Reviews

Comprehensive Survey of Chemical Libraries for Drug Discovery and Chemical Biology: 2009

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This is the thirteenth installment of the comprehensive survey series in high-throughput chemistry.[1] Biologically active libraries reported in 2009 are captured in Tables 1−5 under the headings of proteases, nonproteolytic enzymes, GPCRs, nonGPCRs, and oncolytics/antiinfectives. Table 6 lists molecular probes. Compound collections without disclosed biological activity are delineated in Tables 7−10 under the headings of scaffold derivatization/acyclic synthesis, monocyclic-, bicyclic/spirocyclic-, and polycyclic/macrocyclic synthesis. Polymer-supported reagents/scavengers/linkers are presented in Tables 11 (nonfluorous) and 12 (fluorous). There are 370 libraries and 24 molecular probes extracted from 355 literature citations.[2−172]

This year's 18 vignettes include (a) biologically active libraries HDAC1/HDAC2 inhibitors,[134] H_3 antagonists,[136] glucagon receptor antagonists,[179] purinergic $P2Y_{12}$ receptor antagonists,[221] heat shock protein 90 (Hsp90) inhibitors,[41] selective norepinephrine reuptake inhibitors,[73] allosteric modulators of mGluR4[287] and mGluR5[71] Bcl-2 inhibitors via DOS library;[182] (d) high-throughput chemical methodology catch-and-release synthesis of substituted guanidines[289] and substituted pyrimidines via a 3-component reaction;[257] (c) molecular probes Ned-19[340] and DG-041;[338] and (d) fluorous technology displaceable fluorous dihydropyran[322] and isonitrile linkers,[327] fluorous synthesis of 1,4-benzodiazepine-2,5-dione,[327] piperazinedion-fused tricyclic[328] compound libraries, and a fluorous mixture synthesis of natural product resorcyclic acid lactone library.[329]

Related publications and reviews appeared in 2009 on microwave-assisted of *N*-heterocyclic synthesis[356] and convertible isonitriles,[365] click chemistry,[358] dynamic combinatorial chemistry,[363] large scale preparation of silicon-functionalized SynPhase lanterns,[370] kinase inhibitors,[357] heat shock protein 90 inhibitors,[376] biologically active benzoannelated nitrogen heterocycles,[361] library automation and analysis,[360,368] library design,[375] NMR-based screening,[377,378] fragment libraries and fragment hopping,[366,367,369] review of Ellman's libraries,[374] solid-phase resin specifications,[359] microelectrode arrays for monitoring ligand−receptor binding events,[364] yactoliter-scale DNA reactor for small molecule evolution,[362] DNA encoded libraries,[379] and fluorous chemistry and separations.[380−383] In a three-part series, Scott and co-workers proposed to galvanize the worldwide high-throughput chemistry community to share technology, resources, and compounds in the context of "Distributed Drug Discovery" to find treatments for diseases of the developing nations.[371−373]

Selective HDAC1/HDAC2 Inhibitors[134]

Histone deacetylases (HDACs) are enzymes involved in the remodeling of chromatin. Several classes of HDAC inhibitors have been found to have potent and specific anticancer activities, and the common pharmacophore identified contains a surface recognition domain, a linker region and a metal binding region. Kattar and co-workers set out to improve upon the selectivity and tolerability of Zolinza **1**, Merck's first-in-class mixed HDAC 1, 2, 3, and 6 inhibitor used for the treatment of cutaneous manifestation of T-cell lymphoma (Figure 1).[134] In their initial library, keeping the metal binding domain constant and varying both linker and surface recognition domains, scaffold **A** had already been identified. Reacting 4-formylmethyl-benzoate and polystyrene bound sodium triacetoxyborohydride with 48 R^1-amines, followed by hydroxamate formation with NH_2OH for their first follow-up library, 3-chlorobenzylamine was found to be preferred in the R^1-position over phenethyl or aniline analogs, yielding compound **2** (HDAC IC_{50} = 348 nM).

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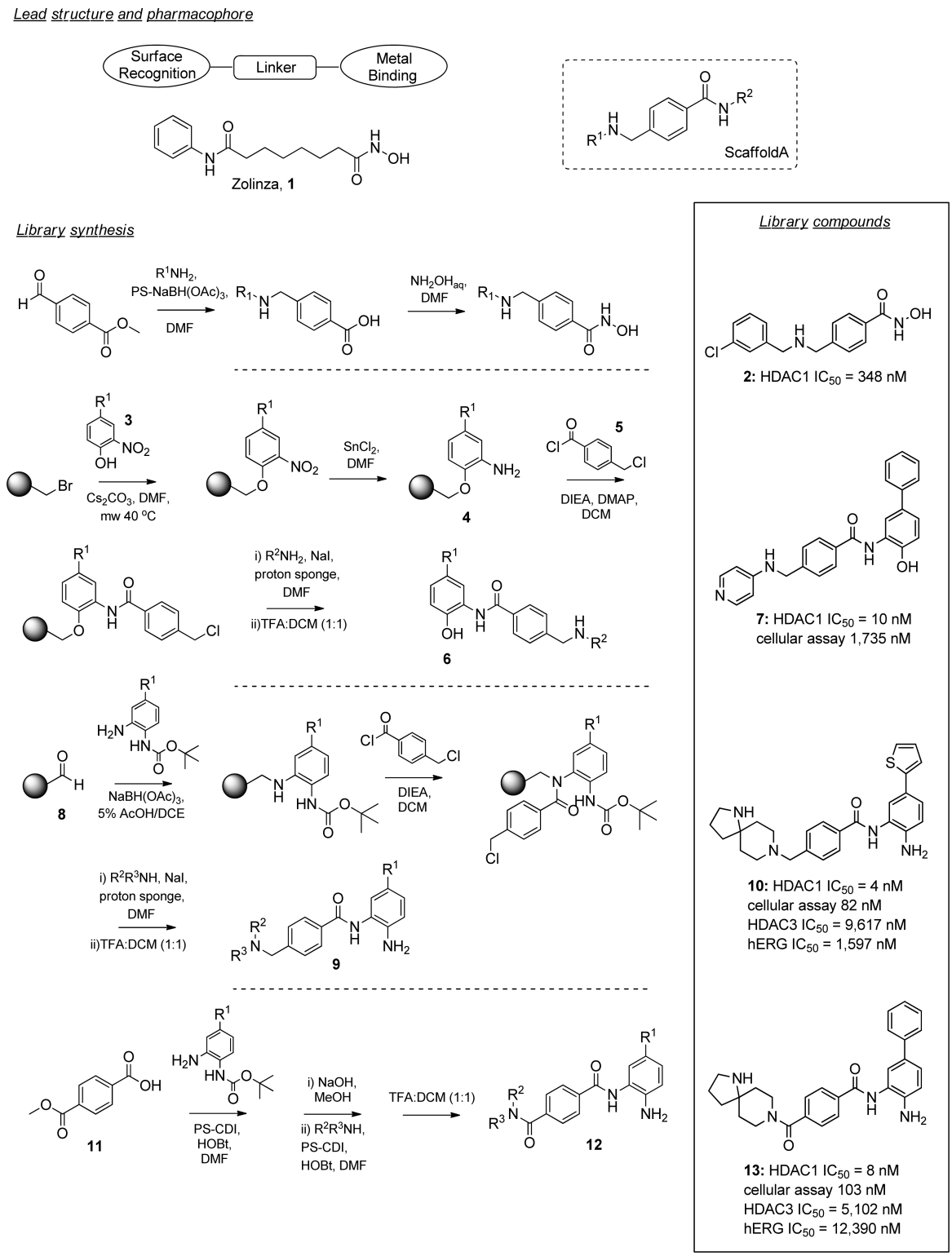


Figure 1. HDAC1/HDAC2 inhibitors.[134]

Modifying the metal binding domain next, 2-aminophenols were chosen to replace the hydroxamate moiety. R^1-substituted 2-nitrophenols **3** were reacted with bromo-Wang resin, cesium carbonate, and DMF under microwave irradiation at 40 °C. The nitro group was reduced with $SnCl_2$ in DMF and the resulting resin-bound anilines **4** coupled with the linker unit 4-chloromethyl benzoyl chloride **5**, DMAP and DIEA in DCM. Attachment of R^2-amines was accomplished using sodium iodide and a proton sponge in DMF. Final compounds **6** were released from resin with TFA/DCM. Aromatic substituents in R^1 and anilines in R^2 demonstrated 10−30-fold increased potency for HDAC1 (e.g., **7**, IC_{50} = 10 nM, cellular assay = 1,735 nM). To improve cellular potency the aminophenol metal binding site was replaced with a primary amine. Monoprotected R^1-substituted dianilines were bound to aldehyde resin **8** via reductive amination using sodium triacetoxyborohydride in AcOH/DCE. 4-Chloromethyl benzoyl chloride was attached

next, followed by reaction with surface binding domain R^2-amines, sodium iodide, and a proton sponge. Exposure to TFA/DCM yielded final products **9**. Amino spirocyclic building blocks in the R^2-position retained affinity toward HDAC1 and improved selectivity over HDAC3 as well as improved potency in the cellular assay. Unfortunately this series exhibited activity against hERG (**10** HDAC1 IC_{50} = 4 nM, cellular assay = 82 nM, HDAC3 IC_{50} = 9617 nM, hERG IC_{50} = 1597 nM). Eliminating one amino-functionality by switching to a terephthalamide linkage successfully mitigated hERG liabilities. This last set of compounds was synthesized via solution-phase, starting from **11** and mono-protected R^1-substituted dianilines, which were combined with PS-CDI and HOBt in DMF. After ester saponification, the spirocyclic amine was coupled using PS-CDI again. The final 26 compounds **12** were obtained after deprotection with TFA/DCM. Compound **13** showed the best overall profile (HDAC1 IC_{50} = 8 nM, cellular assay = 103 nM; HDAC3 IC_{50} = 5102 nM, hERG IC_{50} = 12 390 nM) and demonstrated in vivo efficacy in an acute PD HCT-116 xenograph model study. This successful combination of solid and solution phase library synthesis led to the efficient optimization of a novel HDAC inhibitor series, continuously improving additional properties within each library iteration.

H_3 Antagonists[136]

The histamine H_3 receptor is an attractive G protein-coupled receptor drug target that regulates neurotransmission in the central nervous system. There has been considerable effort by both academic and industrial laboratories to develop potent and selective H_3 receptor antagonists for the potential treatment of attention-deficit hyperactivity disorder, dementias, schizophrenia, as well as obesity and sleep disorders resulting in a refined H_3 antagonist pharmacophore model containing two basic nitrogens separated by a spacer and a central core that also carries a polar group and a lipophilic residue (Figure 2). After having completed its total synthesis, Kennedy and co-workers recognized that the marine alkaloid dispyrin **14** perfectly maps onto this pharmacophore model.[136] Dispyrin **14** indeed displayed some H_3 antagonist activity (IC_{50} = 2.35 μM) and was used as the starting point for a natural product guided iterative parallel synthesis campaign. Starting from 3-bromo-4-methoxyphenylethylamine **15** five heterocyclic carboxylic acids R^1 were coupled using DIC, HOBt, and DIEA in DCM. The methyl ether was removed with BBr_3 and the resulting phenols alkylated with five R^2-aminoalkyl chlorides under microwave irradiation conditions generating 25 different compounds **16**. All the compounds showed activity against H_3 with more potent compounds containing an ethyl pyrrolidinyl residue in the R^2 position (K_i values < 200 nM), with the best compound **17** (H_3 K_i = 80 nM, H_3 IC_{50} = 180 nM). Retaining the 4-bromo-thiophene residue from **17**, functionalized pyrrolidines were explored next. Phenol **18** was reacted first with 2-bromo-1,1-dimethoxy ethane and then with tosylic acid to yield aldehyde **19**. Final compounds **20** were obtained via reductive amination utilizing resin-bound triacetoxyborohydride together with the functionalized pyrrolidines. No potency improvement was observed in final compounds **20**.

The last library reexamined the R^1 residue, including additional heterocycles and aromatic moieties. Protecting bromomethoxy phenethyl amine **21** as the phthalimide by reacting it with 1,2-dicarboxybenzene, DIC, HOBt, and DIEA, followed by BBr_3 demethylation, yielded phenol **22**. Alkylation with chloroethyl pyrrolidine and deprotection with hydrazine, both under microwave conditions, followed by coupling with a diverse set of R^1-acids with DIC and HOBt, yielded final compounds **23**. Five-membered heterocycles in the R^1-position showed superior activities compared to pyridine and substituted benzenes, with 2-thiazole (**24**) and 5-oxazole (**25**) displaying the best potencies, K_i values = 30 nM each and IC_{50} = 70 and 80 nM, respectively. This iterative parallel library campaign successfully optimized H_3 antagonism properties of a natural product lead structure over 30-fold.

Human Glucagon Receptor Antagonists[179]

The glucagon receptor is a member of the class B G-protein coupled family of receptors. Glucagon maintains glucose homeostasis during the fasting state by promoting hepatic gluconeogenesis and glycogenolysis. Antagonizing the glucagon receptor is expected to result in reduced hepatic glucose overproduction, leading to overall glycemic control and a possible treatment for type 2 diabetes. Only a few classes of nonpeptidic glucagon receptor antagonists are known (Figure 3). Madsen and co-workers had previously described β-alanine and isoserine urea based human glucagon receptor (hGluR) antagonists **26** and **27**, whereby **27** showed improved selectivity over the related human glucose-dependent insulinotropic receptor (hGIPR). Here the authors explored the replacement of the urea linkage with a heterocyclic scaffold, thus rigidifying the molecule.[179] A library-assisted optimization strategy was pursued, combining solid and solution phase synthesis approaches, with the goal of finding a novel, potent, orally available hGluR selective antagonists. For the first library on solid support, 4-formylbenzoic acid was coupled to deprotected Fmoc-β-Ala-Wang resin with HOBt/DIC, followed by reductive amination with R^1-amines and treated with Fmoc-NCS to afford resin-bound Fmoc protected thioureas. Thiazole formation was accomplished through reaction with α-bromoketones after Fmoc-deprotection and final compounds **28** were obtained after cleavage from resin with TFA. Over 800 analogs were prepared via this procedure. Compounds were also prepared via solution-phase starting from 4-formylbenzoic acid methyl ester **29**, which was reductively aminated with R^1-amines using sodium cyanoborohydride. The benzylic amines **30** were converted to their corresponding thioureas employing different methods depending on the reactivity of the respective secondary amine. The aminothiazole **31** was obtained via reaction with α-bromoketones in acetic acid. The methyl ester was cleaved with NaOH and the resulting carboxylic acid **32** was coupled with either β-alanine or (*R*)-isoserine methyl ester, followed by hydrolysis to yield the final compounds **33** and **34**, respectively. Compounds **35** with the aminothiazole directly attached to the aromatic ring were prepared in similar fashion both on solid support and solution-phase. 4-Nitrobenzoyl chloride was reacted with

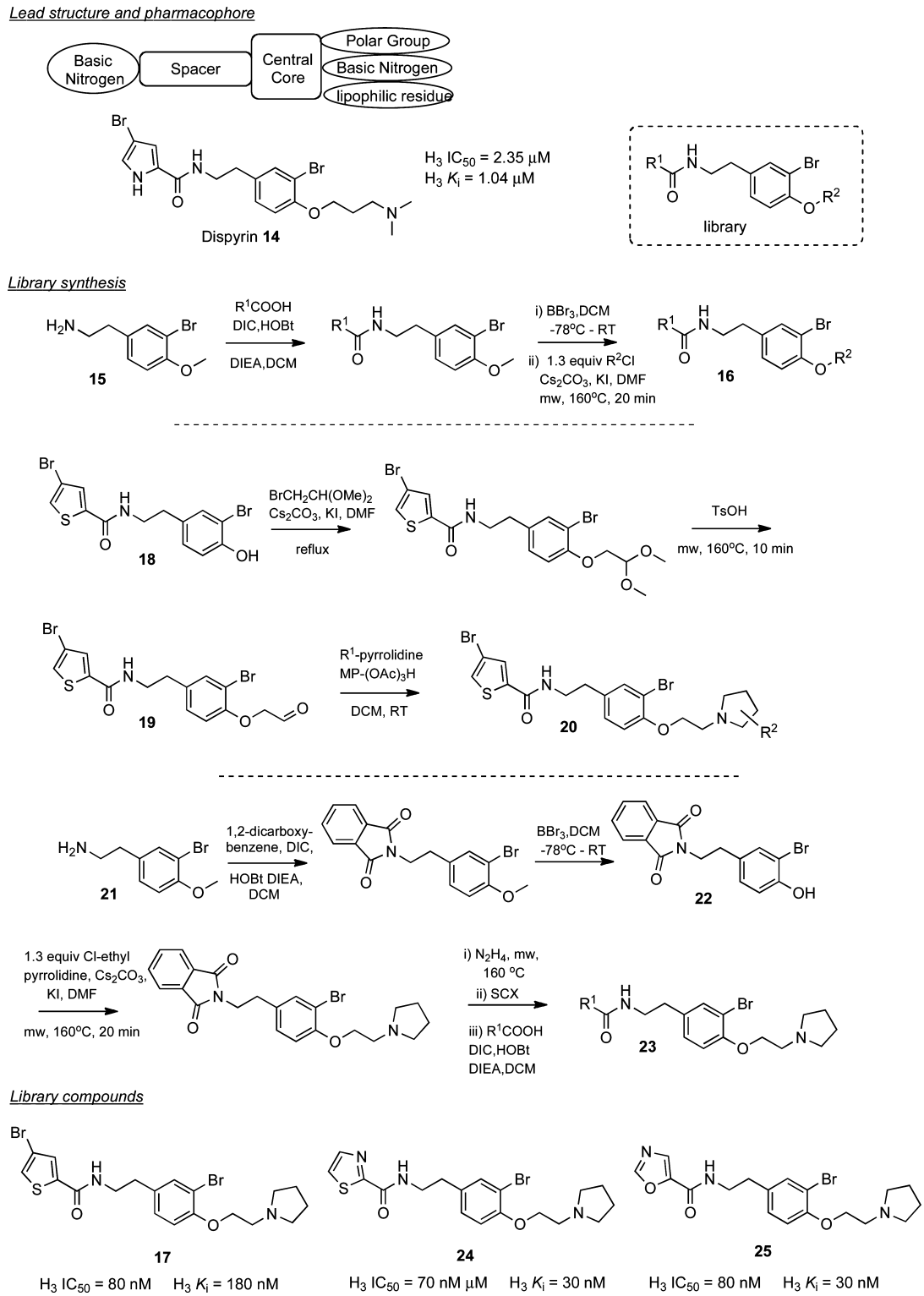


Figure 2. Histamine H_3 antagonists.[136]

resin-bound β-alanine, the nitro group was reduced with $SnCl_2$, followed by reductive alkylation with R^1-aldehydes. Thiourea **36** was obtained after reaction with Fmoc-isothiocyanate. After deprotection, cyclization with α-bromoketones and cleavage from resin final compounds **35** were obtained in high yields and purities. Using a solution-phase approach, compounds from this type were obtained by reductive amination of 4-aminomethyl benzoate **37** with R^1-aldehydes, followed by reactions with EtO_2C-NCS, NaOH, α-bromoketones and subsequent EDAC, HOBt coupling with β-alanine methyl ester, and hydrolysis to give **38**. Finally, compounds **39** containing a 5-alkylthiazole core were prepared starting with a Knoevenagel condensation of 4-methyl benzoate **40** with phenyl acetonitriles, followed by reduction with $NaBH_4$ in THF and treatment with dithiophosphoric acid *O*,*O*-diethylester. The resulting saturated thioamide **41** was reacted with α-bromoketones and coupled to β-alanine methyl ester, followed by hydrolysis. Aliphatic R^1 groups were not well

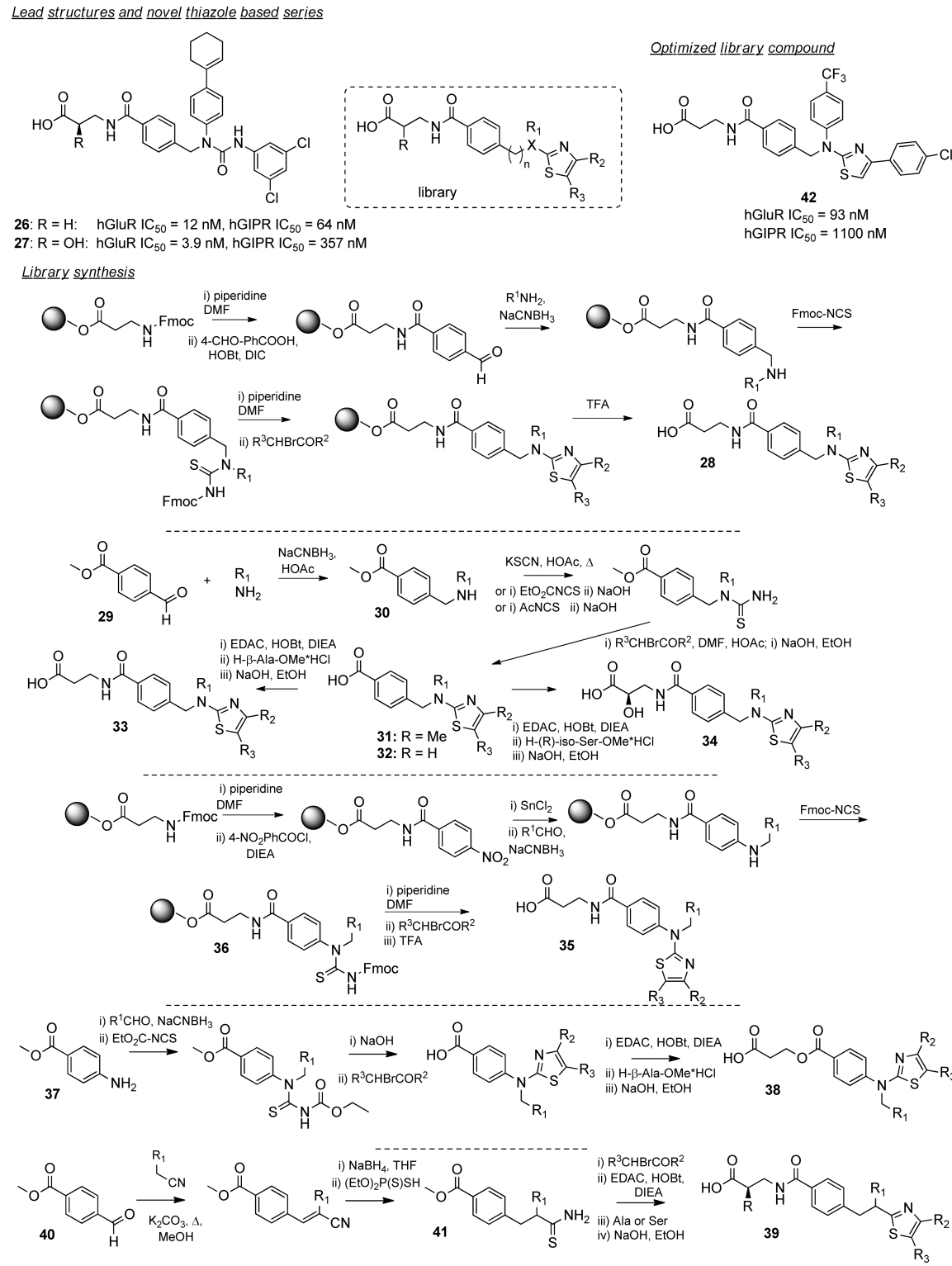


Figure 3. Glucogon receptor antagonists.[179]

tolerated. Compounds with 4-CF_3-, 4-OCF_3-, and 4-SCF_3-phenyl in the R^1 position displayed good binding affinities and superior rat PK properties. Compound **42** (hGluR IC_{50} = 93 nM, hGIPR IC_{50} = 1100 nM) showed high oral bioavailability (58%), low clearance (1 mL/min)/kg, long plasma $T_{1/2}$ (228 min after i.v. administration), and extremely high plasma exposure (C_{max} = 2100 ng/mL) in the rat (3 mg/kg, p.o.). Changing the β-alanine to isoserine in this series did lead to a loss of mGluR activity. Compounds with modified core structures retained binding affinities but displayed less favorable PK profiles. The SAR for R^2 and R^3 residues is of minor importance as long as the substituents on R^2 are lipophilic and in meta or para position of the phenyl ring. Compound **42** was tested in a nonhuman primate model of hyperglucagonaemia and hyperglycaemia. It dose-dependently decreased glucagon stimulated glycaemia and abolished the hyperglycemic effect of exogenously administered glucagon completely at i.v. doses of 1 and 3 mg/kg.

