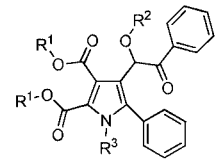
- Chaudhry [56]
- reactions of 1,2- and 1,3-hydroxyalkyl azides and aldehydes in the presence of Lewis acid



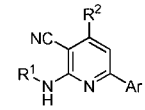
- Manyem [234]
- [3+2] cycloaddition of nitrilimines with enoyl oxazolidinones



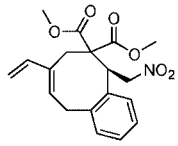
- Bremner [45]
- MW-assisted 3-CR by continuous flow synthesis



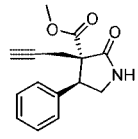
- Nasiri [278]
- reaction of enaminones with dibenzoylacetylene then ROH and HCl

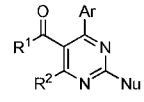


- Tu [396]
- MW-assisted multi-component reaction

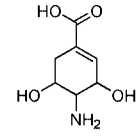


- Comer [69]
- Diversification of enantioenriched Michael adducts through intramolecular functional group pairing (ester + nitro; aldehyde + nitro)

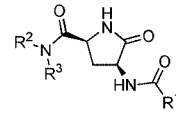




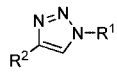
- Matloobi [242]
- five-step sequence starting with Biginelli MCR



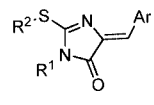
- Hu [144]
- derived from ring-closing enyne metathesis products



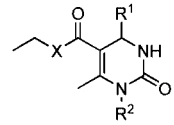
- Malavasic [228]
- five-step sequence from (*S*)-pyroglutamic acid



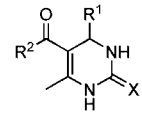
- Smith [362]
- [3+2] cycloaddition of acetylenes with azides in a modular flow reactor



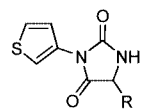
- Renault [315]
- domino reaction from thiohydantoins, arylaldehydes, and halogenoalkanes



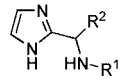
- Pisani [305]
- MW-assisted Biginelli reaction mediated by TMSCl



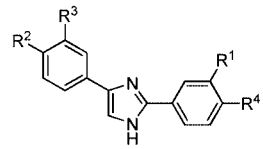
- Yu [449]
- from aldehydes, 1,3-dicarbonyl compounds and urea or thiourea using chloroacetic acid as catalyst under solvent-free conditions



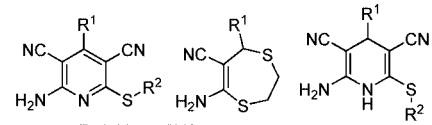
- Brouillette [46]
- MW-assisted reaction of 1*H*-thienol[3,2-*d*][1,3]oxazine -2,4-dione with α-amino acids



- Gulevich [126]
- diastereoselective thio-Ugi reaction

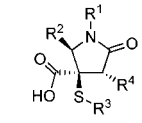


- Zuliani [464]
- from arylglyoxals, ArCHO and NH_4OAc

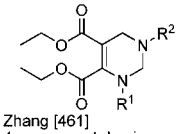


- Evdokimov [99]
- MCR of R^1CHO, R^2SH and malononitrile

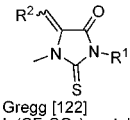
Table 8. Continued



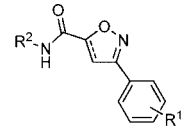
• Wei [422]
• 4-CR between amines, maleic anhydrides, aldehydes, and thiols



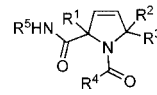
• Zhang [461]
• 4-component domino reaction of DMAD, R^1NH_2, HCHO and R^2NH_2



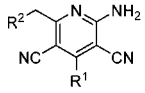
• Gregg [122]
• $In(CF_3SO_3)_3$-catalyzed condensation of RCHO with 3-substituted 1-methyl-2-thiohydantoins



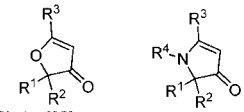
• Jeddeloh [158]
• nitrile oxide 1,3-dipolar cycloaddition with methyl acrylate followed by amide formation



• Werner [424]
• silver-catalyzed intramolecular cyclization of aminoallenes followed by *N*-functionalization reactions



• Guo [277]
• 3-CR with R1CHO, $NCCH_2CN$, R^2SH

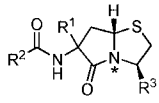


• Binder [32]
• Pt (II)-catalyzed heterocyclization-migration reactions from 2-alkynyl-2-hydroxy carbonyls

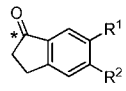
[a] Asterisk is the point of attachment to resin.

Table 9. Bicyclic and Spirocyclic Synthesis[a]

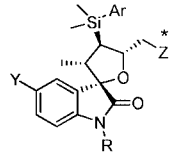
Solid-phase



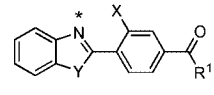
• Scott [341]
• derived from resin-bound amino acid aldehydes



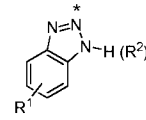
• Senaiar [342]
• [2+2+2] cyclotrimerization reactions of resin-bound diyne and alkyne



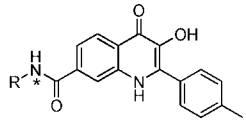
• Franz [108]
• Lewis acid-mediated annulations of isatins using macrobead-bound crotylsilanes



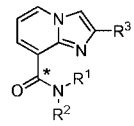
• Hioki [183]
• products were released from the polymer support by imine-exchange process coupled with air oxidation using a traceless 4-alkoxy-aniline linker