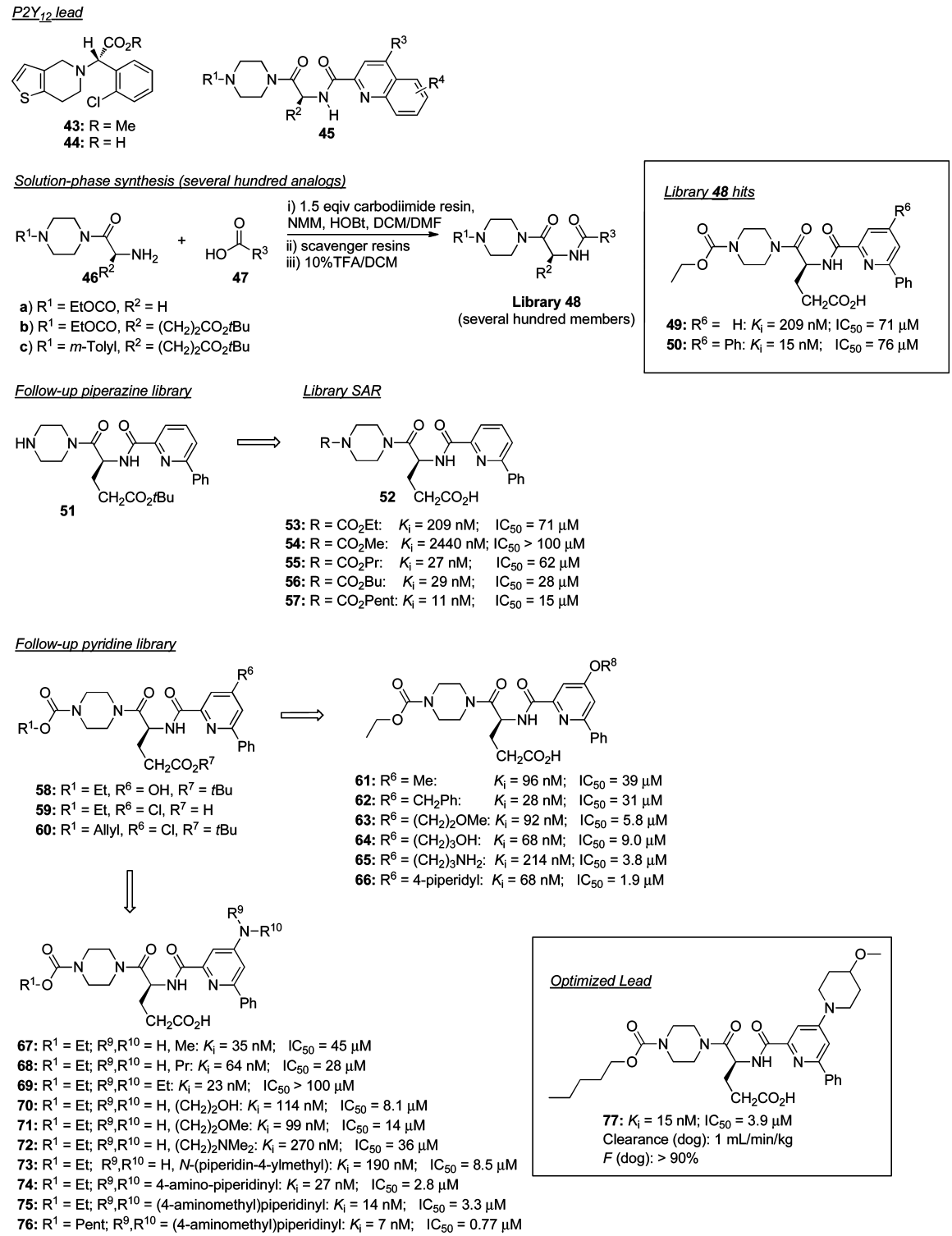


Figure 4. $P2Y_{12}$ receptor antagonists.[221]

Compound **42** also showed high plasma exposure and a long plasma half-life in monkeys. This library approach demonstrated that the urea linkage in previously reported hGluR antagonists can be successfully replaced by a number of different thiazole cores and established SARs for binding, selectivity and PK properties for this novel chemical class.

Purinergic $P2Y_{12}$ Receptor Antagonists.[221] Plavix (clopidogrel, **43**) is an antiplatelet agent approved for stroke and myocardial infarction in patients with atherosclerosis. Its mechanism of action is thought to proceed via metabolism to acid **44**, followed by irreversible inactivation of $P2Y_{12}$, a platelet specific GPCR (Figure 4). This in turn leads to a reduction in adenosine diphosphate (ADP)-stimulated platelet aggregation and the formation of platelet aggregates thereby providing therapeutic benefit. Because **43** is a prodrug requiring metabolic activation, it cannot be used effectively in patients that require emergency treatment (delayed time of action) or in patients who cannot metabolize **43**. Recognizing the shortcomings of **43**, Parlow and colleagues sought to find a new class

of $P2Y_{12}$ receptor antagonists having direct action on the receptor.[221] $P2Y_{12}$-based quinoline antagonists were previously reported by Berlex and this class was used as a starting point for library design and SAR exploration. Initial efforts focused on replacing the quinoline moiety employing polymer-assisted solution-phase chemistry. Piperazine derivatives **46** were coupled with heteroaromatic carboxylic acids **47** in the presence of resin-bound carbodiimide and HOBt. Excess reactants were sequestered with resin-bound isocyanate and a resin-bound secondary amine providing clean intermediates that, post TFA treatment, afforded desired carboxylic-acid-containing analogs **48**. Hundreds of compounds were prepared using this approach. The library was evaluated in a human-derived $P2Y_{12}$ receptor binding assay, screening for % inhibition at 10 μM. K_i values and inhibitory effects in a human platelet rich plasma (PRP) assay were obtained for the more potent compounds. The results from the first round of library evaluation indicated that replacing the original quinoline group with pyridine generally produced compounds with nanomolar K_i values, although with poor PRP inhibitory effects. Since the most potent compounds had one or two phenyl groups on the pyridine ring (**49** and **50**, respectively), the authors selected **49** as the lead for further SAR exploration and optimization. The next step consisted of SAR exploration around the piperazine moiety **51**. A broad range of alkylating, acylating and sulfonating agents were used in conjunction with a scavenger resin to remove residual electrophile reactants. Biological assays showed that activity was driven by the carbamate group where the longer the aliphatic carbamate chain, the greater receptor affinity binding and, importantly, inhibitory PRP activity (**53**−**57** K_i values = 2440 to 11 nM; IC_{50} values $\geqslant$100 to 15 μM).

The next SAR campaign focused on the 4-position of the pyridine ring. The authors opted to make chloro- and phenol-containing intermediates (**58**−**60**) to use these functional groups as handles to introduce chemical diversity. Phenol **58** was *O*-alkylated with alcohols under Mitsunobu reaction conditions (DEAD, PPh_3, THF) or with halides (Cs_2CO_3, KI, DMF) ultimately yielding carboxylic acid ethers **61**−**66**. Although the SAR was rather flat, a trend emerged for increased PRP activity with the phenolic ethers (**65**, **66** IC_{50} = 3.8 and 1.9 μM, respectively).

In addition to 4-ether substitution, 4-amino substitution was explored. This was carried out by treating carbamate **59** with 20 equiv of amine to displace the 4-chloro group yielding 4-aminopyridine ethyl carbamates **67**−**76**. Simultaneous variation of the 4-position and the carbamate moiety was achieved using the same 4-chloro displacement strategy with **60**, followed by alloc deprotection, *N*-piperidine carbamoylation, and TFA deprotection. Small secondary alkyl amines were preferred over tertiary amines (IC_{50}s for **67** and **68** versus **69**) while amino ethers exhibited higher PRP inhibitory activity (**70, 71**); particularly effective were the amino piperidyl and amino piperazine groups (**72**−**75**). Lastly, increasing the length of the alkyl carbamate chain led to further increases in K_i and IC_{50} (**76** K_i = 7 nM; IC_{50} = 0.77 μM). Evaluation of the most potent candidates in this series led to the discovery of **77** with a satisfactory in vivo profile, oral bioavailability, and some 340-fold more selective for the $P2Y_{12}$ receptor versus its closest homologue, the $P2Y_{13}$ receptor.

Heat Shock Protein 90 (Hsp90) Inhibitors[41]

Hsp90 has gained attention in the pharmaceutical industry because of its participation in multiple cell signaling pathways in cancer cells (e.g., PI3K/Akt). Hsp90 is an ATPase protein that acts as a chaperone, binding to multiple oncology relevant client proteins (e.g., Her2, cKit, MET), stabilizing these proteins so to permit their cell signaling function. Inhibition of Hsp90 prevents the necessary folding required to bind and stabilize client proteins. This results in the degradation of the client proteins via the ubiquitin proteasome pathway making Hsp90 an attractive oncology target. Geldanamycin and close synthetic analog 17-allylamino-17-demethoxygeldanamycin (17-AAG) bind to the ATP active site in the *N*-terminal domain inhibiting Hsp90 function validating this to be a viable mode of action to disrupt Hsp90's biological function. Poor water solubility and hepatotoxicity limit the clinical utility of these agents and thus, new small molecules are sought targeting the ATP binding site to inhibit Hsp90 function. Radicicol is an inhibitor of Hsp90 via ATP competition binding. Promising results have been noted by several research programs with resorcinol-based Hsp90 inhibitors. However, a common limitation to this compound class is that the phenol groups can be substrate sites of metabolic degradation processes (e.g., glucuronidation) resulting in fast in vivo clearance.

Cho-Schultz and colleagues focused their attention on compound **78**, an amide-containing polyphenol and ATP binding site-directed inhibitor of Hsp90 (Figure 5).[41] A two-stage solution-phase strategy was devised to explore the chemical space and develop an SAR around **78** to produce new potent Hsp90 inhibitors without phenol groups. The first library of compounds focused on the solution-phase synthesis of **79**. The objective was to improve binding affinity and reduce or eliminate glucuronidation by increasing hydrophilicity via the introduction of basic amino fragments. Library synthesis commenced by the addition of Grignard intermediate **81**, derived from *m*- and *p*-1,3-dioxane-subsituted bromobenzene to *N*-vinyl pyrrolidinone **82** affording 2-pyrrolines **83** (23−29% yields). These cyclic imines were reduced to **84** with $NaBH_4$ and then coupled to phenol-protected benzoic acid **85**. Deprotection of the phenol groups with either TFA or HCl resulted in aldehydes **86** that were subjected to reductive amination with ~90 amines to afford the 178-compound library **79**. Compounds were tested in a tritium-labeled-ligand competitive binding assay (K_i), followed by the measurement of Akt-degradation in H1299 lung cancer cells (IC_{50}). The SAR indicated that *para*-substituted compounds had higher binding affinity against Hsp90 and demonstrated superior activity in the cell-based assay (K_i values = 5.4−40 nM; IC_{50} values = 112−668 nM) versus

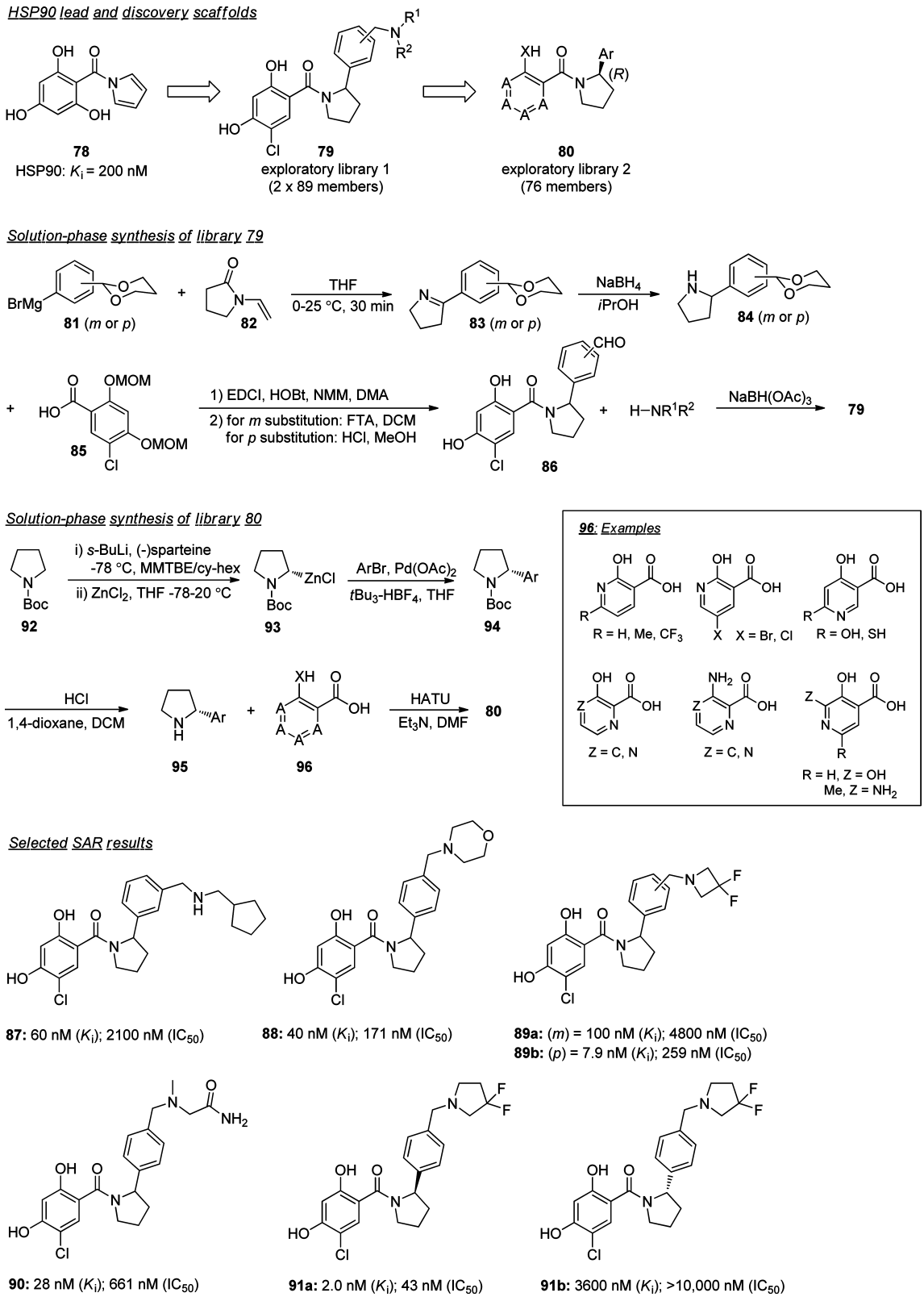


Figure 5. Hsp90 inhibitors.[41]

the *meta*-substituted compounds (K_i values = 60−100 nM; IC_{50} values = 2100−4800 nM). A cocrystal structure of Hsp90α with **91a** (PDB code 3HEK, resolution = 1.95 Å) established the (R) stereochemistry of the pyrrolidine group as crucial for the molecule to adopt the most favorable, lower-energy conformation to bind at the ATP site. In this configuration, the resorcinol group exhibits a salient H-bond interaction with Asp93, the amide group retains its expected planarity, the 3,3-difluororopyrrolidine group is placed into a hydrophobic region (Tyr137, Val136, Gly135), and the pendant phenyl group is also accommodated in a hydrophobic pocket. Chiral separation of other racemates confirmed the (*R*)-enantiomers bound far more potently against Hsp90 than their corresponding (*S*)-enantiomers. Unfortunately, all

of the (*R*)-enantiomers exhibited high clearance in human hepatocytes. Armed with this knowledge, a second library was conceived focusing on the synthesis of (*R*)-enantiomers and the replacement of the phenol groups to improve the ADME profile. The chemistry relied on the enantioselective α-arylation of *N*-Boc-pyrrolidine **92** with (−)-sparteine to prepare chiral **93**. Chiral organometallic **93** was coupled with aromatic bromides to afford key intermediate **94**. Following Boc deprotection, amines **95** were coupled to a diverse group of aromatic carboxylic acids **96** using HATU to afford library **80**. With this methodology enantiomeric ratios of >96:4 were achieved and allowed for the synthesis of a ∼112-membered library. Unfortunately, none of the compounds of library **80** exhibited inhibitory activity against Hsp90 when tested at 10 μM in the binding assay. Lastly, selected synthesis of monophenol analogs revealed that both phenol groups are essential for binding since the removal of either phenol group led to a >190-fold loss in potency.

Selective Norepinephrine Reuptake Inhibitors[73]

The norepinephrine transporter is a membrane bound protein that regulates the uptake of the neurotransmitter norepinephrine (NE) from the presynaptic cleft of noradrenergic neurons during synaptic transmission. It therefore plays an important role in regulating the physiological functions of NE, the deficiency of which has been implicated in a number of neurological disorders. Norepinephrine reuptake inhibitors (NRIs), such as reboxetine and atomoxetine, have been used clinically for the treatment of major depressive disorder and attention deficit hyperactivity disorder (ADHD), respectively. Researchers at Pfizer disclosed recently several new chemical series of selective norepinephrine reuptake inhibitors (sNRI).[73] The two lead compounds **97** and **98**, investigated clinically, were discontinued because of hepatotoxicity (Figure 6). This safety issue identified with **97** and **98** was thought to be related to the high lipophilicity of these compounds (clogP = 4.2−4.4). A search for new NRI templates, providing ligands with reduced lipophilicity when compared to **97** or **98**, was then undertaken. The benzamide derivative **99** was identified from previous lead identification work as a weak norepinephrine reuptake inhibitor with low selectivity over the serotonin transporter (K_i (NET) = 294 nM; K_i (SERT) = 654 nM). The lead optimization objective was to improve the affinity and the selectivity for the norepinephrine transporter, while simultaneously reducing the lipophilicity in this series. Analogs of **99** (205-member library; general structure **100**) were readily available via solution phase parallel synthesis methodology. The *N*-alkyl or *N*-aryl substituted 3-amino-1-Boc-(*S*)-pyrrolidines **102**, obtained from 3-amino-1-Boc-(*S*)-pyrrolidine using common methodologies, were converted to the target compounds **100** via amide formation followed by *N*-Boc deprotection. The binding affinity of the library compounds at the human norepinephrine, serotonin, and dopamine transporters was determined using scintillation proximity assay (SPA) technology. SAR analysis in this series revealed that potent norepinephrine reuptake inhibition could be achieved over a range of lipophilicity (clogP = 3.0−4.4). High affinity for the norepinephrine transporter was obtained when the aryl group of **100** was substituted at the *ortho* position (R^2) by SMe, CF_3, SEt, *i*-Pr, or OPh moieties. The cyclobutylmethyl group was preferred at the R^1 position of **100**. Attempts to substitute this cyclobutylmethyl group by other alkyl moieties led to a significant decrease in the affinity toward the norepinephrine transporter and a decreased selectivity over the serotonin transporter. The best ligands in this benzamide series displayed good in vitro metabolic stability in human liver microsomes. Inhibitory activities at the CYP2D6 isoenzyme and at the hERG channel were generally minimized by decreasing the overall lipophilicity of the molecules. The lead optimization campaign led to the discovery of compound **101**, a potent norepinephrine reuptake inhibitor (K_i = 6 nM) displaying 37-fold and 380-fold selectivity over the serotonin and dopamine transporters, respectively. The lipophilicity of **101** (clogP = 3.3) was also significantly reduced when compared to previous lead compounds **97** and **98** investigated clinically (clogP = 4.4 and 4.2, respectively). Further studies demonstrated that **101** has excellent metabolic stability in human liver microsomes and human hepatocytes, weak CYP (1A2, 2C9, 2C19, 2D6, 3A4) inhibition, and good membrane permeability. In light of its weak inhibitory activities at the hERG (IC_{50} >20 000 nM) and $NaV_{1.5}$ (IC_{50} > 26 000 nM) ion channels, **101** is expected to have a satisfactory cardiovascular safety profile. Off-target profiling of **101** at a panel of 110 receptors, enzymes and ion channels revealed only weak affinity at the M_4 (K_i = 4,300 nM) and M_5 (K_i = 1,800 nM) muscarinic receptors. In vivo rat microdialysis experiments demonstrated that **101** produces a rapid increase in NE levels in the prefrontal cortex after subcutaneous administration demonstrating good CNS penetration. Based on its favorable profile, **101** (PF-3409409) was selected for preclinical evaluation.

Positive Allosteric Modulators of mGluR4[297]

Metabotropic glutamate receptors (mGluRs) play important roles in a broad range of central nervous system functions and have therapeutic potential in a variety of neurological and psychiatric disorders. Activation of metabotropic glutamate receptor 4 (mGluR4) has been shown to modulate neurotransmission in the basal ganglia and results in antiparkinsonian effects in rodent models of Parkinson's Disease (PD). Allosteric binding sites, as opposed to traditional orthosteric binding sites, offer unparalleled opportunities for drug discovery by providing high levels of selectivity, mimicking physiological conditions and affording fewer side effects. VU0155041 **103**, a novel mGluR4 positive allosteric modulator (PAM) discovered in a high-throughput screen was the starting point of a detailed SAR analysis of this compound class (Figure 7). Three parts of the lead molecule were explored separately through an iterative parallel synthesis approach, the aromatic amide moiety, the carboxylic acid residue and the cyclohexyl core. The first library centered around commercially available *cis*-1,2-cyclohexanedicarboxylic anhydride **104**, which was reacted with respective R^1-

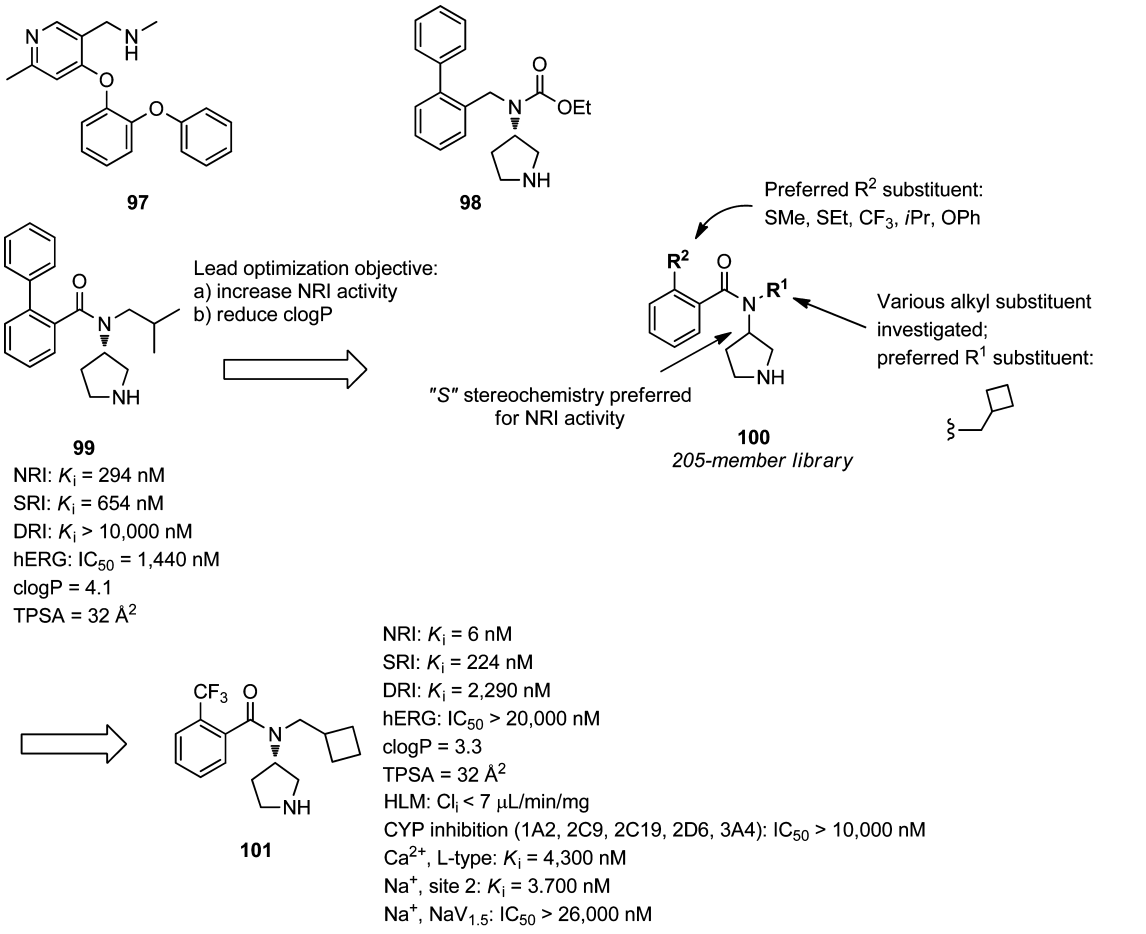


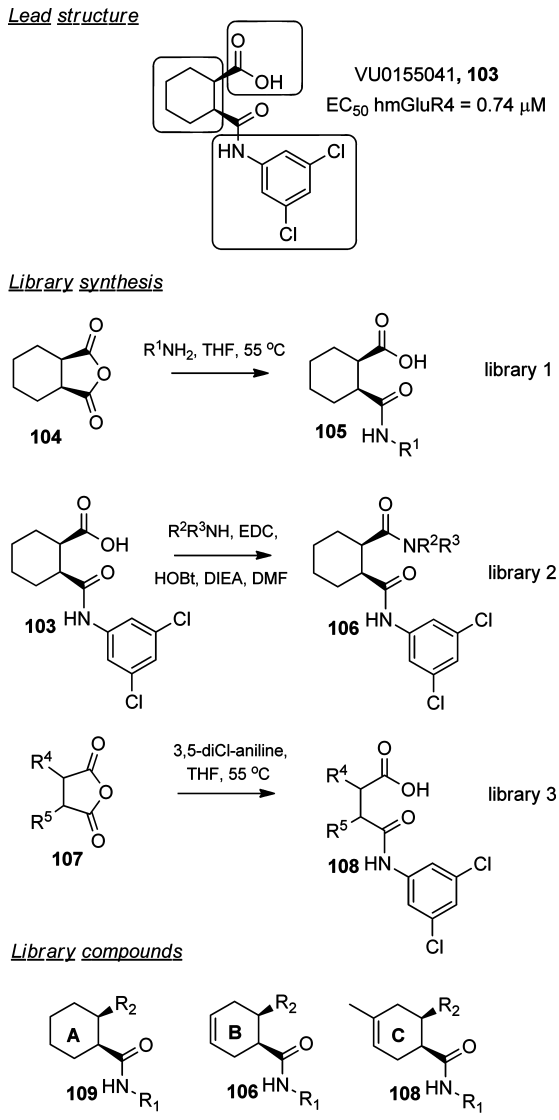
Figure 6. Selective noradrenaline reuptake inhibitors.[73]

amines in THF at 55 °C to give library compounds **105**. Several 3,5- and 3,4-substituted phenyl, unsubstituted phenyl, benzyl and pyridyl, morpholino and cyclo alkyl analogs were evaluated. Besides the original 3,5-dichlorophenyl lead **103** (EC_{50} hmGluR4 = 0.74 μM), only the 3-Cl-5-F-phenyl amide **109** retained some activity (EC_{50} hmGluR4 = 2 μM), all other substitutions led to a loss of activity. Carboxylic acid replacements were investigated next, starting from VU0155041 **103**, coupling respective R^2,R^3-amines with EDC, HOBt, and DIEA in DMF a library of diamides **106** was synthesized. All compounds showed at least a 10-fold loss of activity, with the exception of the primary carboxamide **112**, which retained similar submicromolar activity as the lead (EC_{50} hmGluR4 = 0.95 μM). Variations of the core structure were then examined. Commercially available cyclic anhydrides **107** were reacted with 3,5-dichloroaniline in THF at 55 °C. Only the cyclohexene analog **115** retained some activity (EC_{50} hmGluR4 = 2.7 μM), substituted cyclohexene cores (e.g., **117**) resulted in inactive compounds. Changing the substitution pattern to a 1,3-orientation led to a total loss of activity. Combining the cyclohexene core with a primary carboxamide in compound **116** showed some activity (EC_{50} hmGluR4 = 3.1 μM).

This SAR evaluation around VU0155041 **103**, utilizing a parallel synthesis approach, illustrates another example of the rather flat SAR common to positive allosteric modulators.

GluR5 Allosteric Modulators[71]

Excess dopamine transmission in the brain is believed to be one cause of schizophrenia and antipsychotic agents that antagonize the dopamine D2 receptor are routinely



	R1	R2	EC50 [μM] hmGluR4
Core A			
103	3,5-diCl-phenyl	COOH	0.74
109	3-Cl-5-F-phenyl		2.0
110	phenyl		>10
111	3,5-diF-phenyl		inactive
112	3,5-diCl-phenyl	$CONH_2$	0.95
113		CONHPr	9.6
114		CONMe	10
Core B			
115	3,5-diCl-phenyl	COOH	2.7
116	3,5-diCl-phenyl	$CONH_2$	3.1
Core C			
117	3,5-diCl-phenyl	COOH	inactive

Figure 7. Positive allosteric modulators of mGluR4.[297]

prescribed. Many of these agents display off target pharmacology against a range of neurotransmitters leading to side effects. It was observed clinically that administering glycine, an N-methyl-D-aspartate (NMDA) receptor coagonist, elicited a modest improvement in schizophrenic patients suggesting that activation of the NMDA receptor could be an option for therapeutic treatment. Potentiation of NMDA receptor transmission can occur directly by modulating NMDA receptor sites or indirectly by activating NMDA-receptor-function dependent GPCRs. Metabotropic glutamate receptor 5, mGluR5, is a GPCR that upon activation can potentiate indirectly the NMDA receptor. Using ADX-47273 (**118**), a previously reported positive allosteric modulator of mGluR5 demonstrating in vivo activity in cognition and schizophrenia animal models, Engers and colleagues generated solution-phase libraries around scaffold **119** to flesh out the SAR of **118** and improve its overall physicochemical properties (Figure 8).[71] Two routes were developed for library synthesis. The first route involved simultaneous coupling-cyclization of (*Z*)-*N'*-hydroxyimidamides **120** and (*S*)-1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid **121** using EDCI and HOBt under reflux to give oxadiazoles. Removal of the Boc group and acylation of the piperidine intermediates afforded library **119a**. The second route consisted of the esterification of (*S*)-piperidine-3-carboxylic acid **122**, acylating ester **123**, saponifying *N*-acyl esters **124** with LiOH and then simultaneous coupling-cyclization with (*Z*)-*N'*-hydroxyimidamides **120** to afford desired library **119b**.

In the first exploratory library, the 4-fluorobenzylpiperamide was kept constant and the 4-fluorophenyl ring on the oxadiazole unit was replaced. It was found that 2-pyridyl and 2-thienyl groups were reasonable substitutes for the 4-fluorophenyl group, while the 3- and 4-pyridyl and 2-pyrazinyl groups were not. In the follow-up library **119b**, which retained the original 4-fluorophenyl and now included the 2-thienyl and 2-pyridyl (R^1) groups, the acyl group (R^2) was varied. Biological evaluation of this library revealed the following trends. For R^2, most mono- and difluorophenyl groups exhibited submicromolar ago-potentiation (potentiation of the agonist activity of glutamate at its EC_{90}) while the 2,6-difluorophenyl group did not. The 2-pyridyl analogs, for example, **125**, were 2-times less potent than their 4-fluorophenyl and 2-thienyl counterparts. Unexpectedly pyridyl compounds, for example, **128**, displayed pure mGluR5 positive allosteric modulation as these compounds had no inherent agonist activity. The corresponding HCl salts of the pyridyl analogs exhibited expected improved water solubility. Interestingly, the cyclobutyl analog **129** was a negative allosteric potentiator, an example of an unusual functional switch. Finally, to establish the importance of the chiral center, enantiomeric separations were carried out on **118**, **125**, and **126**. The (*R*)-enantiomers were in general 9- to 10-fold less potent than the (*S*)-enantiomers, yet display similar in vitro efficacy. With this study the SAR features of **118** were quickly identified, particularly the relevance of the (*S*)-chiral center.

Bcl-2 Inhibitors: Diversity-Oriented Synthesis Library[182]

Apoptosis, or programmed cell death, is important for normal development, host defense, and suppression of oncogenesis, and disregulation of apoptosis has been implicated in cancer and many other human diseases. The Bcl-2 family proteins are central regulators of apoptosis and comprise antiapoptotic proteins, such as Bcl-2, Bcl-

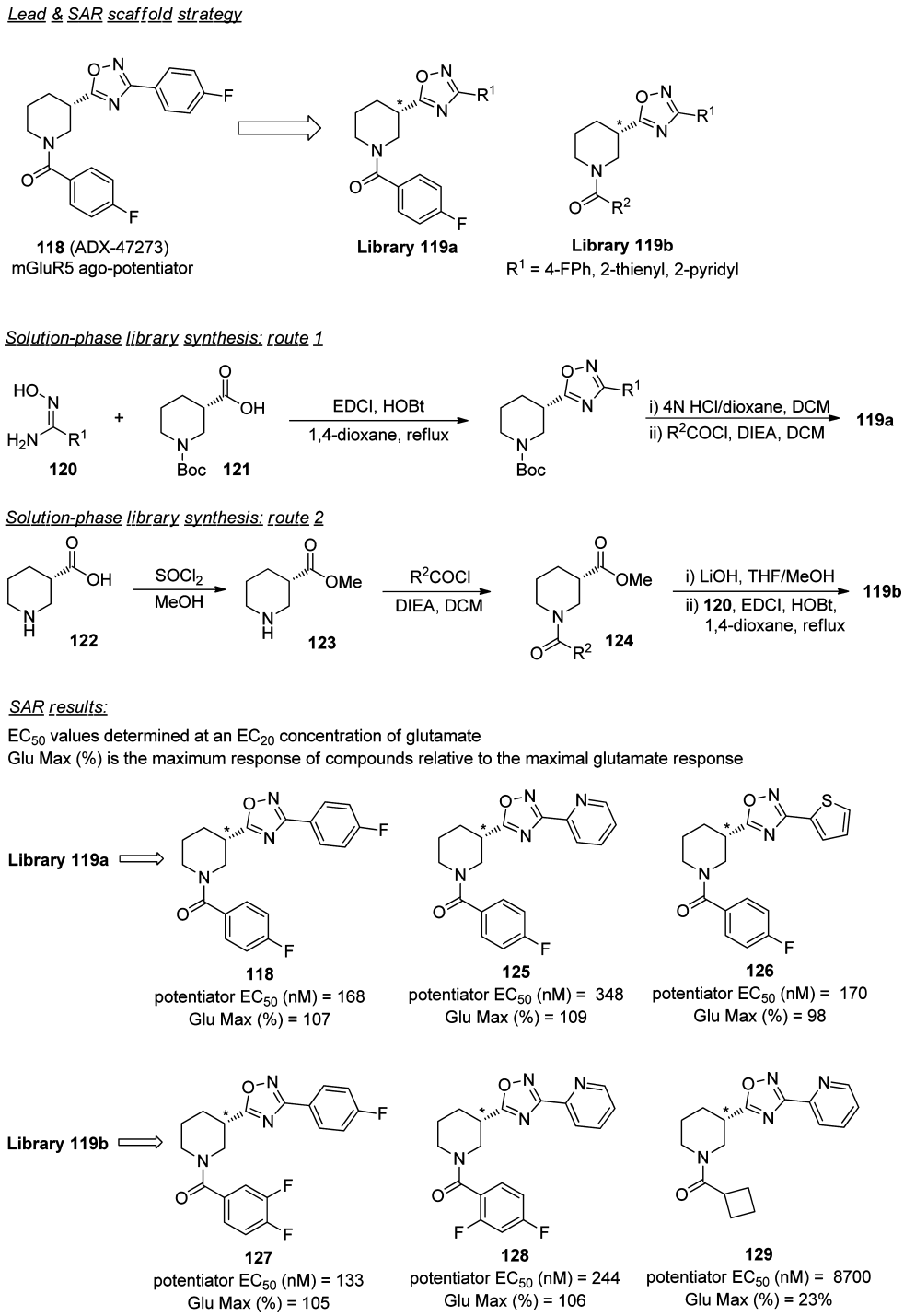


Figure 8. mGluR5 allosteric modulators.[71]

xL, and Mcl-1 and pro-apoptotic proteins, such as Bak, Bax, Bim, Bid, and Bad. Overexpression of the Bcl-2 membrane protein has been observed in 70% of breast cancer, 30−60% of prostate cancer, 80% of B-cell lymphomas, 90% of colorectal adenocarcinomas, and many other forms of cancer. The expression levels of Bcl-2 proteins also correlate with resistance to a wide spectrum of chemotherapeutic drugs and γ-radiation therapy. Bcl-2 is therefore a promising molecular target for the design of an entirely new class of anticancer drugs aimed at overcoming resistance of cancer cells to apoptosis. Consequently, design of nonpeptide small molecule inhibitors of Bcl-2 and Bcl-xL is currently an exciting research area for the development of new anticancer agents. In an effort to identify novel inhibitors of Bcl-2, scientists at Infinity Pharmaceuticals designed and prepared a 15,000-member pyridone library (Figure 9a/b), via discovery oriented synthesis (DOS).[182] The design of this library was based on the structure of the nicotinic agonist (−)-cytisine (**130**) and previous work describing the total synthesis of this natural product. In particular, the pyridone cyclization step, key transformation for the total synthesis of (−)-cytisine, was exploited for the diversity oriented synthesis of heterocycles **131a** and **132a**,

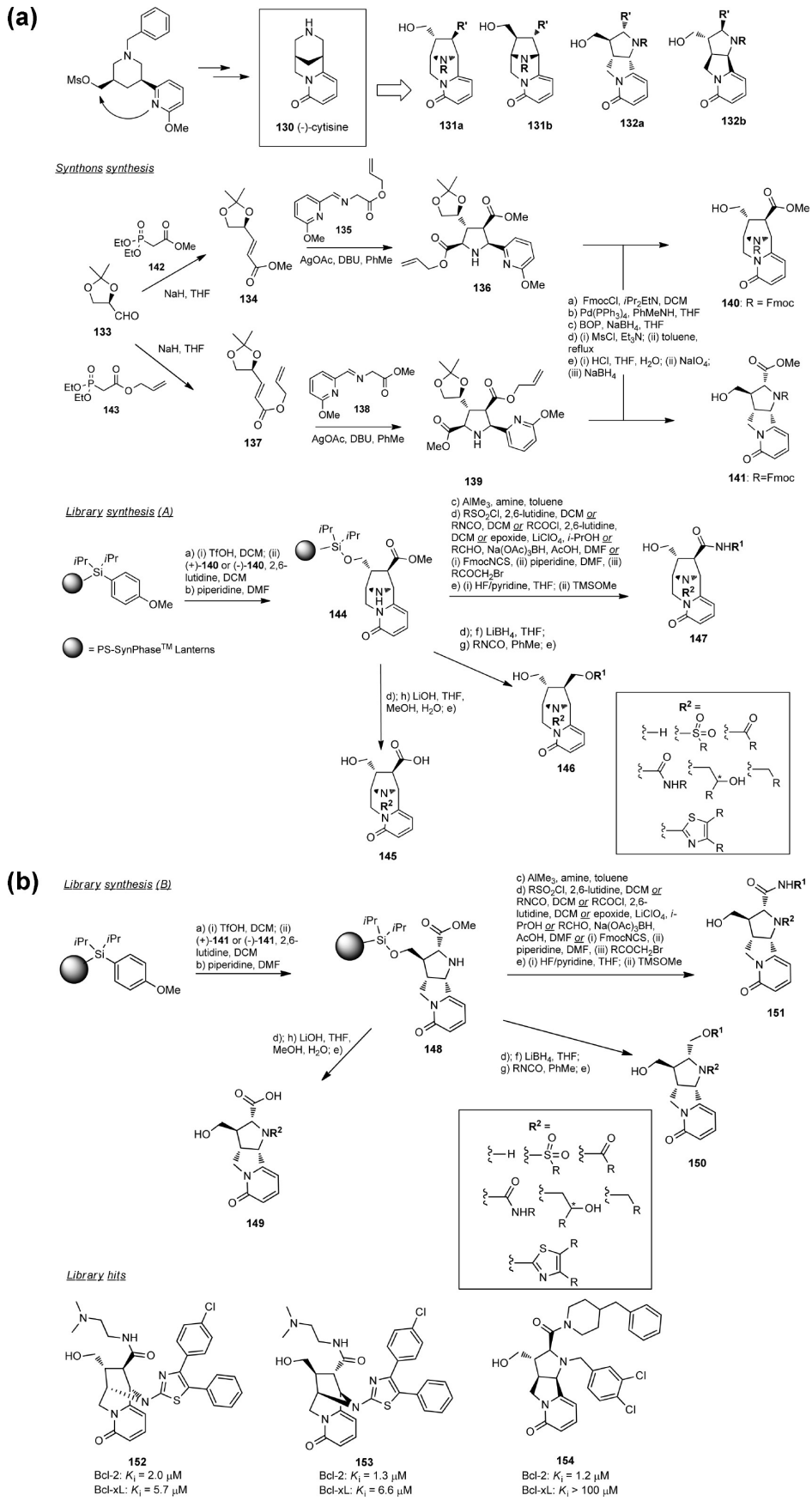


Figure 9. (a, b) Bcl-2 inhibitors via DOS library.[182]

as well as their corresponding enantiomers **131b** and **132b**, respectively. The synthons **140** and **141** used for the diversity oriented library synthesis were prepared according to Figure 9a. Condensation of D-glyceraldehyde acetonide **133** with phosphonate **142**, under Horner−Emmons conditions, provided the α,β-unsaturated ester **134**, which

reacted with the imine **135** in toluene in the presence of AgOAc and DBU to provide the corresponding [3 + 2] azomethine ylide-alkene cycloaddition product **136** in high yield and excellent diastereoselectivity (>95:5). The pyrrolidine derivative **136** was then converted to the bridge bicyclic scaffold **140** in 5 steps, that is, (a) protection of the NH functionality of **136** as the *N*-Fmoc derivative, (b) deprotection of the allyl ester functionality by treatment with $Pd(PPh_3)_4$, (c) conversion of the resulting carboxylic acid to the corresponding primary alcohol, (d) activation of the resulting alcohol with mesyl chloride followed by formation of the pyridone ring via intramolecular cyclization, and (e) conversion of the 1,3-dioxolane, 2,2-dimethyl functionality to the corresponding primary alcohol according to a 3-step sequence. The tricyclic synthon **141** was prepared from phosphonate **143** via a synthetic sequence similar to the one described for the preparation of **140**. The pyridone scaffolds **140** and **141**, prepared in large scale (>75 g), were then loaded onto silicon-functionalized Lanterns via activation with TfOH (average loading level of 15 mmol of compound per Lantern). Deprotection of the *N*-Fmoc functionality provided the resins **144** and **148**, which were converted to the library compounds **145**−**147** and **149**−**151** via classical solid-phase derivatization methodologies (Figure 9b). The 15 000 library compounds, prepared with purities greater than 75% for over 75% of the library, were screened for binding affinity for Bcl-2 and Bcl-xL. The most potent compounds derived from the bridged bicyclic pyridone scaffolds **131a** and **131b**, exemplified by compound **152** [K_i (Bcl-2) = 2.0 μM; K_i (Bcl-xL) = 5.7 μM)] and its enantiomeric analog **153** [K_i (Bcl-2) = 1.3 μM; K_i (Bcl-xL) = 6.6 μM)], contained a chloro-substituted diphenyl 2-aminothiazole and a diamine at the R and R′ position, respectively. Compound **154** was the best ligand identified from the tricyclic pyridone cores **132a** and **132b**. This compound selectivitly binds with micromolar affinity at Bcl-2 (K_i = 1.2 μM) and displays, in contrast to **152** and **153**, high (>100-fold) selectivity for Bcl-2 over Bcl-xL (Figure 9b).