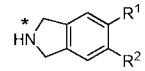
• Zimmermann [466]
• chemoselective reduction of resin-bound nitroarenes in the presence of acid-sensitive functional groups



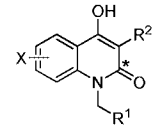
• Soural [367]
• intracyclative cleavage of resin-bound phenacylanthranilates



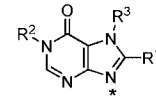
• Kamal [167]
• condensation of 2-aminonicotinate with α-haloketones and cleavage with amines



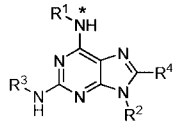
• Shanmugasundaram [348]
• MW-assisted Ir-catalyzed [2+2+2] cycloaddition of resin-bound dipropargylamine with alkynes



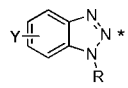
• Jeon [159]
• multistep sequence



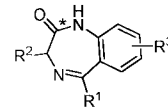
• Fu [110]
• from resin-bound 5-amino-4-chloropyrimidine



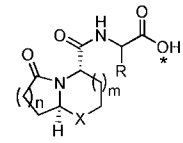
• Hammarstroem [130]
• multistep sequence from resin-bound 4,6-dichloro-(2-methylthio)-5-nitropyrimidine



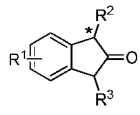
• Zimmermann [465]
• Hartwig-Buchwald amination reactions of bromo- and chloroarenes and resin-bound triazene-linked arenes



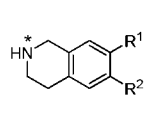
• Laustsen [197]
• catch and release of 2-aminobenzoimines on an amino acid Wang resin then intracyclative cleavage



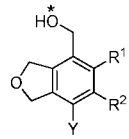
• Le Quement [199]
• intramolecular cascade reactions of resin-bound cyclic *N*-acyliminium intermediates



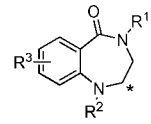
• Xie [433]
• traceless Gassman oxindole synthesis



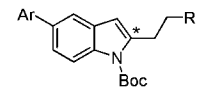
• Young [447]
• cyclotrimerization reaction of a diyne and a mono-alkyne



• Saruta [334]
• intramolecular alkylation of tertiary amines followed by an elimination of resin-bound quaternary ammonium salts

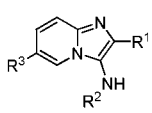


• Lee [202]
• Leuckart-Wallach reaction

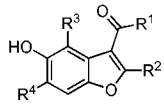


• Main [227]
• diverse 2,5-disubstituted indoles using titanium carbenoids bearing boronate functionality

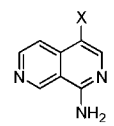
Solution-phase



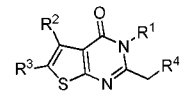
• DiMauro [83]
• from 2-aminopyridine-5-boronic acid pinacol ester via an Ugi-type cyclization, Suzuki coupling sequence



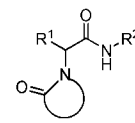
• Cheng [61]
• MW-assisted condensation of enaminone and *p*-quinones



• Zhang [455]
• derived from 4-methyl-3-cyanopyridine

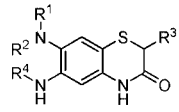


• Ryabukhin [329]
• Knoevenagel condensations of ArCHO with various methylene active compounds

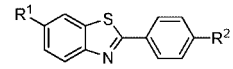


• Trifilenkov [392]
• Ugi 4-CR followed by intramolecular cyclization *via* C-C bond formation

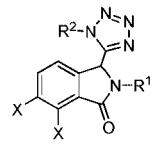
Table 9. Continued



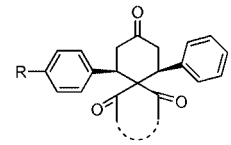
- Wang [420]
- multistep sequence from 1,5-difluoro-2,4-dinitrobenzene



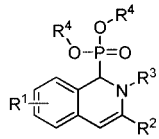
- Bose [39]
- intramolecular cyclization of thioformanilides using DDQ



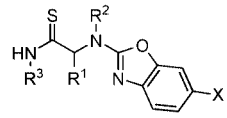
- Marcos [236]
- Ugi 4-CR between methyl *O*-formybenzoates, anilines, isocyanides and trimethylsilyl azide then cyclization



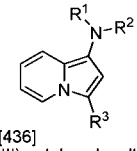
- Pizzirani [306]
- 3-CR Domino Knoevenagel/Diels-Alder sequence coupled to Suzuki reaction



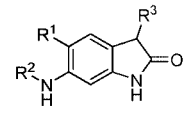
- Sun [379]
- AgOTf-catalyzed 3-CR of 2-alkynylbenzaldehydes, amines, and diethylphosphite



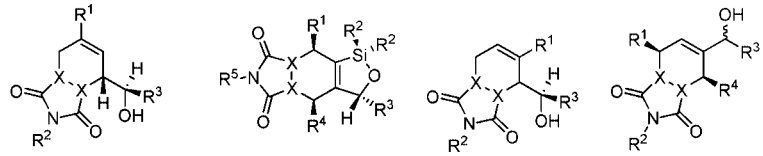
- El Kaim [96]
- Ugi-Smiles couplings of heterocyclic thiols



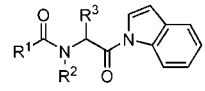
- Yan [436]
- gold(III)-catalyzed multicomponent coupling/cycloisomerization reaction of heteroaryl aldehydes, amines, and alkynes



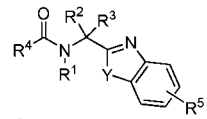
- Yang [440]
- multistep sequence from 1,5-difluoro-2,4-dinitrobenzene



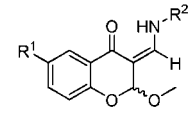
- Gray [121]
- small-molecule diversity initiated by different Pd/ligand combinations derived from silyl-ether tethered diynes



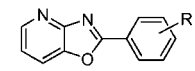
- Kreye [186]
- application of 2-(2,2-dimethyloxyethyl) phenyl isonitrile in Ugi, Passerini, and Ugi-Smiles reaction



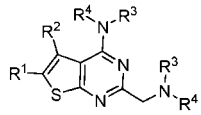
- Spatz [368]
- use of *O*-halophenylisocyanides in Ugi 4-CR followed by Cu-catalyzed cyclization



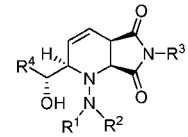
- Neo [280]
- Ugi 4-CR of 3-formylchromones, followed by a base-promoted ring-opening/ring-closing



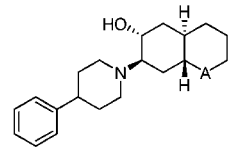
- Myllymaeki [275]
- MW-assisted condensation of 2-amino-3-hydroxypyridine with carboxylic acids



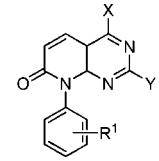
- Bogolubsky [36]
- derivatization of 4-chloro -methylthienopyrimidines



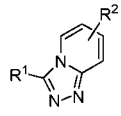
- Ulaczyk-Lesanko [398]
- tandem aza[4+2]cycloaddition /allylboration MCR between 1-aza-4-boronobutadienes, maleimides, and aldehydes



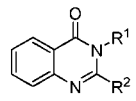
- Scheunemann [336]
- multistep sequence involving sequential ring-opening of *trans*-1,4 -cyclohexadiene dioxide with amines



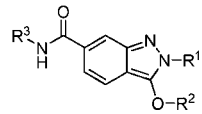
- Yan [437]
- multistep sequence from 2,6-dichloro-6-thiomethylpyrimidine-3-carboxaldehyde



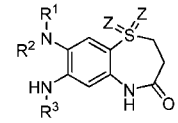
- Wang [416]
- condensation of carboxylic acids with 2-hydrazinopyridines using PS-PPh_3 resin and MW heating



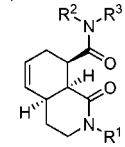
- Carpintero [51]
- multistep sequence from isatoic anhydride



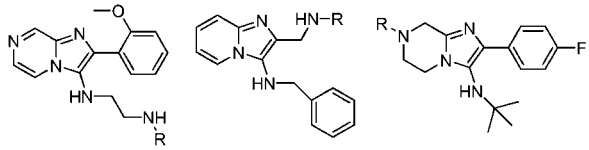
- Mills [263]
- reaction of 4-bromomethyl-3-nitrobenzoic acid with amines then alkoxides



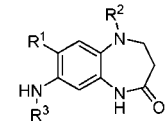
- Zhao [354]
- multistep sequence from 1,5-difluoro-2,4-dinitrobenzene



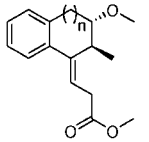
- Frankowski [107]
- tandem Diels-Alder /acylation sequence



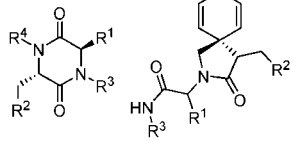
- Kercher [175]
- 3-CR involving partial reduction of imidazo[1,2-*a*]pyrazines to the tetrahydroimidazo[1,2-*a*]pyrazines and regiospecific Mannich-type bond formation



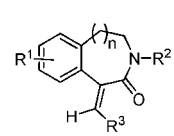
- Zhao [467]
- multistep sequence from 1,5-difluoro-2,4-dinitrobenzene



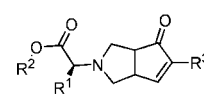
- Kesavan [176]
- enantioselective crotylation /Heck cyclization sequence