Catch and Release Synthesis of Substituted Guanidines[289]

One of the most common methods to prepare substituted guanidines **156** involves the condensation of amines with *S*-methylated thioureas **156** (Figure 10). This method suffers from the formation of noxious and toxic methyl mercaptan side product, which limits application for high-throughput parallel synthesis. To overcome this problem, scientists at Abbott designed a solid-phase strategy for the synthesis of *N*,*N*,*N*′-substituted guanidines using a catch and release methodology inspired from the solution phase synthesis described above.[289] In this method, the thioureas **155** immobilized on solid support react with various amines to provide the desired guanidine derivatives, free of mercaptan side products. Using this new methodology, and after several optimization of the reaction conditions, various substituted guanidines were prepared from thioamides in a one-pot process. Hence, loading of *N*-substituted thiourea **157** to brominated polystyrene resin

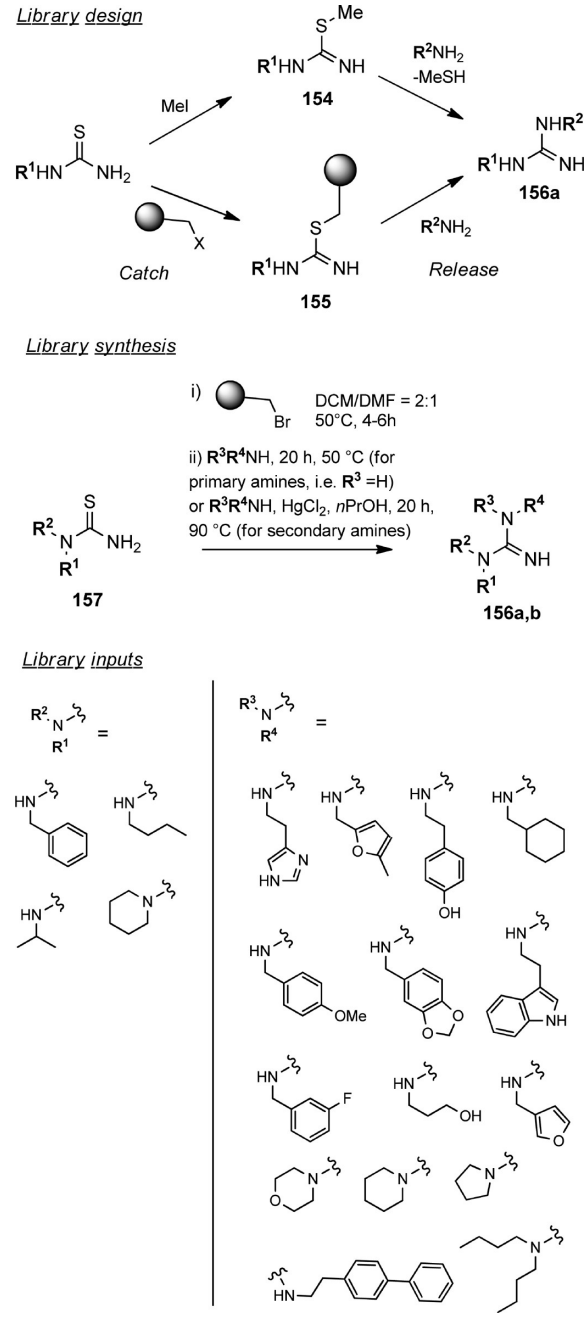


Figure 10. Catch-and-release synthesis of substituted guanidines.[289]

in a mixture DCM/DMF (2:1) at 50 °C for 4−6 h provided the thiourea resins **155**, which could be washed, dried, and stored or used without isolation for the next step. Condensation of the resin-bound thioureas with primary amines at 50 °C for 20 h provided, in high yield, the desired substituted guanidines **156a,b** purified by HPLC and isolated as their TFA salts. The reaction conditions were modified to allow the formation of *N*,*N*,*N*′-trisubstituted guanidines from the corresponding secondary amines in good yields. In the modified method, the condensation of secondary amines to the resin-bound thioureas was conducted in methoxyethanol in the presence of 1.5 equiv of $HgCl_2$. Using this new solid phase methodology, a total of 17 *N*,*N*′-disustituted or *N*,*N*,*N*′-trisubstituted guanidines **156a**,**b** were prepared, from the

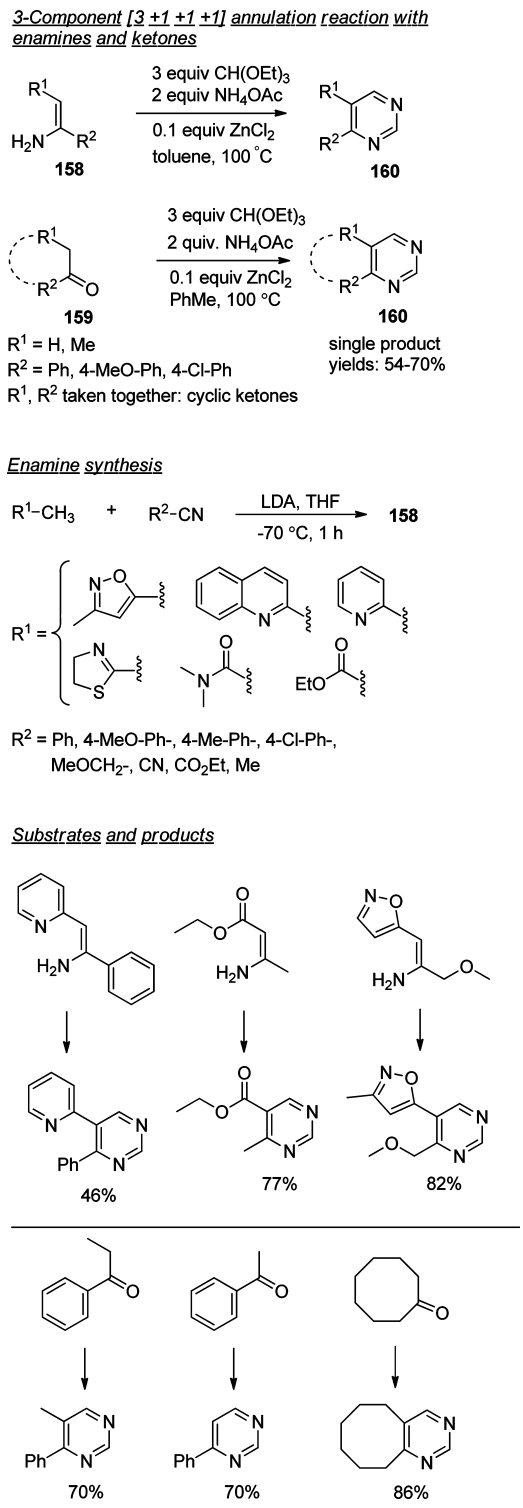


Figure 11. MCR to pyrimidine derivatives.[257]

corresponding thioureas, in isolated yields ranging from 42% to 99%.

Substituted Pyrimidines via a 3-Component Reaction[257]

Konakahara and co-workers developed a novel three-component coupling reaction of enamines **158**, triethyl orthoformate and ammonium acetate providing a facile route to 4,5-disubstituted pyrimidine derivatives **160** (Figure 11). Pyrimidine derivatives exhibit biological activity against all major classes of molecular targets including kinases, proteases, nuclear hormone receptors and GPCRs. Bredereck- and Pinner-type chemistries are established routes for the preparation of pyrimidines. However, challenging multistep synthesis of reactive intermediates and harsh reaction conditions limit their general utility, particularly for the preparation of pyrimidine-based arrays. The initial 3-CR was conducted by simply heating enamines **158** with 3 equiv of orthoester and 2 equiv of NH_4OAc in toluene at 100 °C for 20 h. Optimized reaction conditions included the addition of 0.1 equiv of $ZnCl_2$, which improved the overall yield (>70%), accelerated reaction time, and enhanced the range of substrates. Noncommercially available enamines were prepared in high yield (>90%) by the addition of electron-withdrawing stabilized carbon nucleophiles to arylnitriles. The $ZnCl_2$-catalyzed three-component reaction was expanded by using ketones **159** in place of enamines. The 3-CR with ketone substrates required 72 h for completion affording the desired products in good yields (54−70%).

Discovery of Ned-19[340]

Second messengers play enormously important roles in transduction of cellular signals and govern cellular responses to stimuli. Molecular and cellular biology has benefited greatly from molecular tools like Forskolin, which alters cellular levels of the critical second messenger cAMP. Nicotinic acid adenine dinucleotide phosphate (NAADP, **161**) is recognized as a critical regulator of Ca^{2+} release in numerous human tissues in response to several reported stimuli (Figure 12). Controversies surrounding the exact nature of NAADP as a secondary messenger and its mechanism of action permeate the literature. Furthermore, the lack of chemical probes of this important biomolecule hamper studies into the cause and consequences associated with Ca^{2+} release. To rectify this inadequacy, Churchill and co-workers reported the discovery of Ned-19 (**162**), a potent inhibitor of NAADP signaling.[340] Utilizing the chemical structure (including electrostatic surface assessments) of NAADP, a ligand-based virtual screen was performed in which novel structures were sought with sufficient overlap with NAADP while maintaining drug-like properties in the "hit" compounds. One agent that was discovered was an (*S*)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole-3-carboxylate designated as Ned-19. This commercially available agent inhibited NAADP signaling in a sea urchin egg assay at nanomolar concentrations. The stereochemistry at the 1 position of the tetrahydro-1*H*-pyrido ring was explored via an independent synthesis. The synthesis was initiated by installment of a chloromethyl group at the 3-position of commercially available 4-methoxybenzaldehyde. The resulting aldehyde was subjected into a Pictet−Spengler reaction with (*S*)-methyl 2-amino-3-(1*H*-indol-3-yl)propanoate to afford the core (*S*)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate scaffold. Displacement of the benzyl chloride with 1-(2-fluorophenyl)piperazine and saponification of the methyl ester provided Ned-19. The diastereomeric mixture was separated following the

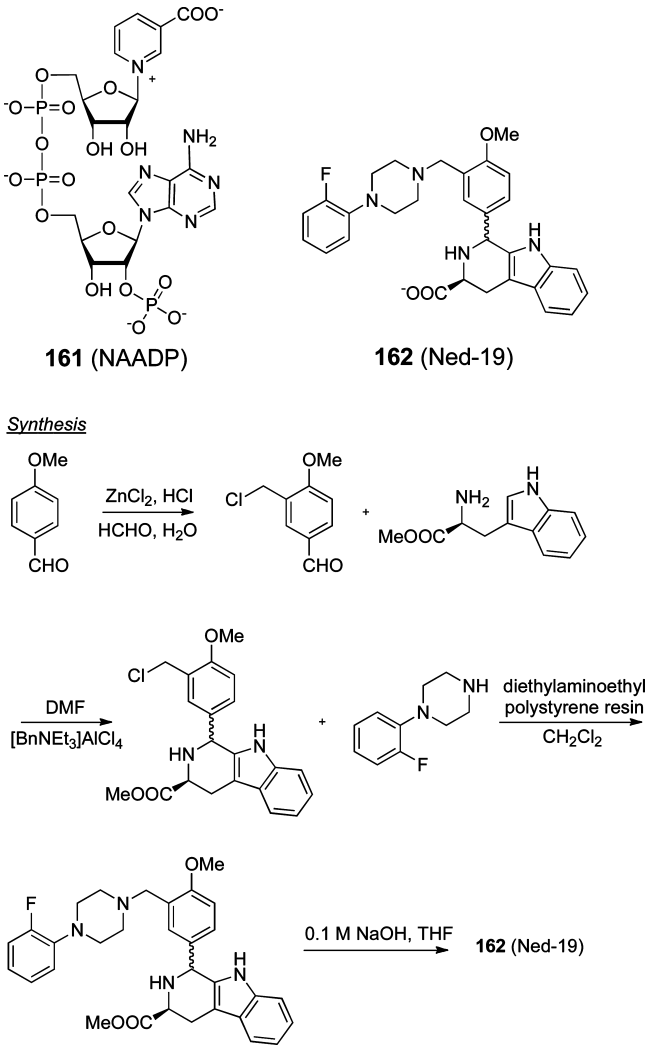


Figure 12. Discovery of Ned-19.[340]

Pictet−Spengler reaction. The specific activity of both the *cis* and *trans* isomers of Ned-19 were evaluated and the trans isomer was significantly more active than the cis isomer. Biochemically, Ned-19 was able to eliminate all NAADP-mediated Ca^{2+} signaling at 100 μM without altering inositol 1,4,5-trisphosphate-mediated or cADP-ribose-mediated Ca^{2+} release. These experiments suggest that Ned-19 is selective as a NAADP signaling probe rather than a nonspecific modulator of Ca^{2+} release. Ned-19 blocks NAADP signaling in intact cells and it can serve as a fluorescent label for NAADP receptors. Finally, Ned-19 was used to demonstrate a role for NAADP signaling in glucose signaling and Ca^{2+} release in pancreatic beta cells. While further studies with Ned-19 are required to fully validate its use as a probe of NAADP signaling, this work offers a novel agent to begin to fully dissect the various roles of this important secondary messenger.

Discovery of DG-041[338]

There exists a complex network of signaling events that govern platelet activation and aggregation and great strides have been made in modulating these relevant signaling events to avoid catastrophic acute thrombosis during vascular events like myocardial infarction and stroke. The

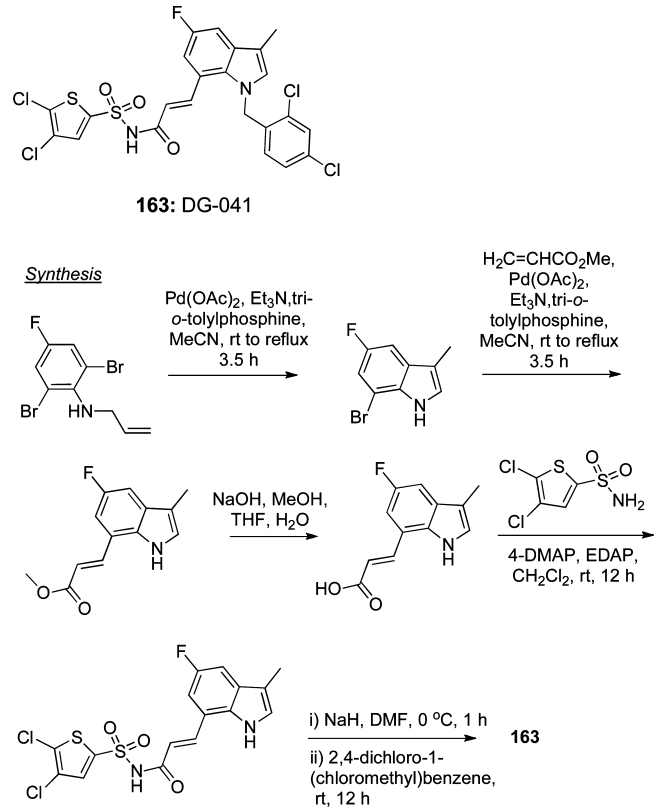


Figure 13. Discovery of DG-041.[338]

recognition that aspirin (acetylsalicylic acid) acts as an antagonist of platelet aggregation can be considered a starting point for research into defining the critical targets associated with platelet function. More recently, the purinergic $P2Y_{12}$ receptor has been shown to play an essential role in platelet signaling following platelet collagen and von Willebrand factor release and Ca^{2+} stimulation of TxA_2 and release of ADP. $P2Y_{12}$ receptor antagonists including prasugrel have proven more effective than aspirin in preventing recurrent myocardial infarction. Both aspirin and $P2Y_{12}$ receptor antagonists, however, have the unwanted side-effect of severe, prolonged bleeding events due to their global impairment of platelet aggregation. Research has continued to shed light on the complex signaling cascade associated with platelet aggregation and today it is known that multiple GPCRs are responsible for both Ca^{2+} release and activation/inactivation of adenylcyclase. One target that is gaining attention is the EP_3 receptor. The EP_3 receptor responds to prostaglandin E_2 (PGE_2) which is produced in low concentrations within atherosclerotic plaque. Importantly, signaling through the EP_3 receptor is not sufficient to produce an aggregation response without cosignaling events at one or more additional receptors that are associated with platelet activation. Studies have showed that platelets lacking the EP_3 receptor were protected from thrombotic events in several models and it has been hypothesized that, since healthy tissues do not produce PGE_2, blocking of the EP_3 receptor should have a diminished effect on bleeding events. To examine this theory, researchers at deCODE chemistry sought out new EP_3 receptor antagonists through a ligand-based design strategy (Figure 13).[338]

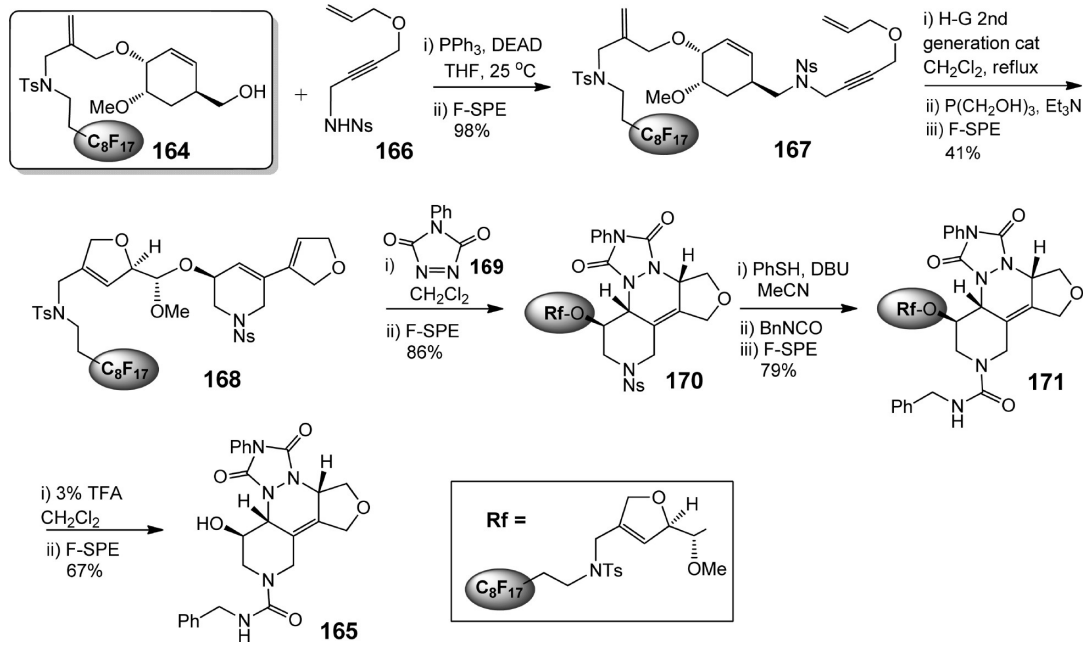


Figure 14. Fluorous dihydropyran linker.[322]

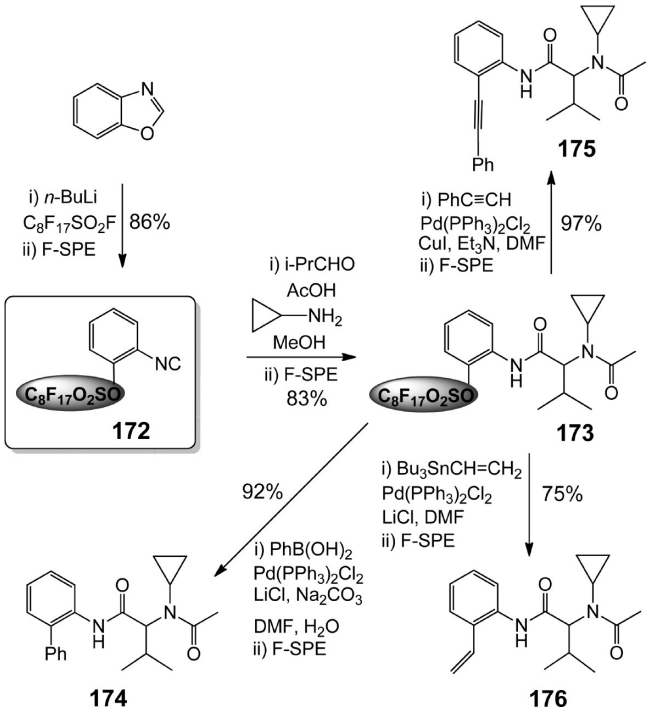


Figure 15. Fluorous isonitrile linker.[327]

The basic strategy was to seek out scaffolds that mimic the three-dimensional shape and electrostatic profile of the native ligand PGE_2. Ultimately efforts focused on a collection of substituted indoles with appendages at the 1 and 7 positions. Their initial leads possessed low-nanomolar activity at the EP_3 receptor and lead optimization included blocking metabolically labile positions at C3 and C5 of the indole ring. The optimization campaign led to the discovery of DG-041 (**163**). DG-041 (**163**) displayed IC_{50} values of 8.1 and 4.6 nM in a Ca^{2+} response assay and a radioligand displacement assay, respectively. DG-041 had no relevant activity versus the functionally related, platelet-associated GPCR targets nor was this agent active across a panel of 50 random GPCRs. DG-041 was also found to be acceptable for both oral and i.v. administration with appropriate PK properties for use as a tool compound in models of platelet aggregation. The synthesis of this agent was accomplished via sequential intramolecular and intermolecular Heck couplings to arrive at an appropriately 7-substituted indole intermediates. Saponification followed by coupling to 4,5-dichlorothiophene-2-sulfonamide and subsequent *N*-alkylation with 2,4-dichloro-1-(chloromethyl)benzene provided DG-041. DG-041 was found to inhibit human and rat platelet aggregation in vitro in a collagen induction experiment with several coagonists and, importantly, in the presence of high serum concentrations. Within in vivo systems, DG-041 inhibited platelet aggregation at a dose of 10 mg/kg, while there was no prolongation of bleeding up to a concentration of 100 mg/kg. The authors present several other findings that further validate DG-041 as an important new tool for studying the EP_3 receptor and reference, as yet, unpublished data suggesting that DG-041 is efficacious in a human patient population.