- Santra [333]
- MW-influenced multicomponent reaction cascades

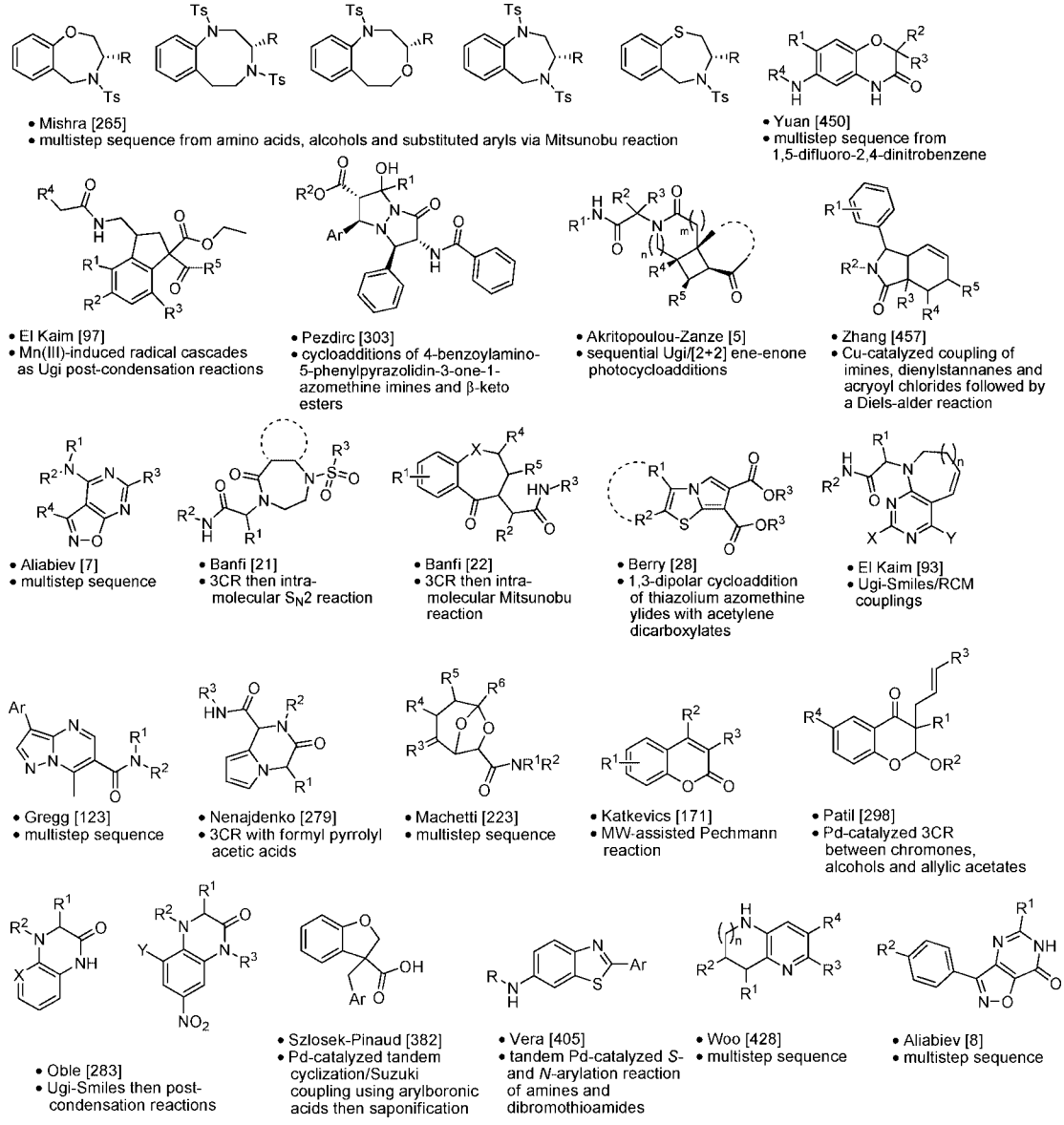


- Donets [89]
- MW-assisted reductive Heck reaction of 2-bromoaryl alkynes



- Cuevas [73]
- Pauson-Khand reaction of amino acid derived 3-pyrrolines

Table 9. Continued



[a] Asterisk is the point of attachment to resin.

Table 10. Polycyclic and Macrocyclic Synthesis[a]

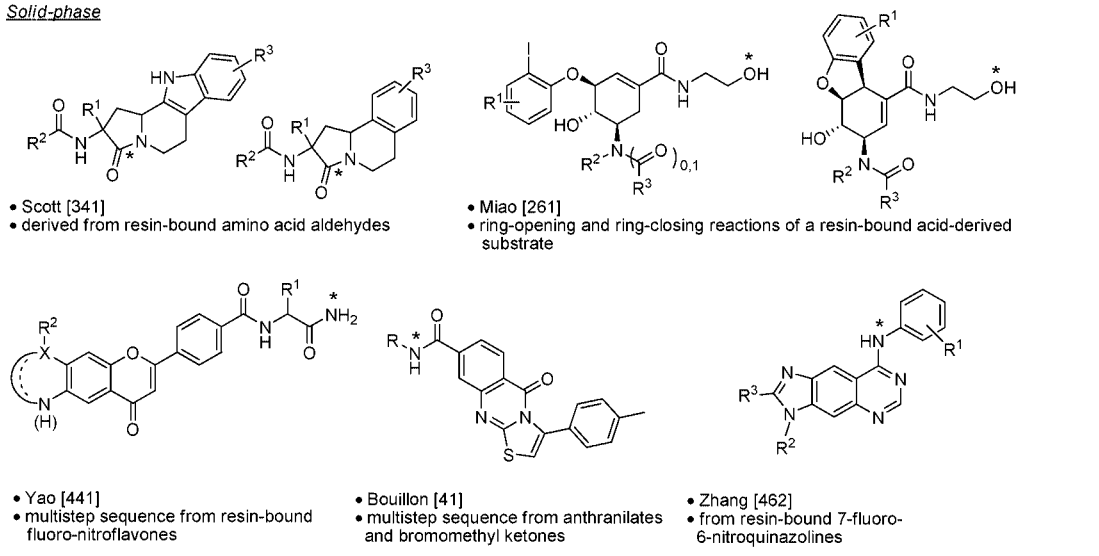
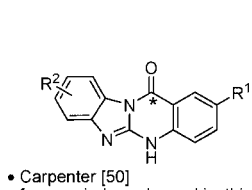
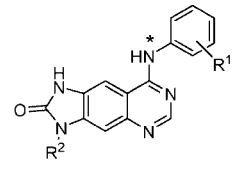


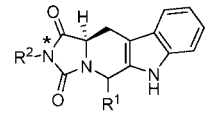
Table 10. Continued



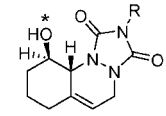
- Carpenter [50]
- from resin-bound *o*-aryl isothiocyanate esters and *o*-phenylenediamines



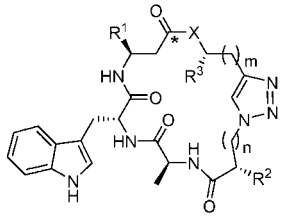
- Zhang [463]
- multistep sequence from resin-bound fluoro-nitroquinazoline



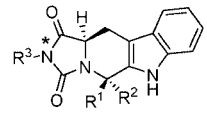
- Yeh [442]
- multistep MW-assisted sequence from resin-bound tryptophan



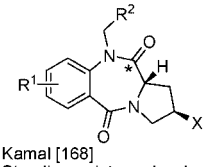
- Kiriazis [180]
- aza Diels-Alder reaction with resin -bound 3-vinyl-2-cyclohexenol



- Hu [145]
- intramolecular azide-alkyne cycloaddition

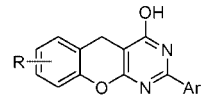


- Chen [59]
- multistep sequence from PEG-bound Fmoc-tryptophan

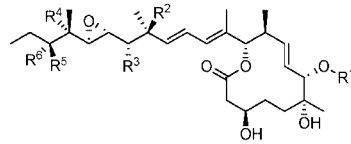


- Kamal [168]
- Staudinger, intermolecular aza-Wittig reaction followed by imine reduction and base-mediated cyclative cleavage

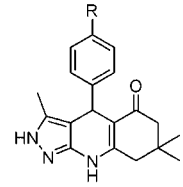
Solution-phase



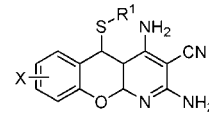
- Borisov [37]
- reaction of 2-iminocoumarin-3-carboxamides with aldehydes



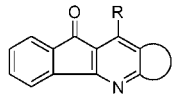
- Mandel [232]
- multistep synthesis involving RCM and Stille coupling



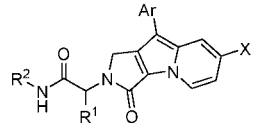
- Bremner [45]
- MW-assisted 3-CR by continuous flow synthesis



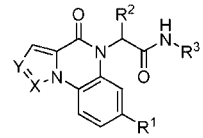
- Evdokimov [99]
- MCR of R^1CHO, R^2SH and malononitrile



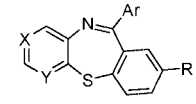
- Manpadi [233]
- 3-CR of indane-1,3-dione, RCHO and amine-containing aromatics



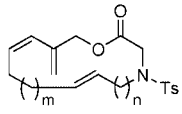
- El Kaim [95]
- formation of pyridinium salts from 4-CR with propargylamine, ArCHO, ^{t}BuNC and $ClCH_2CO_2H$ then Pd-coupling with ArI



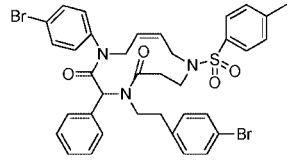
- Spatz [369]
- Ugi 4-CR of 2-fluoroanilines, R^2CHO imidazole/pyrazole carboxylic acids and R^3NC then intramolecular cyclization



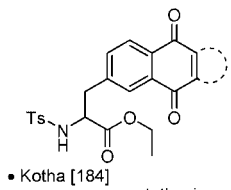
- Xu [434]
- Bischler-Napieralski then sulfoxide extrusion



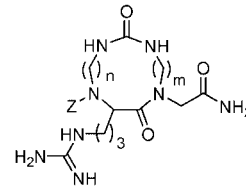
- Kotha [185]
- cross-enyne and RCM cascade



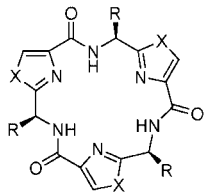
- Oikawa [285]
- Ugi 4-CR then RCM

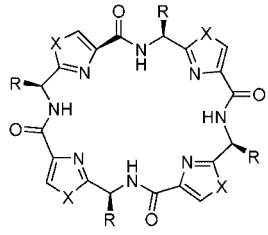


- Kotha [184]
- cross-enyne metathesis and Diels-Alder reaction

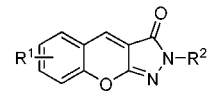


- Hurevich [150]
- multistep sequence

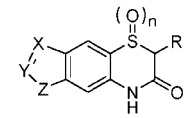




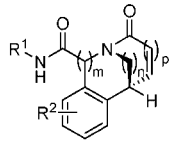
- Bertram [29]
- macrolactamisation using FDPP-DIEA



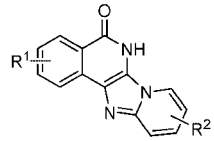
- Borisov [38]
- MW-assisted synthesis from 2 -iminocoumarines and hydrazines



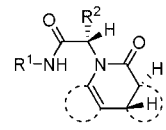
- Li [210]
- tricycles derived from *4H*-benzo[1,4]thiazin-3-one and related heterocycle



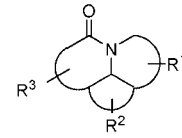
- Ribelin [317]
- sequenced Ugi/RCM /Heck reactions