Displaceable Fluorous Dihydropyran Linker[322]

Fluorous linker combined with fluorous solid-phase extraction (F-SPE) is a powerful reaction and purification technique for solution-phase synthesis.[380] The Nelson group introduced fluorous dihydropyran linkers for the protection of amino and hydroxyl groups. Figure 14 highlights the utility of displaceable linker **164** in the synthesis of highly condensed heterocyclic compound **165**.[322] The fluorous linker was attached to sulfonamide **166** through Fukuyama−Mitsunobu reaction to form compound **167**. Cascade metathesis using Hoveyda−Grubbs second generation catalyst cleaved the central dihydropyran ring and produced compound **168**. This compound was then used for Diels−Alder

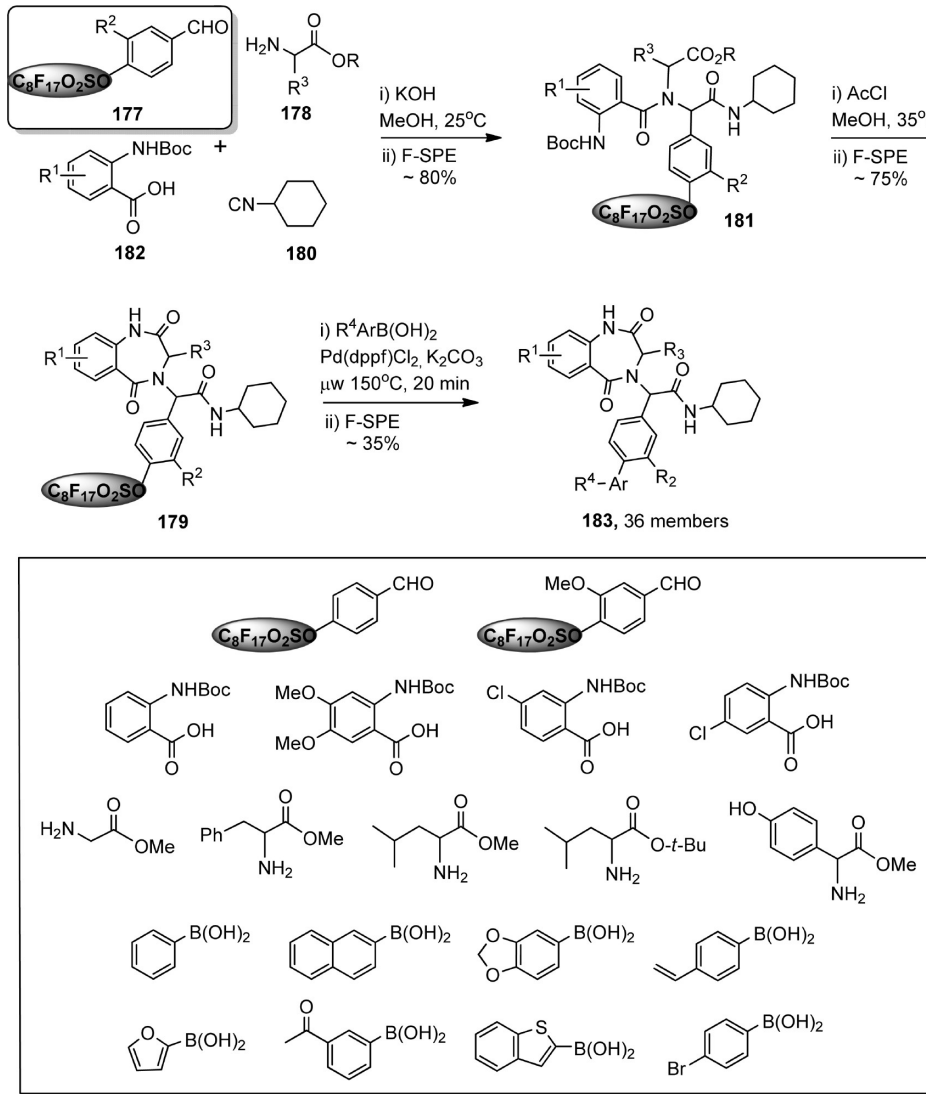


Figure 16. Fluorous synthesis of 1,4-benzodiazepinedione library.[327]

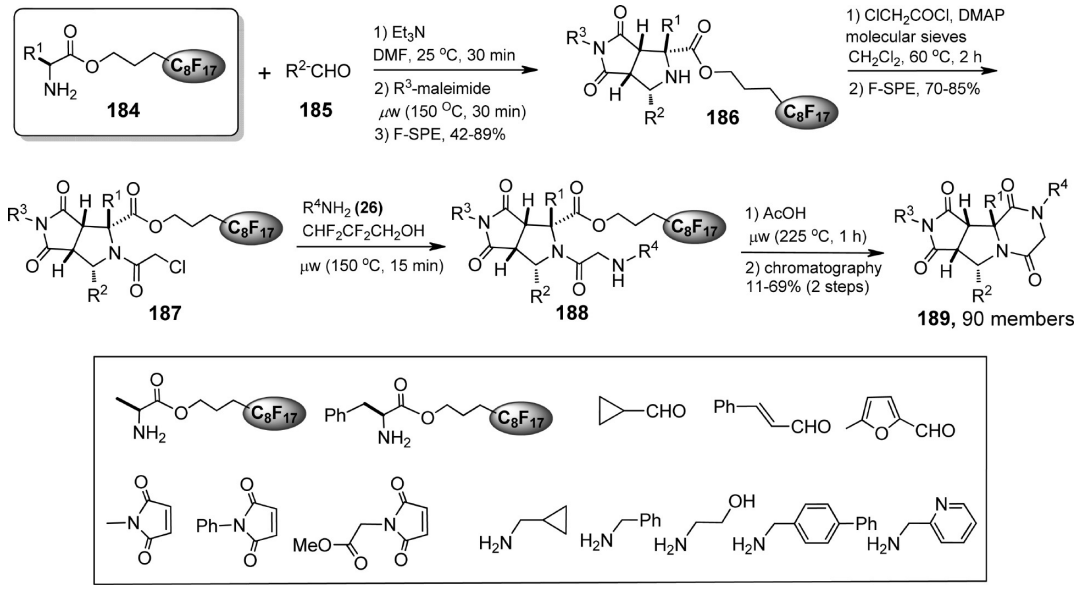


Figure 17. Fluorous synthesis of tricyclic library.[328]

reaction with 4-phenyl-[*1*,*2*,*4*]-triazole-3,5-dione **169** to afford **170** as a single diastereomer. The removal of the *o*-nitrophenylsulfonyl (Ns) group from **170**, followed by the reaction with an isocyanate gave urea **171**. Finally, the fluorous linker was removed by the treatment of 3% TFA to afford product **165**. In this multistep synthesis, all the

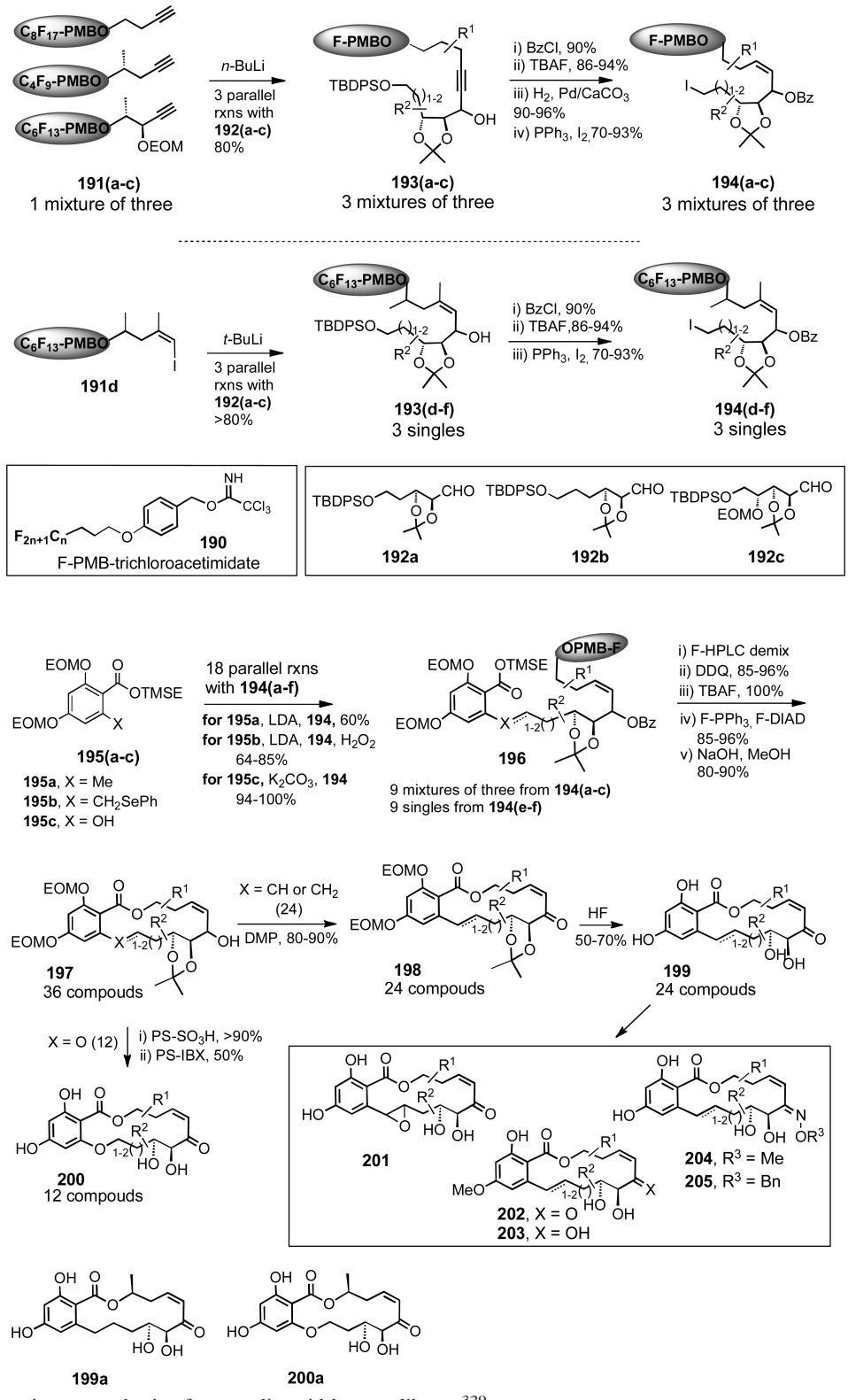


Figure 18. Fluorous mixture synthesis of resorcylic acid lactone library.[329]

intermediates and the final product were isolated from the reaction mixture by F-SPE.

Displaceable Fluorous Isonitrile Linker[327]

Isonitriles are versatile reagents for organic reactions. However, their synthetic advantages are offset by the notorious odor associated with conventional isonitriles. The Pirrung group developed a new process using base-promoted ring-opening of oxazoles to produce aromatic isonitriles that no longer have the unpleasant odors.[228] During the reaction process a fluorous sulfonate group could be introduced to form a fluorous linker. The utility of the displaceable fluorous isonitrile has been demonstrated in the multistep synthesis involving Ugi four-component reaction (U-4CR) and metal catalyst-promoted linker cleavage reactions. Freshly prepared isonitrile **172**

was used as the limiting agent for the Ugi reaction to form **173** (Figure 15). This intermediate was then subject to different coupling reactions to remove the fluorous linker and also to introduce a new functional group to the Ugi condensation product. The developed post-Ugi reactions included Suzuki coupling to form product **174**, Sonogashira reaction to form compound **175**, and Stille coupling to form compound **176**. The protocol is suitable for diversity-oriented synthesis of compound libraries since four substitution groups can be introduced during the Ugi reactions and different linker cleavage reactions could lead to an array of scaffolds.

Fluorous Synthesis of 1,4-Benzodiazepine-2,5-dione Library[327]

In the solution-phase parallel synthesis of a 1,4-benzodiazepine-2,5-dione library, the Yang group developed a new U-4CR using fluorous benzaldehydes instead of fluorous isonitriles (Figure 16) as the displaceable linker.[327] The library synthesis was accomplished in three reaction steps. At the first step of the Ugi reactions, fluorous benzaldehydes **177** were used as the limiting agent to react with Boc-anthranilic acids **182,** amino esters **178**, and cyclohexyl isonitrile **180**. After F-SPE purification, Ugi products **181** were used for the second step of acetyl chloride-promoted de-Boc/cyclizations to form 1,4-benzodiazepine-2,5-diones **179**. The cyclization reactions were selective and only attacked the ester group to form the seven-membered ring. The last step Suzuki reactions were carried out under microwave heating to cleave the fluorous sulfonyl group and introduce the biaryl functional group to form products **183**. The Yang group also used 2-nitrobenzoic acids as anthranilic acid alternatives for the U-4CRs. A demonstration library of 36 analogs was produced with building blocks R^1-R^4 variants.

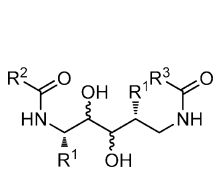
Fluorous Synthesis of Piperazinedione-Fused Tricyclic Compound Library[328]

Fluorous amino esters are useful linkers for library synthesis. In a joint work conducted by the Werner and the Zhang groups, fluorous amino esters **184** were used for solution-phase parallel synthesis of novel piperazinedione-fused tricyclic library compounds **189** (Figure 17).[328] The compounds are structurally similar to the tricyclic thrombin inhibitors and diketopiperazine-based inhibitors of human hormone-sensitive lipase. At the first library synthesis step, azomethine ylides generated from **184** and aldehydes **185** underwent microwave-assisted 1,3-dipolar cycloadditions with maleimides to form **186** in stereoselective fashion. The adducts were treated with chloroacetyl chloride to afford N-acylated products **187**. The chloro group of **187** was displaced with amines to afford **188**. The last step was the microwave-promoted cyclizations to cleave the fluorous linker and generate the piperazinedione ring. The final products were purified by HPLC to ensure >95% purities. Library **189** containing 90 compounds was synthesized with assorted building blocks for R^1-R^4.

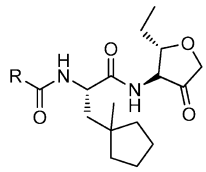
Fluorous Mixture Synthesis of Natural Product Resorcylic Acid Lactone (RAL) Library[329]

Natural resorcylic acid lactones (RAL) containing a *cis*-enone moiety, such as radicicol A, L-783277, and LL-Z1640-2, are known to be potent and irreversible kinase inhibitors. For QSAR studies, the Winssinger group developed a fluorous mixture synthesis (FMS) method based on the previously reported fluorous total synthesis of radicicol A and synthesized a compound library containing 51 analogs (Figure 18).[329] In the FMS, three propargyl alcohols were used each attached to a different *p*-methoxybenzyl (PMB) linker by reacting with F-PMB-trichloroacetimidates **190** to form **191(a−c)** (Figure 18). The equimolar mixture of **191(a−c)** was split to three portions and each reacted with one of three aldehydes **192(a−c)** to afford 3 mixtures of **193(a−c)**. After sequential hydroxyl group protection, TBDPS deprotection, and iodination, compounds **193(a−c)** were converted to 3 mixtures of **194(a−c)** each containing three components. Through a similar pathway, compound **191d** reacted with aldehydes **192(a−c)** to afford compounds **194(d−f)**. The second stage of FMS involved the reaction of three compounds of **195(a−c)** with each of 6 compounds of **194(a−f)** to afford compounds **196**. Among the 18 pools of **196**, 9 are three-component mixtures generated from **194(a−c)** and 9 are single compounds generated from **194(d−f)**. At this point, those 9 three-component mixtures were demixed on HPLC with a fluorous column to afford 27 individual compounds of **196**. These 27 compound and another 9 compounds of **196** generated from **194(e−f)** were treated with DDQ and TBAF to remove both the fluorous linker and the TMSE group. The macrocyclization reactions were promoted by Mitsunobu reaction conditions using fluorous PPh_3 and DIAD. The fluorous derivatives were easily removed from the reaction mixture by F-SPE. The treatment of NaOH removed the Bz group to afford total of 36 macrocyclic compounds **197**. Among them, 24 (X = CH or CH_2) were treated with DMP followed by HF to afford products **199**. Another 12 of **197** were treated with PS-SO_3H and PS-IBX to afford products **200**. Compounds **199** and **200** can be converted to **201−205** through simple transformations to afford a total of 51 macrocyclic compounds. A subset of 28 representative library compounds was assayed against a panel of 19 kinases representing those bearing the adequately positioned cysteine residue, bearing a cysteine residue at a different position within the ATP binding pocket, and those that do not bear a cysteine residue. The screening results indicated that there is very little difference in relative selectivity of kinase inhibition throughout the library compounds. VEGF-R2 is the most highly inhibited kinase followed by PDGFR-α, VEGR-R3, Flt3, VEGF-R1, MEK1 SESE, and KIT. Two representative compounds **199a** and **200a** were evaluated in a larger panel of 402 kinases and also evaluated against a series of mutations of Fli3 and KIT. The screening results provided valuable QSAR information and also led to the identification of several potent inhibitors of multiple oncogenic kinases.

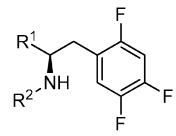
Table 1. Chemical Libraries Targeting Proteases[a]



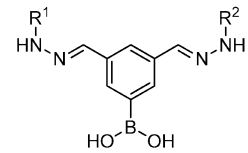
• Shi [265]
• HIV-1 aspartyl protease inhibitors



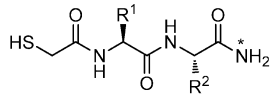
• Ayesa [14]
• cathepsin S cysteine protease inhibitors



• Benbow [20]
• dipeptidyl peptidase-IV (DPP-IV) serine protease inhibitors



• Mugherli [206]
• HCN NS3/4A serine protease

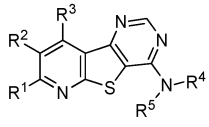


• Cathcart [30]
• pseudomonas elastase (metallo protease) inhibitors (Pseudolysin or LasB)

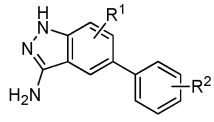
[a] Asterisk is the point of attachment to resin.

Table 2. Chemical Libraries Targeting Nonproteolytic Enzymes[a]

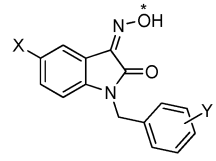
Kinases and Phosphatases



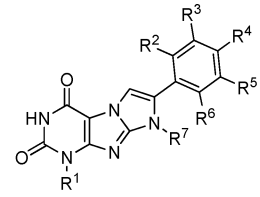
• Zhao [314]
• Cdc7 kinase inhibitors



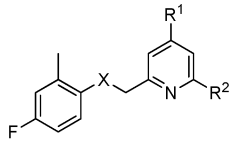
• Antonysamy [12]
• JAK-2 inhibitors



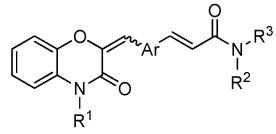
• Cao [29]
• JNK3 MAP kinase inhibitors



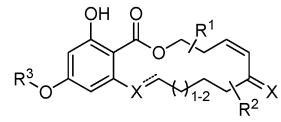
• Lefleur [155]
• inhibitors of the tyrosine kinase erythropoietin producing human hepatocellular carcinoma receptor B4 (EphB4)



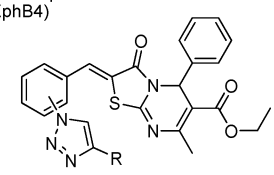
• Cherian [38]
• phosphatidylinositol 3-OH kinase (P13K) inhibitors



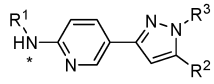
• Honda [105]
• vascular endothelial growth factor receptor 2 tyrosine kinase (KDR) inhibitors



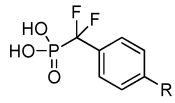
• Jogireddy [329]
• VEGF-R2 kinase inhibitors (activity profiled against 402 kinases)



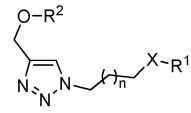
• Duval [62]
• CDC25 phosphatase inhibitors



• Annis [11]
• lipid phosphatase SHIP2 inhibitors

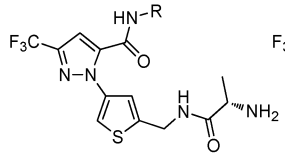


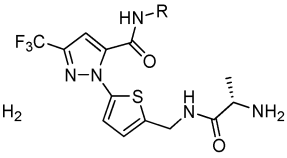
• Rawls [239]
• *Mycobacterium tuberculosis* protein tyrosine phosphatase PtpA inhibitors



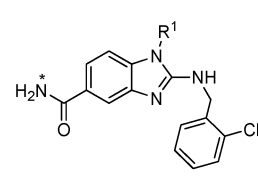
• Tan [281]
• *Mycobacterium tuberculosis* protein tyrosine phosphatase B (MptpB) inhibitors

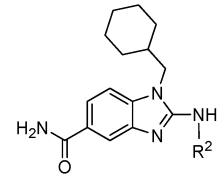
Other targets



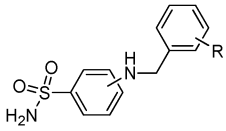


• Allan [9]
• inhibitors of co-activator associated arginine methyltransferase 1 (CARM1)

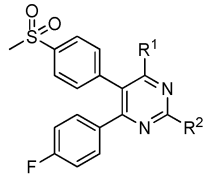




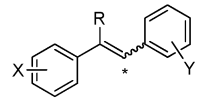
• Cheng [34]
• bacterial biotin carboxylase (AccC) inhibitors



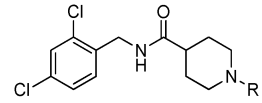
• Nasr [210]
• carbonic anhydrase II inhibitors



• Beswick [21]
• cyclooxygenase-2 (COX-2) inhibitors

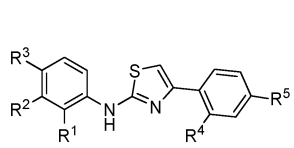


• Kang [132]
• COX-1, COX-2 and NF-κB inhibitors

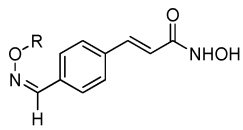


• Xie [300]
• soluble epoxide hydrolase inhibitors

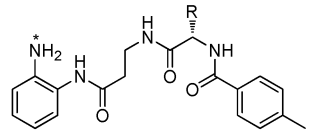
Table 2. Continued



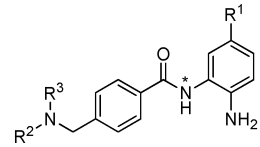
• Heng [99]
• fructose 1,6-bisphosphatase allosteric inhibitors



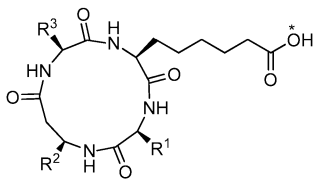
• Giannini [79]
• histone deacetylase (HDAC) inhibitors



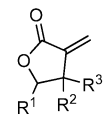
• Hu [106]
• histone deacetylase (HDAC1 and HDAC3) inhibitors



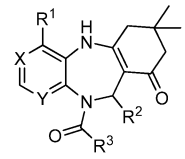
• Kattar [134]
• selective HDAC1/HDAC2 inhibitors



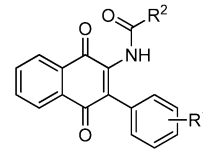
• Olsen [217]
• class II histone deacetylase (HDAC) inhibitors



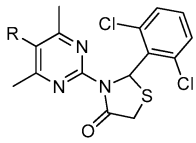
• Elford [70]
• *Haemophilus influenzae* homoserine transacetylase (HTA) inhibitors



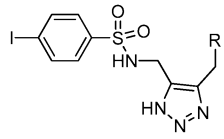
• Mcgowan [185]
• HCV NS5B polymerase inhibitors



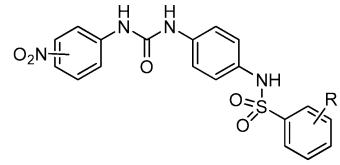
• Hadden [91]
• heat shock proteins (Hsp90) inhibitors



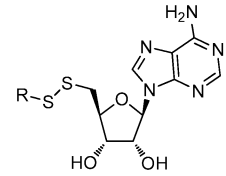
• Chen [33]
• HIV-1 reverse transcriptases inhibitors



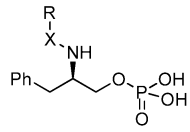
• Minond [197]
• VIM-2 ambler class B metallo -β-lactamase (MBL) inhibitors



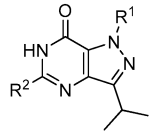
• Moro [202]
• nicotinamide adenine dinucleotide (NAD) synthetase inhibitors



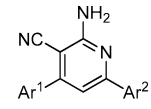
• Scott [258]
• *Mycobacterium tuberculosis* pantothenate synthetase inhibitors



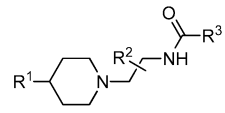
• Guo [90]
• human Pin 1 (Protein Interacting with NIMA) inhibitors



• DeNinno [52]
• phosphodiesterase 9 (PDE9) inhibitors



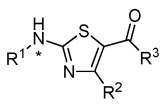
• Abadi [2]
• phosphodiesterase 3 inhibitors



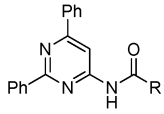
• Scott [259]
• isoform-selective phospholipase D inhibitors

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

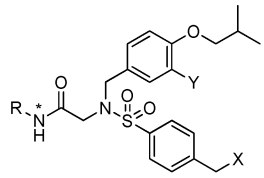
Table 3. Chemical Libraries Targeting G-Protein Coupled Receptors[a]



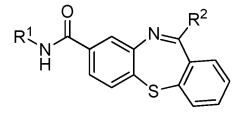
• Cole [45]
• adenosine A_{2A} receptor antagonists



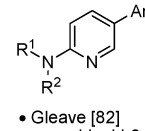
• Yaziji [304]
• A_3 adenosine receptor antagonists



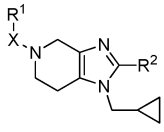
• Cole [44]
• bradykinin B1 receptor antagonists



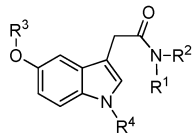
• Petterson [226]
• cannabinoid-1 (CB_1) receptor inverse agonists



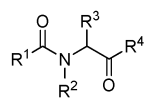
• Gleave [82]
• cannabinoid-2 (CB_2) agonists



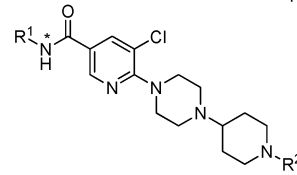
• Ryckmans [249]
• CB_2 agonists



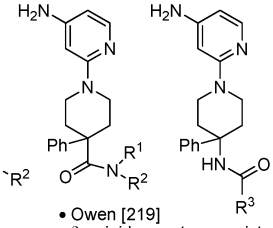
• Pasquini [222]
• cannabinoid-2 (CB_2) receptor ligands



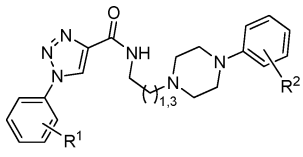
• Sanganee [252]
• human recombinant C5a receptor (C5aR) antagonists



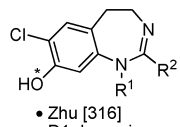
• McGuinness [186]
• CXCR3 antagonists



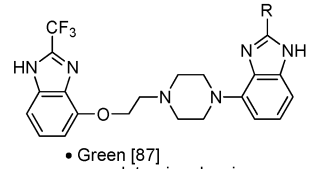
• Owen [219]
• δ-opioid receptor agonists



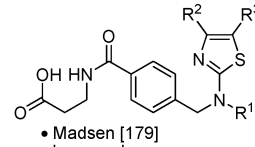
• Loaiza [175]
• dopamine D3 receptor ligands



• Zhu [316]
• D1 dopamine antagonists

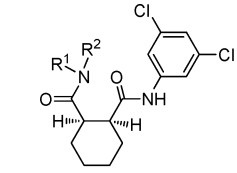


• Green [87]
• gonadotropin releasing hormone antagonists

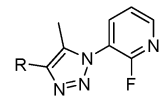


• Madsen [179]
• human glucagon receptor antagonists

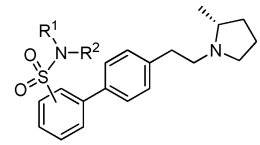
Table 3. Continued



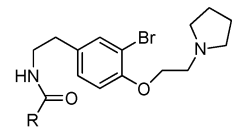
• Williams [297]
• positive allosteric modulator of the metabotropic glutamate receptor 4 (mGluR4)



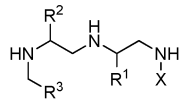
• Ito [117]
• metabotropic glutamate receptor 1 antagonists



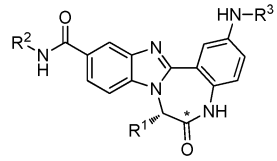
• Covel [47]
• histamine H_3 receptor inverse agonists



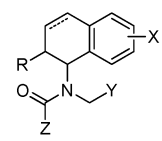
• Kennedy [136]
• H_3 antagonists



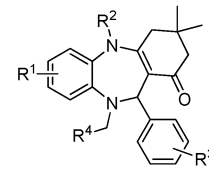
• Yongye [309]
• κ-opioid receptor ligands



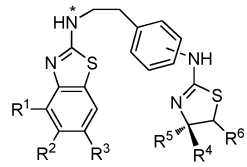
• Malik [181]
• mas-related G-protein coupled receptor (MrgX1, MrgX2) agonists



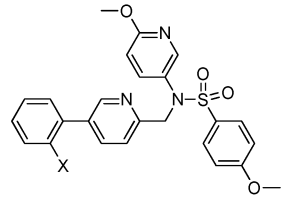
• Dockendorff [58]
• μ-opioid receptor agonists/antagonists



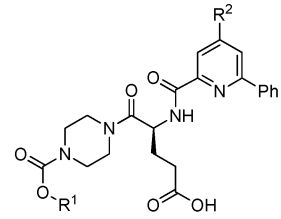
• Fu [75]
• neuromedin B receptor antagonists



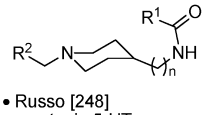
• Sun [280]
• NPY Y_1 receptor antagonists



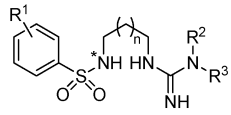
• Barton [18]
• oxytocin antagonists



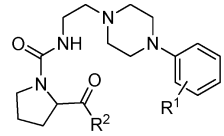
• Parlow [221]
• $P2Y_{12}$ antagonists



• Russo [248]
• serotonin 5-HT_4 receptor (5-HT_4R) agonists



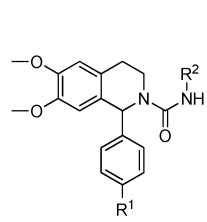
• Zajdel {311]
• 5-HT_7 receptor ligands



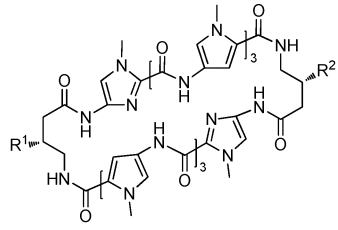
• Zajdel [310]
• 5-HT_{1A} and 5-HT_{2A} receptor ligands

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

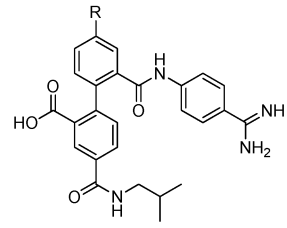
Table 4. Chemical Libraries Targeting Non-G-Protein-Coupled Receptors[a]



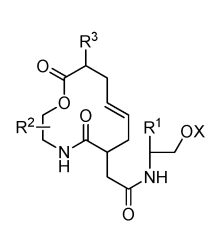
• Gitto [80]
• anticonvulsant activity



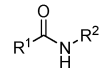
• Chenoweth [37]
• DNA binding agents regulating the expression of AR target genes in cell culture



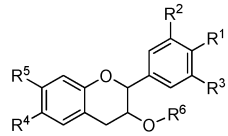
• Kotian [143]
• selective inhibitors of tissue factor FVIIa complex



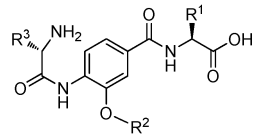
• Peng [224]
• inhibit Shh signaling at the ShhN level



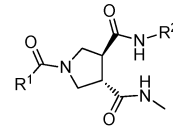
• McNaughton [187]
• activators of melanogenesis



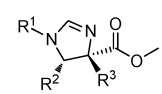
• Mewett [195]
• positive modulators of $GABA_A$ receptors



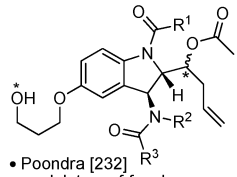
• Shaginian [263]
• MDM2/p53 binding α-helix mimetics



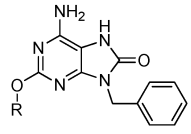
• Shi [266]
• inhibitors of Myc/Max dimerization and Myc-induced cell transformation



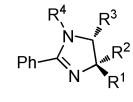
• Srivastava [277]
• MDM2/p53 protein-protein antagonists



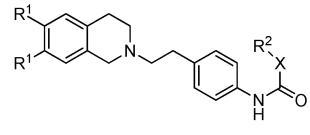
• Poondra [232]
• modulators of focal adhesion kinase (FAK)-mediated signaling pathways



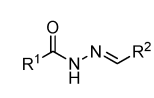
• Weterings [293]
• toll-like receptor 7 (TLR7) agonists inducing dendritic cell maturation



• Kahlon [131]
• nuclear transcription factor-κB mediated IL-6 production inhibitors

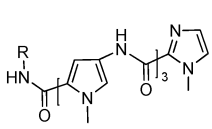


• Klinkhammer [139]
• P-glycoprotein (P-gp) inhibitors

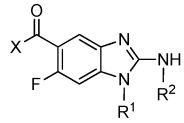


• Kim [138]
• estrogen-related receptor γ agonists

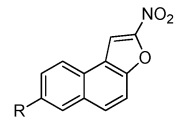
Table 4. Continued



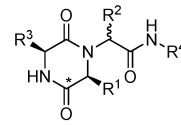
• Chenoweth [36]
• pyrrole-imidazole polyamides as DNA-binding molecules



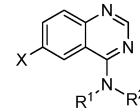
• Lahue [156]
• human kinesin spindle protein (*h*KSP) inhibitors



• Guevel [158]
• regulators of the nuclear receptor HNF4α

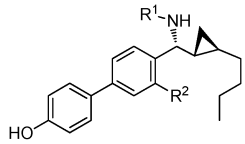


• Campbell [28]
• luminescence inhibitors in the bacterial symbiont *Vibrio fischeri*

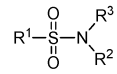


• Rinderspacher [241]
• inhibitors of Huntingtin protein aggregation in a cell-based assay

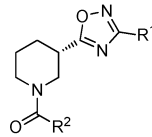
• Wang [286]
• modulation of the dynamics of the M2 proton channel from influenza A virus



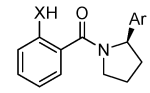
• Sarachine [255]
• estrogen receptors (ERs) ligands



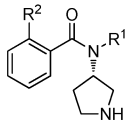
• Ko [140]
• inducers of abnormal heart development in zebrafish



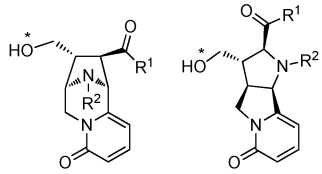
• Engers [71]
• mGluR5 ago-potentiator



• Cho-Schultz [41]
• Hsp90 inhibitors



• Fish [73]
• noradrenaline reuptake inhibitors

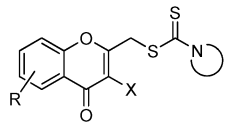


• Marcaurelle [182]
• anti-apoptotic protein Bcl-2 inhibitors

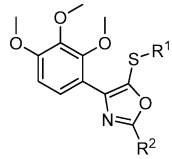
[a] Asterisk is the point of attachment to resin.

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

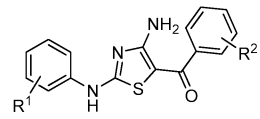
Cytotoxic agents



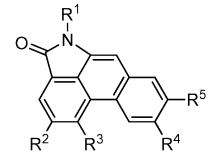
• Huang [109]
• arrest the cell cycle of SW-480 and MDA-MB-435s both in G_2/M phase



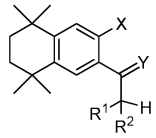
• Liu [174]
• antiproliferative activity against PC-3 cells



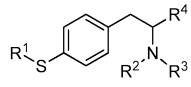
• Romagnoli [244]
• arrest of HeLa cells in the G2/M phase of the cell cycle and induction of apoptosis



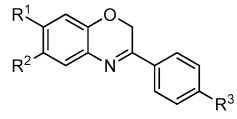
• Choi [40]
• antitumor activities against a broad array of cancer cell lines



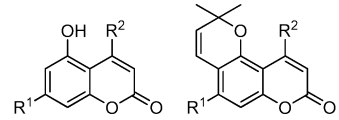
• Nakamura [209]
• adult T-cell leukemia cell-selective proliferation inhibitors



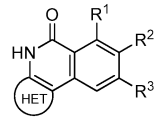
• Cloonan [42]
• antitumor effects in lymphoma, leukaemia and breast cancer cell lines



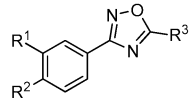
• Das [49]
• inhibitors of hypoxic cancer cell growth



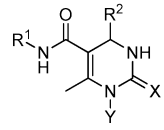
• Mao [183]
• antiproliferative activities against breast cancer cells MCF-7 and MDA-MB-231



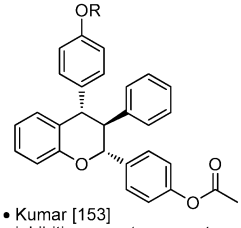
• Xiang [299]
• tumor cell growth inhibitors



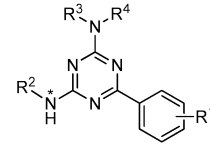
• Kumar [151]
• cytotoxic against prostate cancer cell lines



• Kumar [150]
• cytotoxic activity against MCF-7 human breast cancer cells

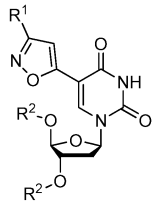


• Kumar [153]
• inhibition as estrogen antagonistic activity and cytotoxic activity against MDA-MB-231 cell line

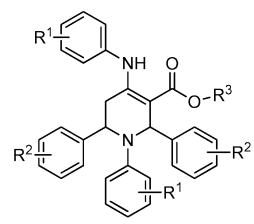


• Hu [107]
• antiproliferative activities against K562, PC-3 and HO8910 cell lines

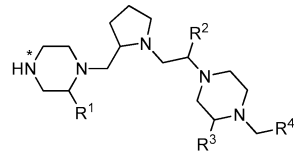
Antiinfective agents



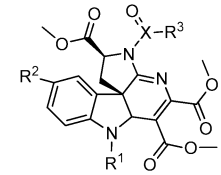
• Lee [165]
• activity against herpes simplex viruses 1 and 2, Encephalomyocarditis virus, Coxsackie B3 and vesicular stomatitis virus



• Misra [198]
• *Plasmodium falciparum* growth inhibitors

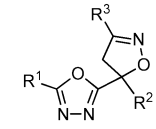


• Nefzi [211]
• *Mycobacterium tuberculosis* strain $H_{37}R_V$ growth inhibitors

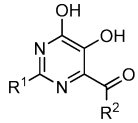


• Wei [292]
• block production of infectious hepatitis C virus in hepatoma cells

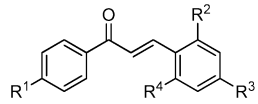
Table 5. Continued



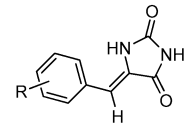
• Milinkevich [196]
• fungicidal activity



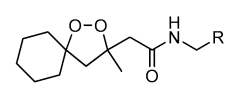
• Boyd [25]
• paramyxovirus inhibitors



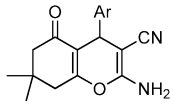
• Montes-Avila [201]
• in vitro antiparasitic activity against *Giardia lamblia*



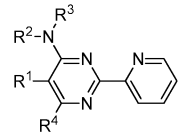
• Mudit [205]
• in vitro anti-growth and anti-invasive properties against PC-3M prostate cancer cells



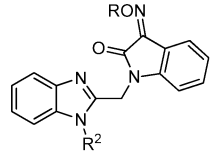
• Martyn [184]
• *Plasmodium falciparum* growth inhibitors



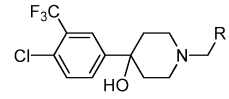
• Kumar [152]
• *E. coli* growth inhibitors



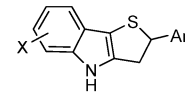
• Musonda [208]
• inhibitors of *Leishmania donovani* parasite development in vitro



• Sin [269]
• respiratory syncytial virus fusion inhibitors



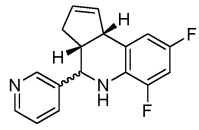
• Sun [279]
• anti-tuberculosis activity



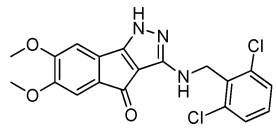
• Karthikeyan [133]
• *Mycobacterium tuberculosis* $H_{37}R_V$ and multi-drug resistant *M. tuberculosis* growth inhibitors

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

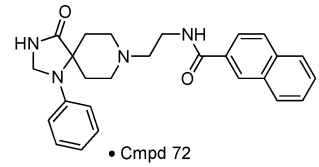
Table 6. Selected Molecular Probes



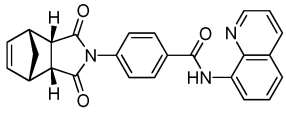
• Golgicide A
• Washington University School of Medicine
• Sáenz [332]
• cis-Golgi ArfGEF GBF1 inhibitor



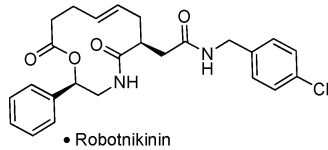
• Cmpd 27
• Johnson and Johnson
• Rosen [333]
• HRI kinase inhibitor



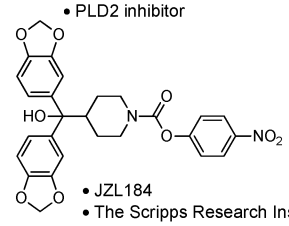
• Cmpd 72
• Vanderbilt University School of Medicine
• Scott [334]
• PLD2 inhibitor



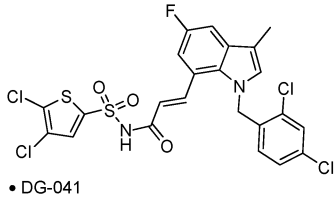
• IWR-1-endo
• UT Southwestern Medical Center
• Chen [335]
• Suppressor of Wnt/β-catenin pathway



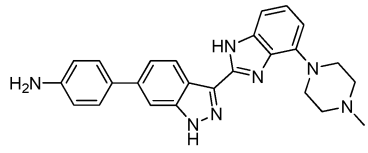
• Robotnikinin
• Broad Institute of Harvard and MIT
• Stanton [336]
• ShhN binding agent and signaling inhibitor



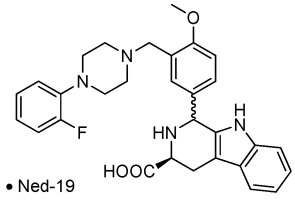
• JZL184
• The Scripps Research Institute
• Long [337]
• Monoacylglycerol lipase inhibitor



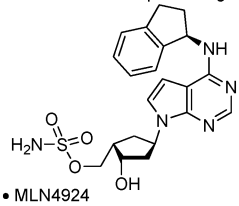
• DG-041
• deCODE Chemistry
• Singh [338]
• Platelet EP3 receptor antagonist



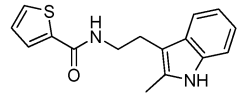
• Cmpd 9
• Pfizer Global Research and Development
• Trujillo [339]
• Protein kinase c-zeta inhibitor



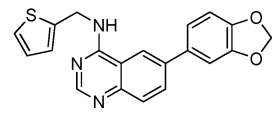
• Ned-19
• University of Oxford
• Naylor [340]
• NAADP signaling inhibitor



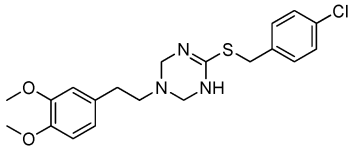
• MLN4924
• Millennium Pharmaceuticals
• Soucy [341]
• NEDD8-activating enzyme inhibitor



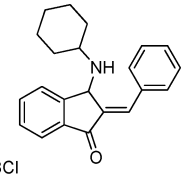
• CK-636
• Yale University
• Nolen [342]
• Arp2/3 complex inhibitor



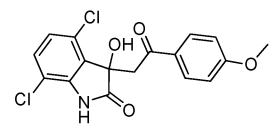
• Cmpd 4
• NIH Chemical Genomics Center
• Mott [343]
• Clk1, Clk4 and Dyrk1A inhibitor



• MAC13243
• McMaster University
• Pathania [344]
• LolA function inhibitor

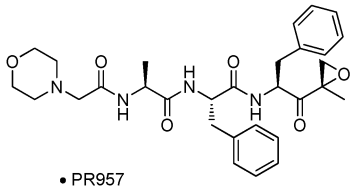


• BCI
• University of Pittsburgh
• Molina [345]
• Dusp6 inhibitor

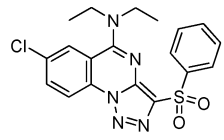


• YK-4-279
• Georgetown University
• Erkizan [346]
• RHA/EWS-FLI1 binding inhibitor

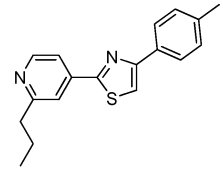
Table 6. Continued



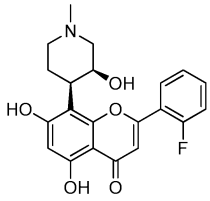
• PR957
• Proteoliz, Inc
• Muchamuel [347]
• LMP7 inhibitor



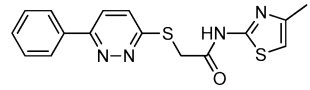
• 1835F03
• Harvard Medical School
• Swoboda [348]
• Teichoic acid biosynthesis inhibitor



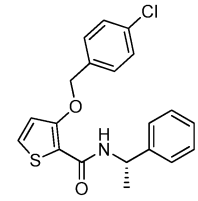
• Fatostatin
• Kyoto University and Baylor College of Medicine
• Kamisuki [349]
• inhibitor of SREBP activation