- Che [57]
- 3-CR of 2-amino heterocycles, RNC and 2-formylbenzoates

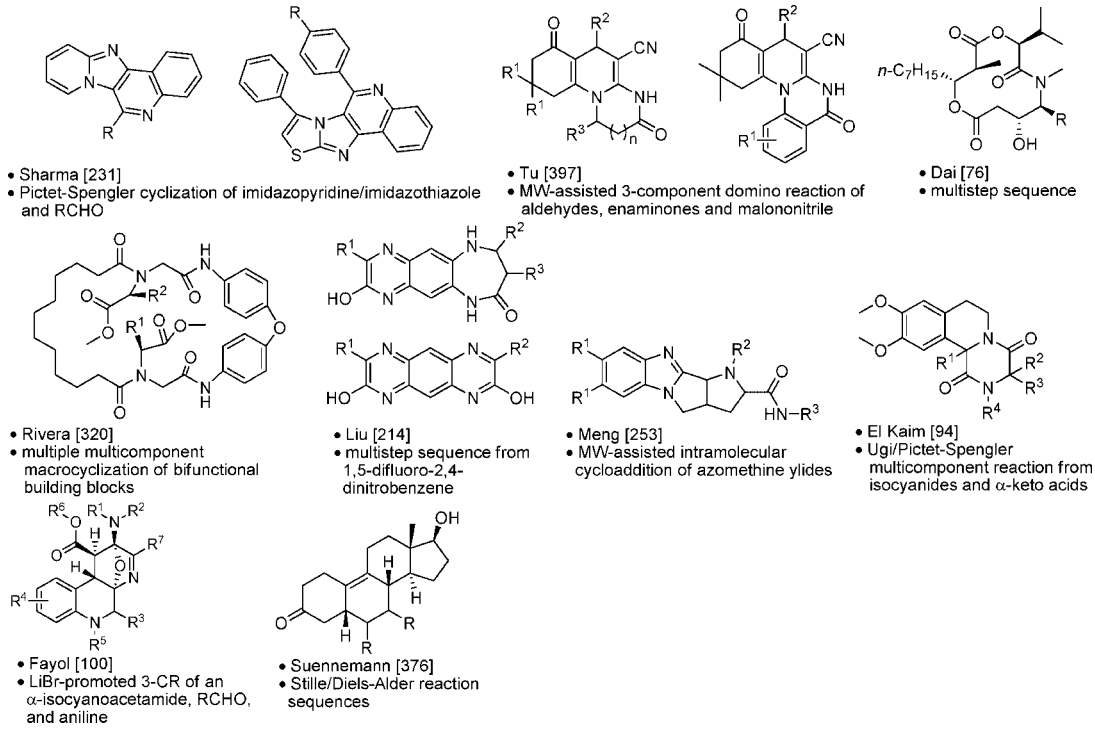


- Akritopoulou-Zanze [6]
- sequential Ugi/acrylanilide [6π]-photocyclizations



- Sunderhaus [381]
- 4-CR of aldehydes, primary amines, acid chlorides and nucleophiles, then ring-forming reactions

Table 10. Continued



[a] Asterisk is the point of attachment to resin.

Table 11. Polymer-Supported Reagents, Scavengers, and Linkers

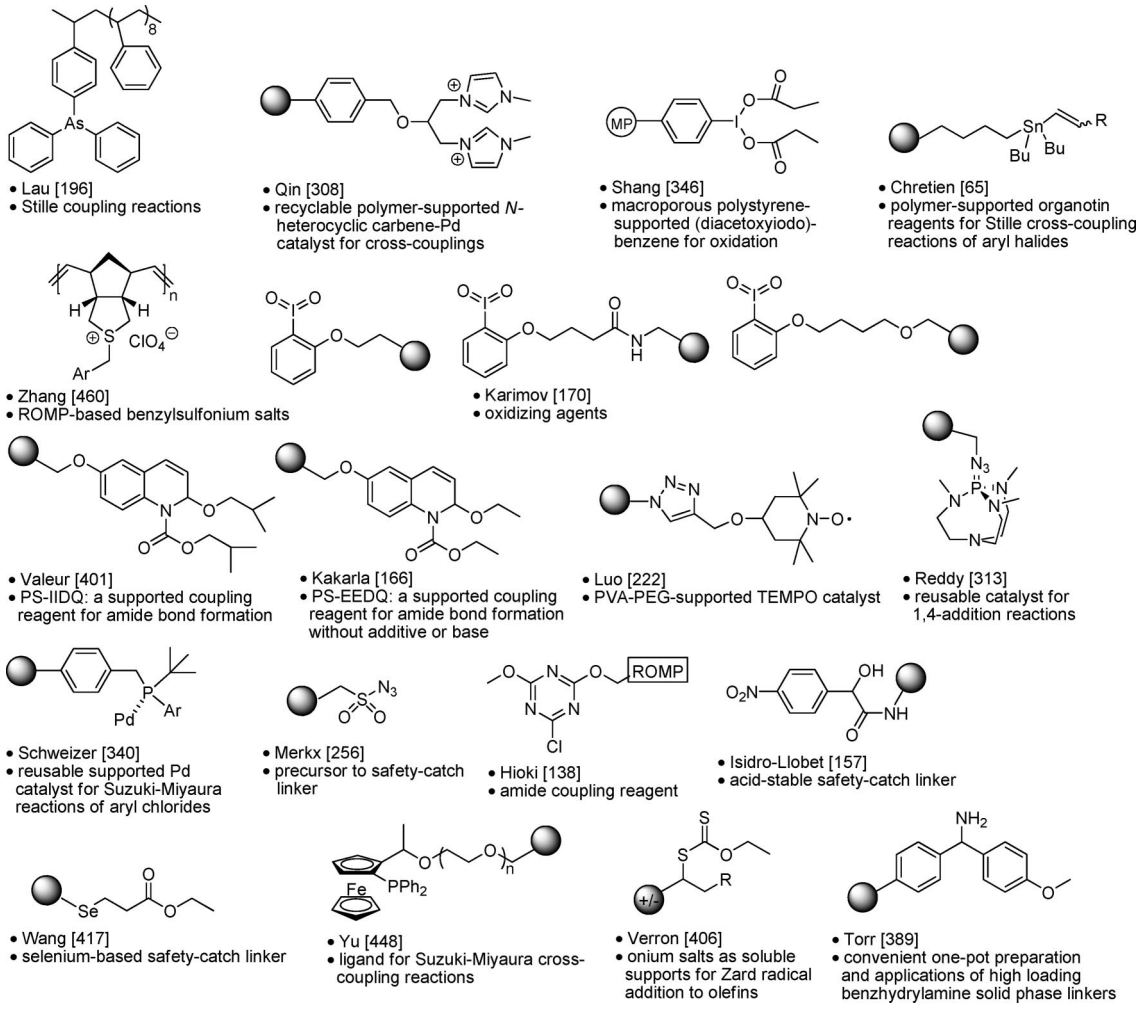
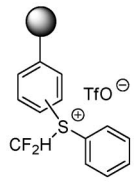
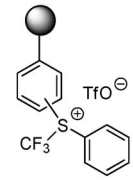