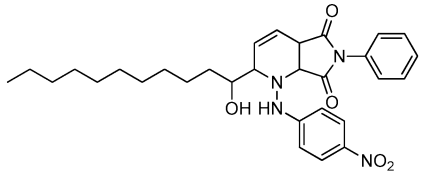
• Cmpd 12d
• University of Massachusetts Medical School
• Ali [350]
• selective P-TEFb inhibitor



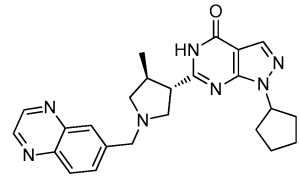
• Cmpd 6l
• Vanderbilt University School of Medicine
• Delpire [351]
• KCC2 inhibitor



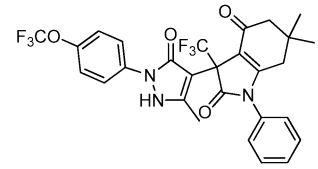
• AS1949490
• Astellas Pharma
• Suwa [352]
• SHIP2 inhibitor



• A12B4C3
• Cross Cancer Institute
• Freschauf [353]
• hPNKP inhibitor



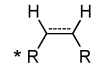
• Cmpd 19
• Pfizer Global Research and Development
• Verhoest [354]
• PDE9A inhibitor



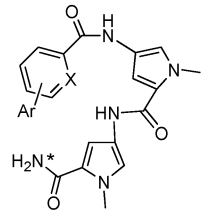
• Cmpd 37
• Tsukuba Research Institute
• Takahashi [355]
• ELOVL6 inhibitor

Table 7. Scaffold Derivatization and Acyclic Synthesis[a]

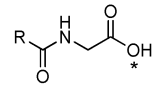
Solid-phase



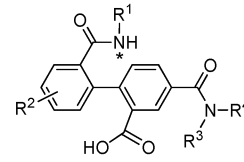
• Dickson [55]
• reduction of solid-supported olefins and alkynes



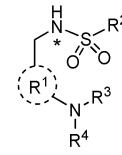
• Brucoli [26]
• multistep sequence on SynPhase Lanterns



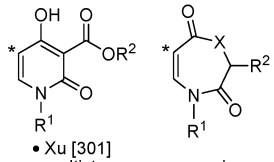
• Perez-Pineiro [225]
• coupling reaction between glycine-preloaded Wang resin and carboxylic acids



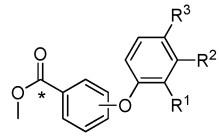
• Shi [267]
• multistep sequence



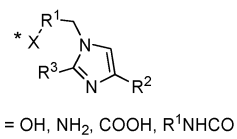
• Torr [284]
• multistep sequence



• Xu [301]
• multistep sequence using organoselenium resins

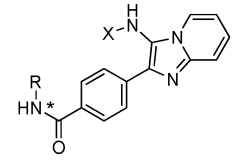


• Jung [130]
• Cu-catalyzed coupling of resin - bound phenols or arylhalides

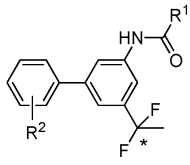


X = OH, NH_2, COOH, R^1NHCO

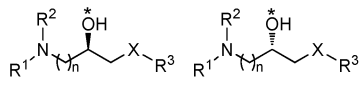
• Koci [141]
• from resin-bound α-acylamino ketones



• Sandulenko [251]
• resin-assisted derivatization of 4-[3-(trifluoroacetylamino)imidazo-[1,2-α]pyridin-2-yl]benzoic acid



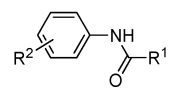
• Wiehn [294]
• ketones immobilized on dithiane linker, derivatization then fluorination cleavage



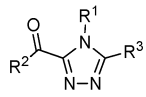
• Roberge [242]
• multistep sequence from resin-bound triol

Table 7. Continued

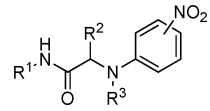
Solution-phase



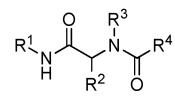
• Colombo [46]
• MW-assisted synthesis of amides bearing strong electon-withdrawing group substituted anilines



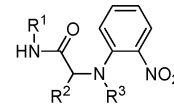
• El Kaim [68]
• three-component Nef-Huisgen reaction



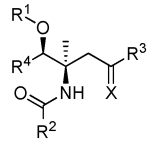
• El Kaim [67]
• Ugi-Smiles coupling with *in situ* generated isocyanides



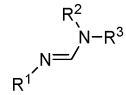
• El Kaim [66]
• Ugi reactions with in *situ* prepared isocyanides



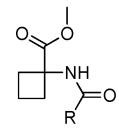
• El Kaim [65]
• 3-CR Ugi-Smiles couplings of cyclic imines



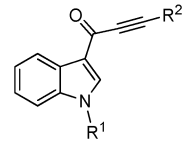
• DeBenedetto [51]
• hydrozirconation of nitriles, acylation then reaction with π-nucleophiles in the presence of Lewis acids



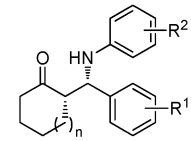
• Porcheddu [233]
• coupling of *N,N*-dimethyl-formamide dimethylacetal and primary amines



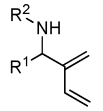
• Pirrung [229]
• Ugi reactions of cyclobutanone



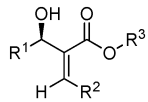
• Merkul [193]
• consecutive 3-CR synthesis of Ynones by decarbonylative Sonogashira coupling



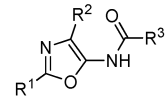
• Mukhopadhyay [207]
• boric acid and glycerol catalysed 3-CR Mannich reaction of RCHO, $ArNH_2$ and cyclic ketones



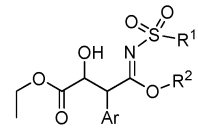
• Seomoon [261]
• 3-CR of aldehydes, amines and organo-indium reagents



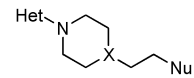
• Senapati [260]
• 3-CR of RCHO, 2-alkynylesters and iodine then cross coupling



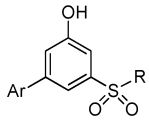
• Thompson [283]
• derivatization of 5-amino-oxazoles



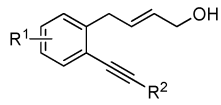
• Yoo [308]
• 4-CR of ethyl glyoxylates, aryl acetylenes, sulfonyl azides and alcohols using a copper catalyst



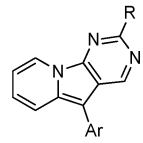
• Wang [285]
• *N*-arylation/dealkylation of electron-deficient heteroaryl chlorides and bicyclic tertiary amines under MW irradiation



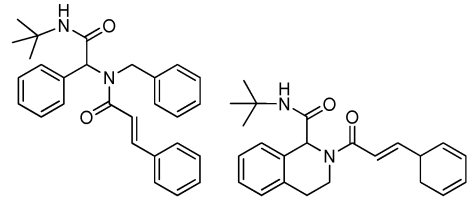
• Jeges [123]
• multistep reaction sequence



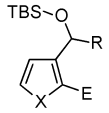
• Jeganmohan [122]
• 3-CR of benzynes, allylic epoxides and terminal alkynes



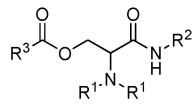
• Jiang [129]
• Pd catalyzed direct arylation of 2/9-substituted pyrimido[5,4-*b*]indolizines



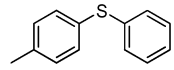
• Jiang [128]
• oxidative Ugi-type reactions with singlet oxygen



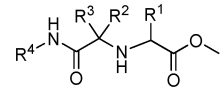
• Devarie-Baez [54]
• multicomponent type II anion Relay Chemistry (ARC) mediated by a solvent-controled $C(sp^2)$-O 1,4-brook rearrangement



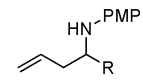
• Mossetti [204]
• Passerini-Ugi hybrid adducts via 4-CR using glycoaldehyde dimer



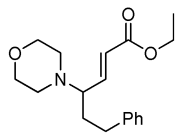
• Ku [147]
• Fe/Cu-cocatalyzed *S*-arylations of thiols with aryl halides



• Wang [285]
• amino acid derived Ugi products with subsequent amidation

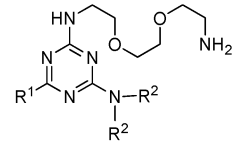


• Grote [88]
• 3-CR of aldehydes, anisidine, and allyl trifluoroacetate

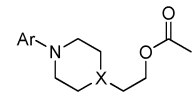


• Kudirka [148]
• Pd-catalyzed insertion of α-diazoesters into vinyl halides

• Gall [157]
• 3-CR Mannich of organic halides, RCHO and amines

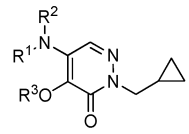


• Lee [162]
• aryl/alkyl triazine captured by a resin-bound amine followed by amination and acidic cleavage

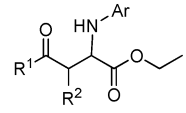


• Gladstone [81]
• 3-CR of electron-deficient aryl halides, and KOAc with either 1,4-diaza-bicyclo[2.2.2]octane or quinuclidine

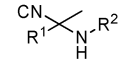
• Gonzalez-Arellano [86]
• MW-assisted *S*-arylation of thiols with aryl iodides using supported metal nanoparticles



• Humphries [115]
• multistep sequence from mucobromic acid

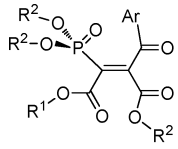
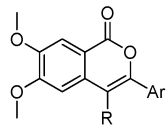
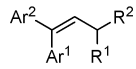
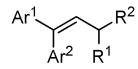
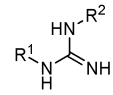
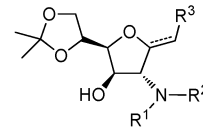


• Izumiseki [118]
• catalytic enantioselective 3-CR Mannich of alkenyl trichloroacetates, ethyl glyoxalates, aniline derivatives and an (*S*)-BINOL-derived chiral tin dibromide



• Jarusiewicz [120]
• 3-CR Strecker of aldehydes/ketones via NHC-amidate Pd(II) catalysis

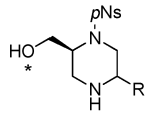
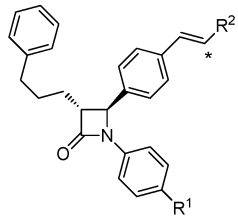
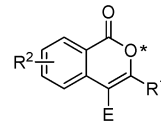
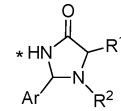
Table 7. Continued

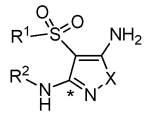
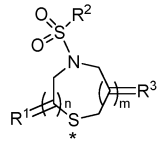
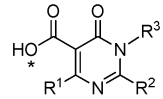
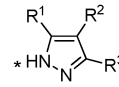
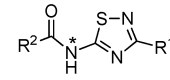
		 		
• Rostamnia [245] • 3-CR of phosphites, acetylenic esters, and aroyl chlorides	• Roy [246] • derivatization of 4-iodoisocoumarins	• Li [168] • acid-catalyzed 3-CR of terminal alkynes, benzylic alcohols, and arenes	• Wang [289] • 'catch and release' two-step one-pot protocol of guanidines from thioureas and amines	• Gomez [83] • 3-CR of amines, boronic acids, and a polyfunctionalized furanose

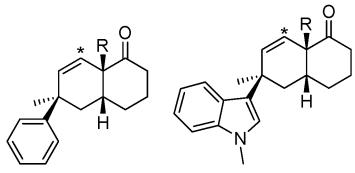
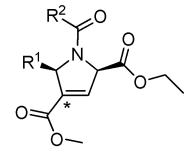
[a] Asterisk is the point of attachment to resin.

Table 8. Monocyclic Synthesis[a]

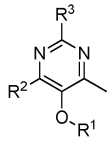
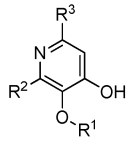
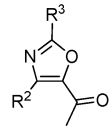
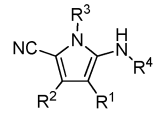
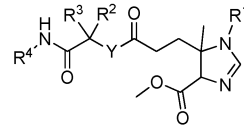
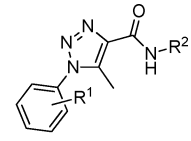
Solid-phase

				
• Ottesen [218] • MW-assisted ring-opening of resin-bound aziridine with 2-amino alcohols then intramolecular cyclization	• Poeylaut-Palena [230] • Staudinger reaction of imines immobilized on a metathesis-cleavable linker	• Peuchmaur [227] • Sonogashira cross-coupling between polymer-bound 2-bromobenzoates and terminal alkynes, then an electrophile-induced halocyclization	• Qin [238] • MW-assisted condensation of an α-amino amide on solid support with aldehydes	

				
• Ma [176] • 3-CR two step "catch and release" from resin-bound sulfonyl intermediate	• Saruta [256] • intramolecular alkylation of sulfides followed by release of desired products from generated sulfonium salts	• Hamper [92] • condensation of resin-bound methylenemalonate with amidines	• Harju [98] • 1,3-dipolar cyclo-addition of resin-bound sydnones with alkynes	• Ryu [250] • multistep sequence from resin-bound carboxamidine thioureas

		
• Yoshida [309] • tetrazole-based traceless linker for Diels-Alder on solid support cleaved by Pd(0), Cu(I) and Ag(I) assisted nucleophilic displacements	• Huang [112] • 1,3-dipolar cycloaddition of resin-bound methyl 2-seleno acrylate with azomethine ylides	

Solution-phase

  				
• Lechel [159] • from alkoxy-substituted enamides starting from lithiated alkoxyallenes, nitriles and carboxylic acids	• Fontaine [74] • consecutive [4+1] reaction cycloaddition of α-imino-nitriles with isocyanides	• Elders [69] • one-pot reaction of up-to eight components by the union of multicomponent reactions	• Pokhodylo [231] • 3-CR of azides, amines, and diketene	

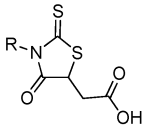
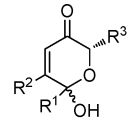
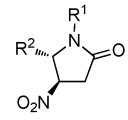
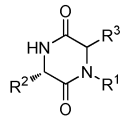
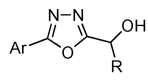
				
• Alizadeh [8] • 3-CR of primary amine, carbon disulfide and fumaryl chloride	• Bagley [16] • MW-assisted barium manganate mediated oxidation of diols	• Borisov [24] • multistep sequence	• Cheng [35] • catalytic asymmetric alkylation of 2-furfurals yields enantio-enriched furyl zinc alkoxides then NBS and water	• Pelletier [223] • nitro-Mannich/ lactamization cascade of nitroester, amine, and aldehyde

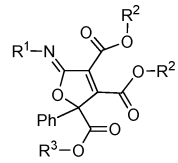
Table 8. Continued



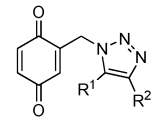
• Rhoden [240]
• one-pot Ugi-4-CR/ deprotection and activation/cyclization



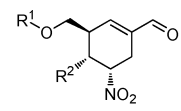
• Adib [3]
• 3-CR of *N*-isocyanimino triphenylphosphorane, RCHO, and ArCOOH



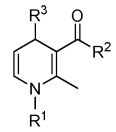
• Esmaeili [7]
• 3-CR of isocyanides, dialkyl acetylenedicarboxylates, and α-ketolactones



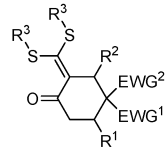
• Algi [6]
• 1,3-dipolarcyclo-addition then oxidation



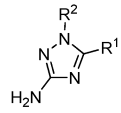
• Zhang [312]
• quadruple domino reaction initiated by oxa-Michael addition of alcohols to acrolein



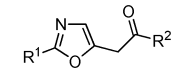
• Maiti [180]
• 4-CR of RNH_2, β-keto esters/ thioesters, α,β-unsaturated aldehydes and alcohols



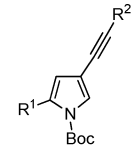
• Ma [177]
• 3-CR of α-alkenoyl ketene *S*,*S*-acetals, aldehydes, and active methylenes



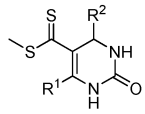
• Meng [189]
• MW-assisted synthesis from carboxylic acids and hydrazines



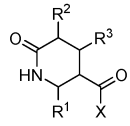
• Merkul [192]
• consecutive 3-CR sequence from propargylamine and acid chlorides then amidation and cross-coupling



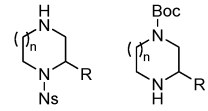
• Merkul [191]
• 3-CR synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation



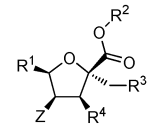
• Mukherjee [270]
• 3-CR Biginelli reaction involving $SnCl_2$-catalyzed cyclocondensation of β-oxodithioesters with aldehydes and urea



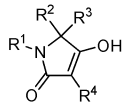
• Zhu [315]
• diene and the cycloaddition in a 4-CR of RCHO, NH_3, acyl chloride and dienophile



• Crestey [48]
• aminolysis of aziridines with amino alcohols and subsequent Fukuyama-Mitsunobu cyclization

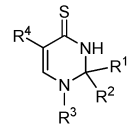


• DeAngelis [50]
• Rh-catalyzed 3-CR of aldehydes, α-alkyl-α-diazo-esters, and dipolarophiles

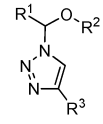


• Spatz [273]
• Ugi-Dieckmann reaction

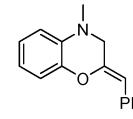
• Wang [287]
• 3-CR of α-halogenated methylene compounds, aromatic aldehydes, and acetonitrile derivatives



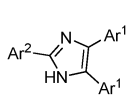
• Wang [290]
• multicomponent coupling of terminal alkynes, elemental sulfur, and carbodiimides



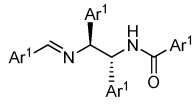
• Yadav [303]
• Cu(OTf)$_2$/Cu-catalyzed 4-CR of R^1CHO, R^2CH_2OH, R^3CCH, $TMSN_3$

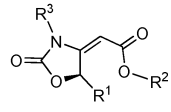


• Xu 302]
• 3-CR of 2-(methylamino)-phenyl-4-methylbenzene-sulfonate, $(CH_2O)_n$, PhCCH then KOH

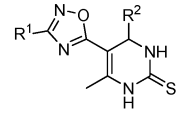


• Jiang [127]
• 4-and 6-component domino reactions

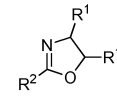




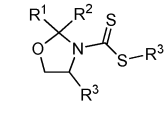
• Kojima [142]
• diethylzinc-mediated asymmetric alkynylation of aldehydes with propiolates in the presence of a chiral ligand; followed by treatment with isocyanates



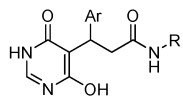
• Kharchenko [137]
• Biginelli-type 3-CR

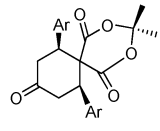


• Kempe [135]
• automated synthesis from nitriles with 2-aminoethanols

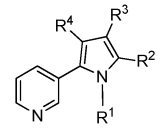


• Han [93]
• 4-CR of aminoethanols, ketones, carbon disulfide, and halides

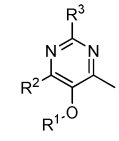




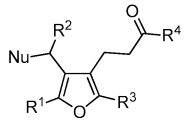
• Hao [96]
• MW-assisted reaction of arylidene-Meldrum's acid, 6-hydroxypyrimidin-4(3*H*)-one, and amines



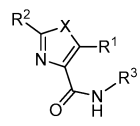
• Harju [97]
• multistep sequence from *N*-acylated amino acids



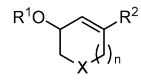
• Lechel [160]
• 3-CR of lithiated alkoxyallenes, nitriles, and carboxylic acids then condensation with ammonium salts



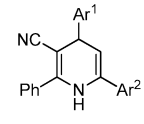
• Liu [193]
• Pd-catalyzed 3-CR domino reactions of 2-(1-alkynyl)-2-alken-1-ones with nucleophiles and vinyl ketones or acrolein



• Sanz-Cervera [254]
• α-amido-β-ketoesters dehydrated to 1,3-oxazoles or reacted with Lawesson's reagent to 1,3-thiazoles

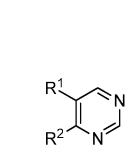


• O'Leary-Steele [322]
• fluorous-tagged "safety catch" linker and ring-closing metathesis

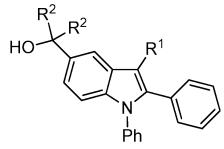


• Jiang [125]
• 4-CR of aldehydes, 3-aryl-3-oxopropanenitrile, 2-acetyl-pyridine, and NH_4OAc

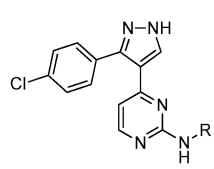
Table 8. Continued

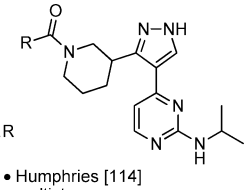


• Sasada [257]
• $ZnCl_2$-catalyzed 3-CR of functionalized enamines, $CH(OEt)_3$, and NH_4OAc

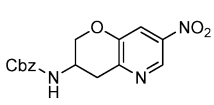


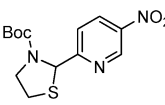
• Worlikar [298]
• Pd/Cu catalyzed coupling of terminal acetylenes with *N*,*N*-dialkyl-*o*-iodoanilines

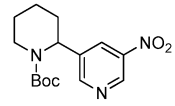




• Humphries [114]
• multistep sequence





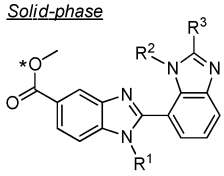


• Henry [110]
• MW-assisted condensation of *N*-carbamate α- and β-amino carbonyl derivatives with 1-methyl-3,5-dinitro-2-pyridone

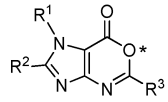
[a] Asterisk is the point of attachment to resin.

Table 9. Bicyclic and Spirocyclic Synthesis[a]

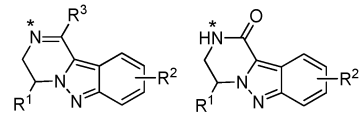
Solid-phase



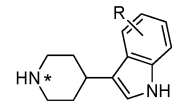
• Chen [32]
• MW-assisted multistep sequence from resin-bound *o*-phenylenediamine



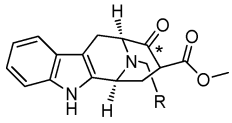
• Che [31]
• MW-assisted multistep sequence



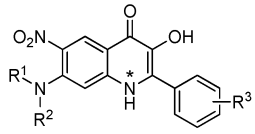
• Pudelova [237]
• traceless solid-phase synthesis from diamines, 2-nitrobenzenesulfonyl chlorides, and bromoketones/bromoacetates



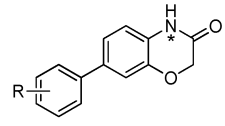
• Mentel [190]
• domino hydroformylation/indole synthesis from resin-bound olefins



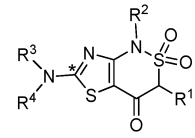
• Wilk [296]
• Pictet-Spengler reaction then diversification



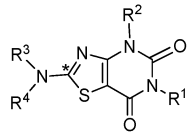
• Krupkova [146]
• multistep sequence from resin-bound 4-chloro-5-nitroanthranilic acid



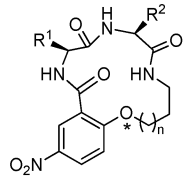
• Lee [161]
• MW-assisted cyclization of resin-bound, *N*-substituted-α-(2-chloro-4-bromophenoxy)-acetamide *via* a Smiles rearrangement followed by Suzuki coupling



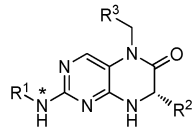
• Lee [163]
• multistep sequence from resin-bound cyano-carbonimidodithioate



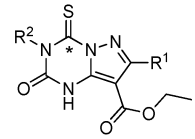
• Lee [164]
• multistep sequence from resin-bound thiazole amino ester



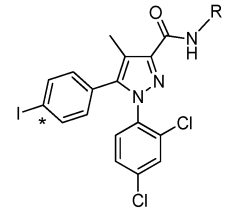
• Li [170]
• cyclic peptidomimetics via "volatilizable" supports



• Metzger [194]
• multistep sequence

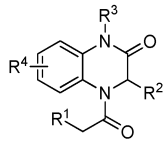


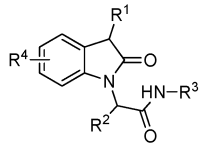
• Gong [85]
• from resin-bound 5-amino-1-dithiocarboxy pyrazoles and aryl isocyanates



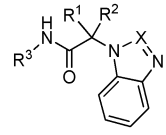
• Spivey [4760]
• multistep sequence using Me_2Ge-linker then *ipso*-iododegermylative cleavage using NaI/NCS

Solution-phase

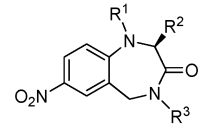




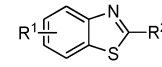
• Erb [72]
• Ugi-Post functionalization from a single set of Ugi-adducts to two distinct heterocycles by MW-assisted Pd-catalyzed cyclization



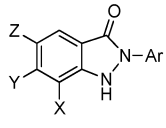
• Coffinier [43]
• Ugi-Smiles couplings of *o*-niyrophenols



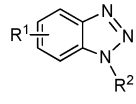
• Deschrijver [53]
• multistep sequence from 2-fluoro-5-nitro-benzaldehyde



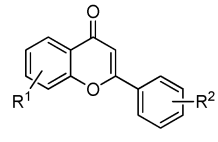
• Ding [56]
• Lawesson's reagent mediated cascade reaction of 2-iodo-anilines with acid chlorides



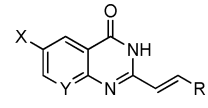
• Dou [61]
• cyclization of nitro-aryl substrates mediated by a low-valent titanium reagent



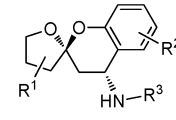
• Ankati [10]
• MW-assisted benzyne-click chemistry



• Awuah [13]
• MW-assisted Sonogashira-carbonylation-annulation

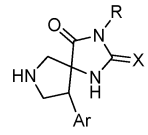


• Baghbanzadeh [15]
• MW-assisted 3-CR of anthranilic acids with acetic anhydride and NH_4OAc

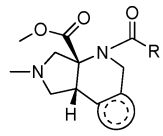


• Barluenga [17]
• Pd-catalyzed multicomponent cascade reaction of alkynols, salicylaldehyde, and amine

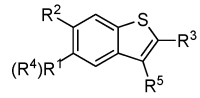
Table 9. Continued



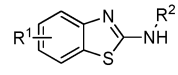
• Blanco-Ania [22]
• multistep sequence



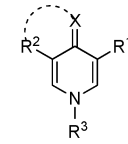
• Blanco-Ania [23]
• multistep sequence



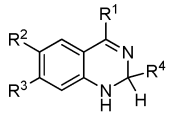
• Cho [39]
• multistep sequence from 3-iodobenzo[*b*]thiophenes



• Ding [57]
• Cu-catalyzed tandem reaction of 2-iodobenzenamine with isothiocyanate



• Baskovc [19]
• cyclization of bis-enaminones and primary amines



• Portela-Cubillo [234]
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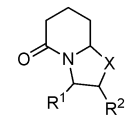

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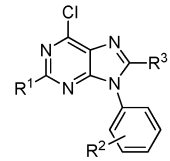

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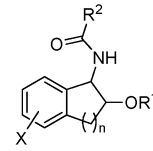

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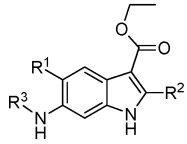

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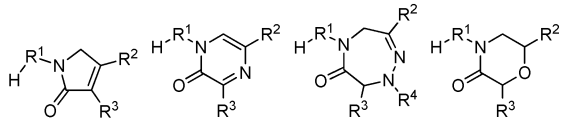

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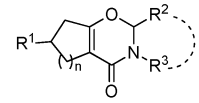

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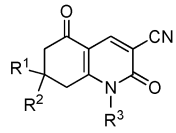

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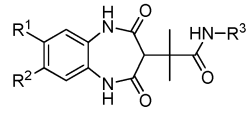

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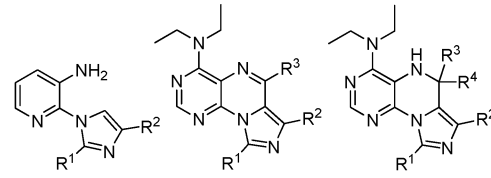

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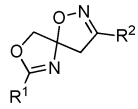

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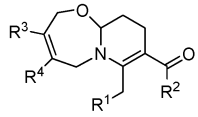

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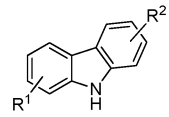

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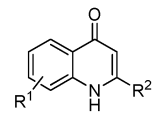

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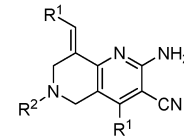

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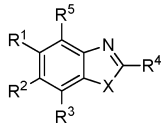

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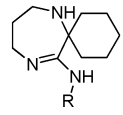

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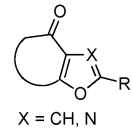

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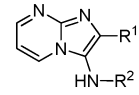

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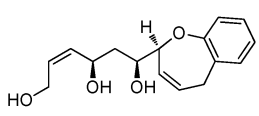

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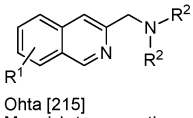

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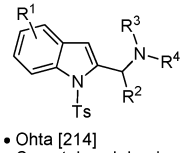

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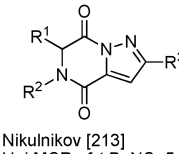

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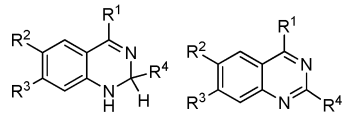
Table 9. Continued



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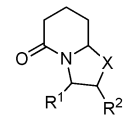

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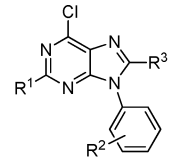

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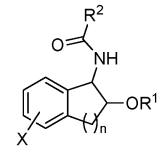

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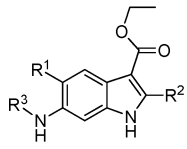

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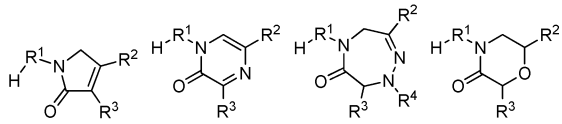

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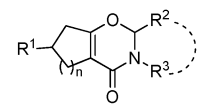

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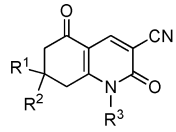

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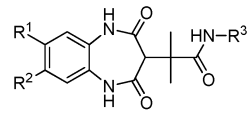

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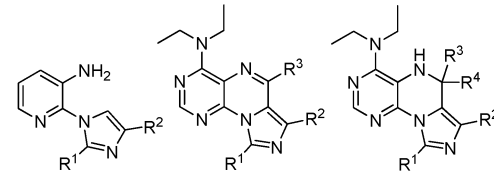

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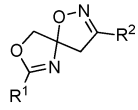

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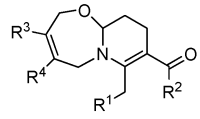

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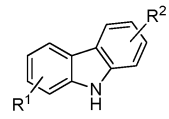

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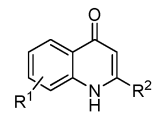

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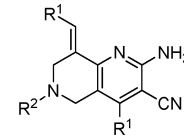

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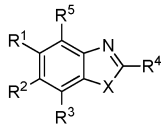

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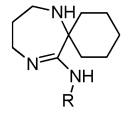

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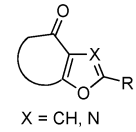

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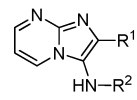

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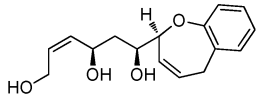

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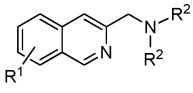

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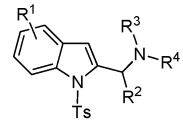
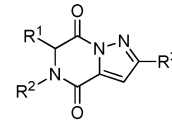
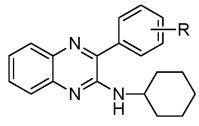


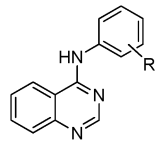
• Ohta [214]
• Cu-catalyzed domino 3-CR coupling-cyclization of 2-ethynylanilines with R^3R^4NH and R^2CHO



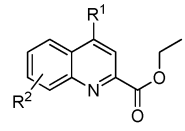
• Nikulnikov [213]
• Ugi MCR of *t*-BuNC, 5-substituted-1*H*-pyrazole-3-carboxylic acids, R^1CHO and R^2NH_2 then cyclization



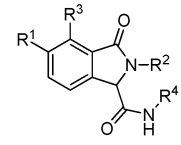
• Heravi [101]
• 3-CR of *o*-phenylenediamine, aromatic aldehydes, and cyclohexyl isocyanide



• Heravi [103]
• 3-CR of 2-amino-benzamide, orthoesters, and substituted anilines

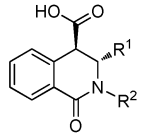


• Huang [108]
• Cu-catalyzed intermolecular addition of alkynes onto imines and subsequent intramolecular ring closure by arylation

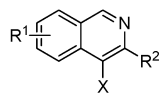


• Huang [111]
• Ugi 4-CR condensation/ Diels-Alder cycloaddition/ deselenization-aromatization sequence

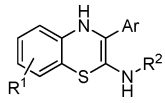
Table 9. Continued



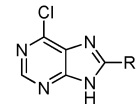
• Humphries [113]
• 3-CR of R^1CHO, R^2NH_2 and homophthalic anhydride



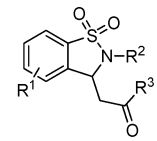
• Yu [306]
• CuX_2-mediated cyclization of 2-alkynylbenzaldehyde *O*-methyl oximes then cross-coupling reactions



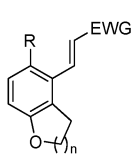
• Heravi [102]
• 3-CR of ArCHO, R^2NC, and *o*-amino thiophenol using PTSA catalyst

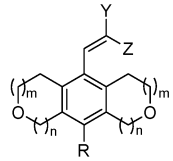


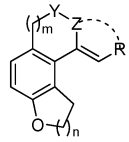
• Ibrahim [116]
• cyclization of 6-chloro-4,5-diaminopyridine with arylcarboxylic acids or chlorides followed by S_NAr with amines and alkoxides or Pd-catalyzed amidations



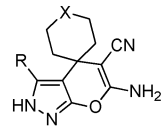
• Rolfe [243]
• 3-CR domino Heck-aza-Michael sequence using functionalized benzylsulfonamides



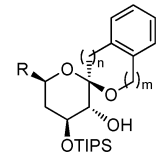




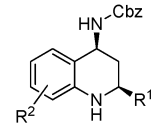
• Thansandote [282]
• Pd-catalyzed domino *o*-alkylation/alkenylation reaction



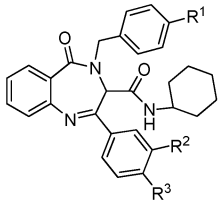
• Litvinov [167]
• 4-CR of aromatic aldehydes or heterocyclic ketones, malononitrile, β-ketoesters, and hydrazine



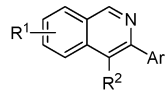
• Liu [169]
• kinetic spirocyclization of glycal epoxides



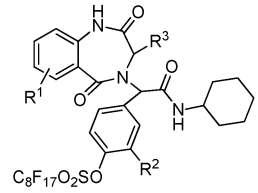
• Liu [171]
• chiral Bronsted acid-catalyzed enantioselective 3-CR Povarov reaction



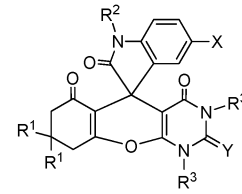
• Sanudo [253]
• Ugi 4CC/Staudinger/Aza-Wittig sequence



• Roy [247]
• Pd- and Cu-catalyzed cyclization of iminoalkynes and the Pd-catalyzed iminoannulation of internal alkynes, followed by diversification



• Liu [327]
• perfluorooctanesulfonyl protected 4-hydroxy benzaldehydes used as the limiting agent for Ugi 4-CR to form condensed products

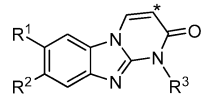


• Jadidi [119]
• 3-CR of barbituric acids, isatins and cyclohexane-1,3-diones in the presence of *p*-TSA

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

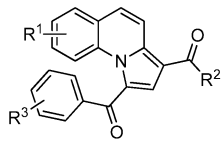
Table 10. Polycyclic and Macrocyclic Synthesis[a]

Solid-phase

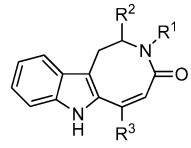


• Huang [110]
• condensation of resin-bound 3-(2-aminophenylamino)-2-seleno-ester with isothiocyanates and α-amino-acids

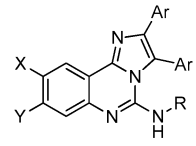
Solution-phase



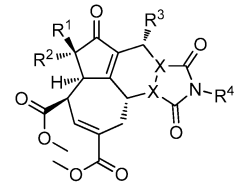
• Georgeseu [76]
• 3-CR of quinolines, bromoacetophenones, electron-deficient alkynes



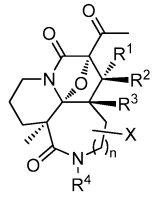
• Donets [59]
• MW-assisted $Hg(OTf)_2$ catalyzed intramolecular alkyne carbocyclization



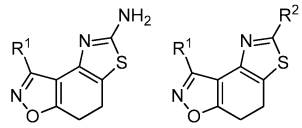
• Dou [60]
• cyclization of thiourea intermediates mediated by low-valent titanium



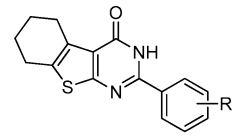
• Brummond [29]
• tandem cyclopropanation/Cope rearrangement followed by a Diels-Alder sequence



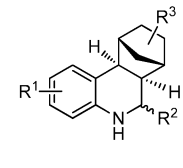
• Mizoguchi [199]
• multistep sequence from Ugi products



• El-Badri [64]
• bromination of dihydrobenzo[*d*]isoxazol-4-(5*H*)-one followed by cyclocondensation with thiourea in the presence of DDQ or cyclocondensation with thioamides

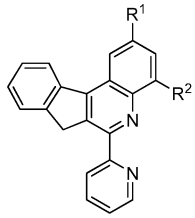


• Dzhavakhishvili [63]
• reduction of N2-substituted Gewald's amides with aromatic aldehydes

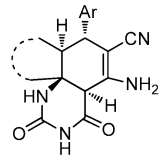


• Smith [271]
• Lewis acid catalyzed 3-CR hetero-Diels-Alder of *N*-aryl-imines with strained norbornene-derived dienophiles

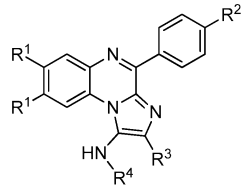
Table 10. Continued



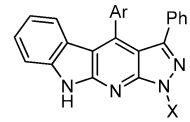
• Kouznetsov [144]
• 3-CR imino Diels-Alder reaction



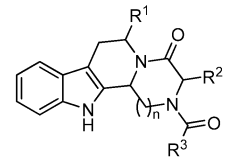
• Jiang [126]
• 4-CR domino reaction of ArCHO, ketones and cyanoamides



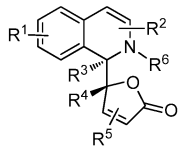
• Krasavin [145]
• two tandem isocyanide-based multicomponent reactions



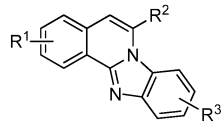
• Ghahremanzadeh [77]
• 4-CR of indolin-2-one, 3-oxo-3-phenylpropanenitrile, and hydrazines and aldehydes



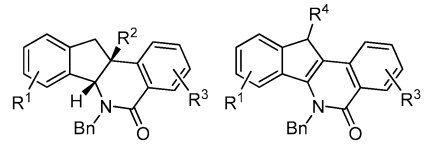
• Liu [172]
• Ugi and Pictet-Spengler reactions



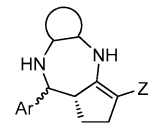
• Hermange [104]
• diastereoselective 3-CR vinylogous Mannich between isoquinolines, acyl/sulfonyl chlorides, and silyloxyfurans



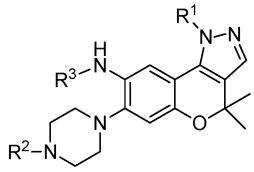
• Okamoto [216]
• MW-assisted condensation of 2-bromoarylaldehydes, terminal alkynes, and 1,2-phenylenediamines



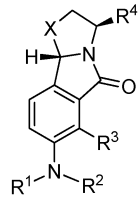
• Jayanth [121]
• Cu-catalyzed coupling of imines, vinylstannanes, or alkynes and *o*-bromoaroyl chlorides followed by Pd(0)-catalyzed annulations



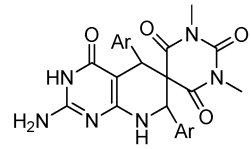
• Sotoca [272]
• cyclodehydrative 3-CR with 1,3-dicarbonyls



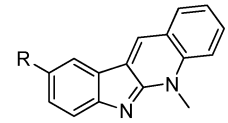
• Park [220]
• regioselective condensation of β-keto aldehydes with hydrazines



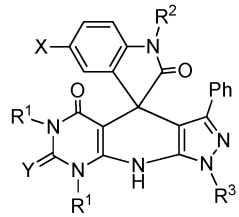
• Medimagh [188]
• 3-CR cascade process via formation of a transient imine followed by Diels-Alder cycloaddition, oxazolidine ring closure, and lactamization



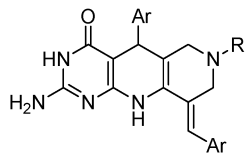
• Jiang [124]
• MW-assisted domino synthesis from ArCHO and barbituric acids



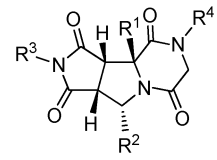
• Miller [330]
• reaction of fluorous thiols with glyoxamides via Pummerer-type cyclization



• Ghahremanzadeh [78]
• 3-CR of barbituric acids, 1*H*-pyrazol-5-amines and isatins



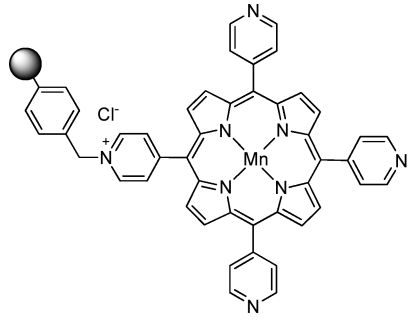
• Han [95]
• MW-assisted condensation of 3,5-dibenzylidenepiperidin-4-ones with 2,6-diaminopyridin-4(3*H*)-one and other enamine-like substrates



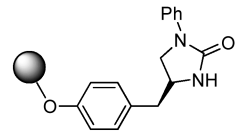
• Werner [328]
• [3+2] cycloaddition of fluorous amino esters, aldehydes, and maleimides

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

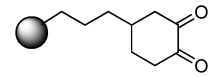
Table 11. Polymer-Supported Reagents, Scavengers, and Linkers



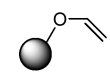
• Moghadam [200]
• reusable catalyst for biomimetic oxidative decarboxylation of carboxylic acids with $NaIO_4$



• Nguyen [212]
• 2-imidazolidinone chiral auxiliary for solid phase asymmetric alkylation reactions

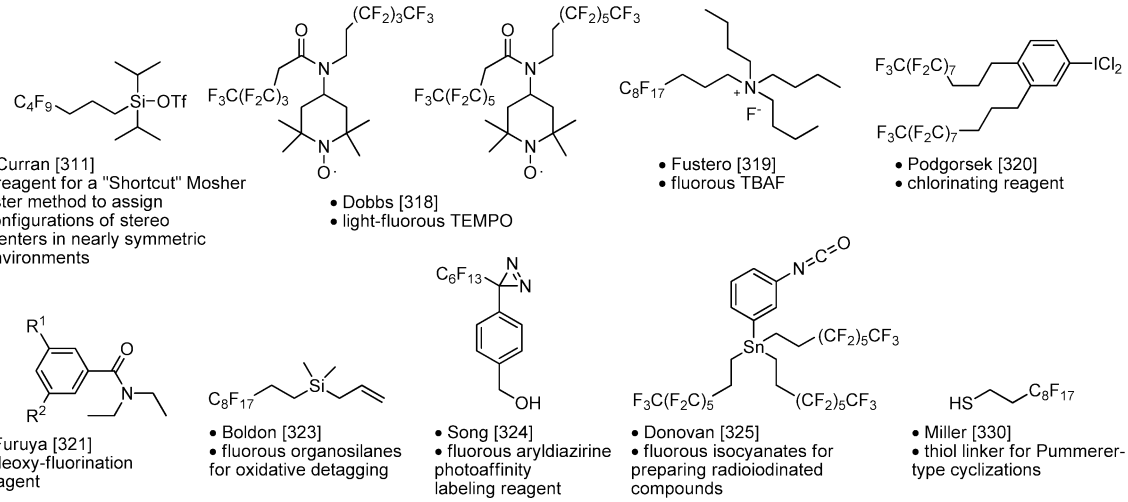


• Lence [166]
• selective resin for immobilizing *trans*-diequatorial-1,2-diols



• Roberge [242]
• linker for immobilizing alcohols

Table 12. Fluorous Catalysts, Reagents, Scavengers, Linkers, and Library Synthesis



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