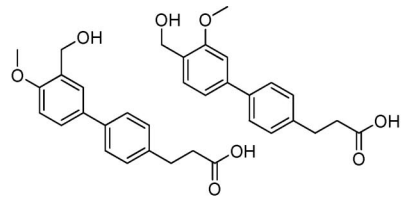
Table 11. Continued



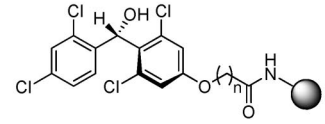
- Prakash [307]
- electrophilic difluoro -methylating reagent



- Prakash [307]
- electrophilic trifluoro -methylating reagent

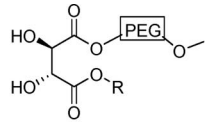


- Colombo [68]
- nonacid degradable linkers for solid-phase synthesis

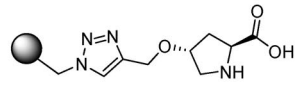


- Kurosu [190]
- HTPM linker utilized for loading carboxylic acids, amines, alcohols and phenols, is stable to Bronsted/Lewis acids, Bronsted bases, and a wide variety of nucleophiles; cleaved by the solvolytic displacement reactions with 20% TFA

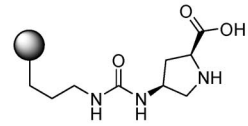
Table 12. Polymer-Supported Chiral Ligands



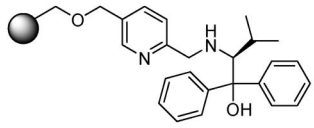
- Gao [112]
- polymer-supported tartrate /Ti catalyst for asymmetric oxidation of prochiral sulfides



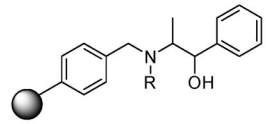
- Font [106]
- enantioselective α-aminoxylation of aldehydes and ketones with a polymer-supported organocatalyst



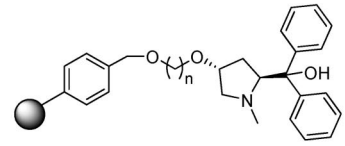
- Doyagueez [90]
- asymmetric aldol reaction catalyst



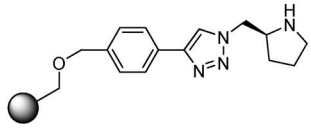
- Kelsen [174]
- enantioselective ethylation of aldehydes



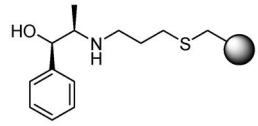
- El-Shehawy [98]
- enantioselective diethylzinc addition to the exocyclic C=N



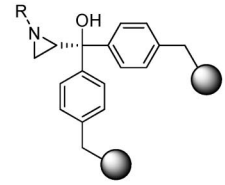
- Wang [413]
- asymmetric addition of diethylzinc to RCHO



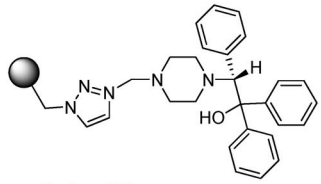
- Alza [9]
- enantioselective Michael addition



- McGhee [246]
- for asymmetric alkylation



- Page [291]
- asymmetric addition of Et_2Zn to RCHO



- Bastero [24]
- enantioselective phenylation of RCHO

Table 13. Fluorous Catalysts, Reagents, Scavengers, Tags and Library Synthesis[a]

F-metal catalysts and organocatalysts

$Yb(OPf)_3$

- Shen [350]
- ytterbium perfluorooctane-sulfonates for benz-imidazoles synthesis in fluorous solvent

$C_8F_{17}SO_3H$

- Yin [446]
- heptadecafluorooctanesulfonic acid for intramolecular hydroamination of olefinic sulfonamides in fluorous biphasic system

$(R_{f8}SO_3)_2Pd$

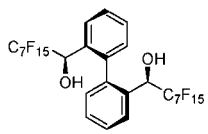
- Shen [351]
- Pd-catalyst for Suzuki reaction in fluorous solvent
- Yi [444, 445]
- Pd-catalyst for Sonogashira and Heck reactions in fluorous biphasic system

$(R_{f8}SO_3)_3Yb$

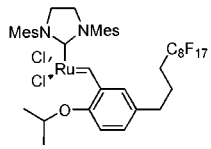
- Yi [443]
- ytterbium/perfluoroalkyated-pyridine catalyst for Baylis-Hillman reaction in fluorous biphasic system

$Hf[N(SO_2C_8F_{17})_2]_4$

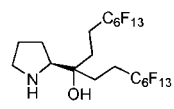
- Hao [131]
- catalytic Friedel-Crafts acylation and Prins reaction in fluorous biphasic system



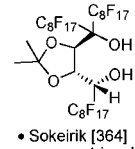
- Omote [286]
- titanium complex for enantioselective addition of methyl group to RCHOs



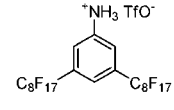
- Moura-Letts [267]
- F-Grubbs-Hoveyda catalyst



- Goushi [120]
- asymmetric borane reduction of ketones

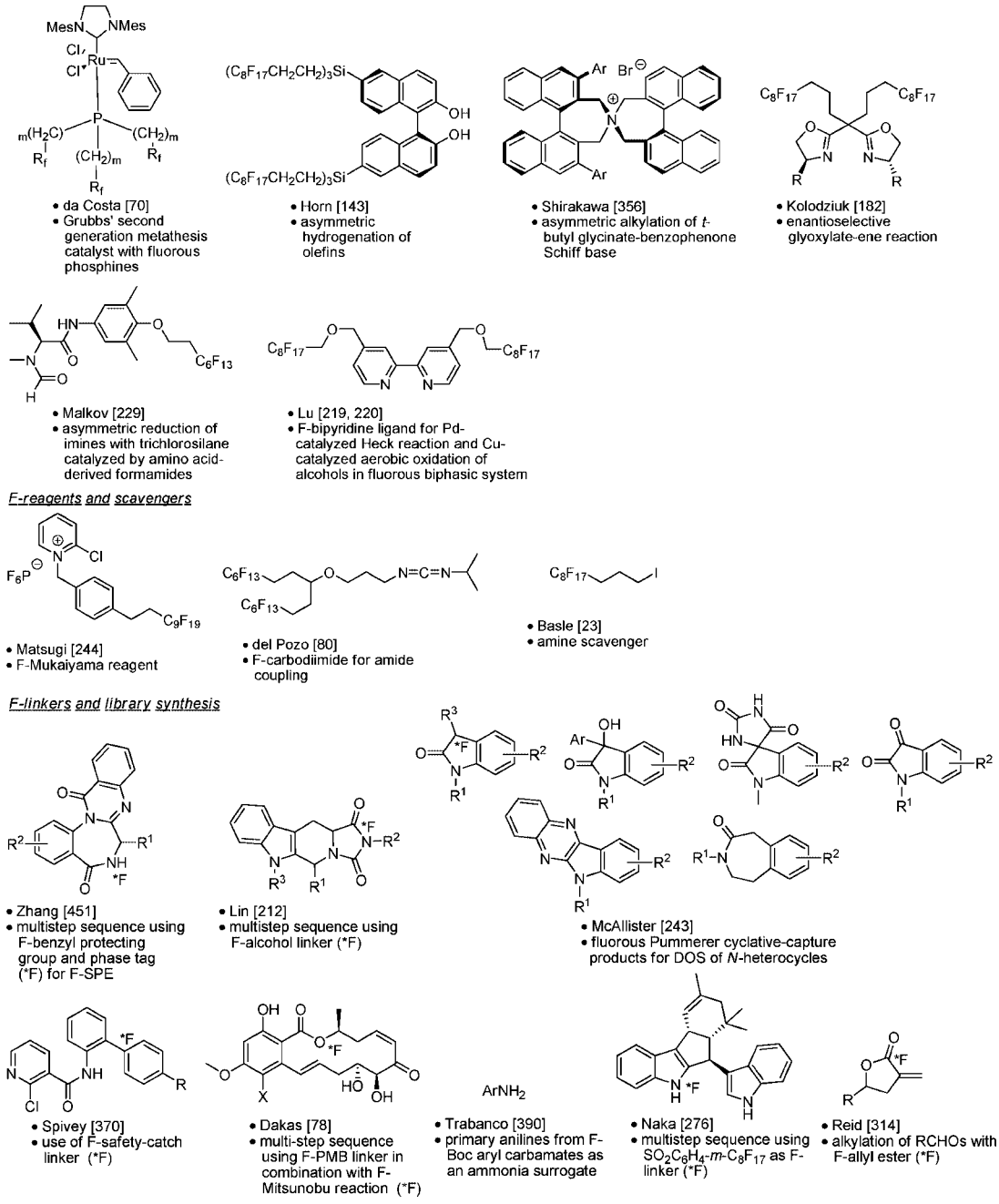


- Sokeirik [364]
- asymmetric addition of Me_2Zn to RCHOs



- Mercs [255]
- fluorous amommonium triflates for esterification of carboxylic acids

Table 13. Continued



[a] Asterisk is the point of attachement to the fluorous linker.

with the vinyl borolane to form *trans*-vinyl borolane **299**. This compound was sequentially converted to *cis*-vinyl bromide, treated with *t*-BuLi, followed by the addition of a TBDPS-protected aldehyde, and then protected with EOMCl to form **300**. Deprotection of TMDBS, followed by iodo exchange of the silyl group, led to the formation of **301**. Alkylation of **301** with an aromatic fragment and removal of the selenide afforded **302**. Cleavage of the F-PMB group of **302**, followed by macrocyclization under fluorous Mitsunobu reaction conditions, afforded **303.** Removal of EOM and acetonide groups led to formation of the final product radicicol A. This is a good example of fluorous tag-facilitated synthesis of natural product. Fluorous tag-attached intermediates, as well as the fluorous catalyst used for the Mitsunobu reaction, were separated by F-SPE. The fluorous tag-facilitated synthetic approach can be readily extended for the parallel synthesis of radicicol A analogs.

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