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Reviews

Comprehensive Survey of Chemical Libraries for Drug Discovery and Chemical Biology: 2008

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This is the twelfth installment of the comprehensive survey series in combinatorial chemistry.[1] Biologically active libraries reported in 2008 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 Table 12 (fluorous). There are 505 libraries and 30 molecular probes extracted from 490 literature citations.[2−491] Approximately 90% of the citations originated from academic laboratories and ∼80% of the chemical libraries relied on solution-phase synthesis for their preparation.

There are 26 vignettes in the 2008 literature review. Selected vignettes on biologically active libraries include HIV-1 nonnucleoside reverse transcriptase inhibitors,[277] Aurora A kinase inhibitors,[72] orexin-2 receptor antagonists,[104] mGluR4 allosteric modulators,[285] p38α kinase inhibitors,[35] TACE inhibitors,[283] cannabinoid-2 receptor agonists,[412] CCR2b receptor antagonists,[275] and DOS-derived MRSA growth inhibitors.[337] The molecular probe selections include: dapagliflozin,[486] dorsomorphin,[473] a neuregulin/ErbB4 signaling inhibitor,[474] and proteinase activated receptor-2 (PAR-2) agonist AC-262613.[468] High-throughput chemical methodology selections include: traceless *gem*-difluorinating cleavage of resin-bound dithianes,[408] traceless solid-phase synthesis of thiomorpholinones[334] and 1,4-diazepinones,[333] *N*-hydroxyethyl-1,4-diazepinone synthesis, and parallel derivatization,[150] multicomponent reactions (MCR) yielding spiroquinolines,[40] tricyclics,[117] 1,2-amino alcohols,[101] and α-amino acid amides (unprotected *N*-terminus) by a novel phenylphosphinic acid-catalyzed Ugi reaction,[296] parallel synthesis of 1,2,4-oxadiazoles via a continuous microfluidic flow reaction sequence,[167] and the use of fluorous technology in natural product mixture synthesis[205] and in the synthesis of β,β-difluoro-α-amino acid derivatives,[458] natural product-like diols,[459] and arrays of substituted 4-thiazolidinones and 4-thiazinanones.[440]

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Related publications and reviews appeared in 2008 on microwave-assisted C−C and C−N bond formation,[492] multicomponent, cascade, and tandem reactions,[493−497] high-throughput heterocyclic synthesis,[498−505] click chemistry,[506−508] dynamic combinatorial chemistry,[509−511] diversity-oriented synthesis (DOS),[512−514] library automation and analysis,[515−524] library design,[525−530] diversity analysis and evaluation,[531−537] chemical genomics,[538−544] colorimetric tests for the detection of amines and thiols,[545] alkylsquarate scaffold synthesis,[546] color-based encoding,[547] new photolabile tags,[548] continuous-flow reactors and application in synthesis,[549−551] strategies for early drug discovery,[552−554] combinatorial libraries against cancer and protease targets,[555] strategies for mixture-based synthetic combinatorial libraries,[556] libraries from libraries,[557] water-accelerated synthetic reactions,[558] estimation of protein−ligand affinity by NMR,[559] metal-catalyzed C−C bond formation in SPOS,[560] affinity selection-mass spectrometry in HTS,[561] and fluorous chemistry and separations.[562−566]

HIV-1 Wild-Type and Mutant Nonnucleoside Reverse Transcriptase Inhibitors.[277] Human immunodeficiency virus (HIV) is a retrovirus causing acquired immunodeficiency syndrome (AIDS). There are two types of HIV, HIV-1 and HIV-2, where the former is highly virulent. Current therapies to control HIV-1 include 22 FDA-approved agents targeting virus-cell fusion, viral protease, and viral reverse transcriptase (RT). The latter target class is divided into two categories: (a) nucleoside and nucleotide analog RT inhibitors (NRTIs) and (b) nonnucleoside RT inhibitors (NNRTIs). Compared to NRTIs, NNRTIs are more specific and exhibit less severe adverse effects; however, these inhibitors are rendered ineffective upon relatively minor HIV-1 RT mutations.

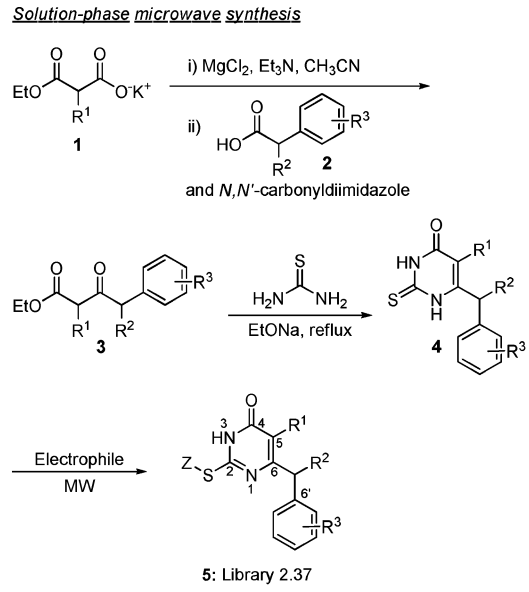
Botta and colleagues previously identified dihydroalkoxybenzyloxopyrimidines (DABOs) as potent NNRTIs.[567] Although their initial research led to the discovery of compounds exhibiting nano- and subnanomolar anti-HIV potency in lymphoid cells, these compounds were not as effective against mutant strains. To identify novel anti-HIV wild-type and mutant RT inhibitors, Mugnaini and colleagues designed a series of arylalkylthio substituted DABOs **5** (Figure 1).[277] The parallel solution-phase synthetic approach began with potassium ethyl 2-substituted malonates **1** which are reacted with $MgCl_2$ and several phenyl acetic acids **2** to afford β-ketoesters **3**. Treatment of **3** with thiourea in the presence of sodium ethoxide produced uracils **4** which in turn were thio alkylated under microwave irradiation conditions with either benzyl/alkyl halides or alcohols under Mitsunobu conditions to afford the desired sulfur-substituted heterocycles **5** (Library 2.37).

Initial structure−activity relationships (SAR) showed a very distinct pattern in which a benzyl group at position 6 was essential for activity and that *para*-substitution on this group was detrimental to activity. With this nascent SAR, the authors proceeded to further explore substitution effects on the benzyl group, determining that 2,6-dichloro and 2,6-difluoro substitutions were favorable for activity. Thiobenzylated analogs (**6**−**11**, **14**−**19**) exhibited submicromolar potency in both enzyme and cell-based (NL4−3 cells) assays. Substitution studies on the aromatic unit of the *S*-benzyl moiety (R^4) indicated that *para*-substitution was highly beneficial to activity regardless of the electronic nature of the substituent (e.g., **6**−**8**, 4-OMe, 4-CN, 4-NO_2; ID_{50} = 0.032, 0.1, 0.075 μM, respectively). A 2-carbon chain between the phenyl and thio groups was tolerated, but a 3-carbon chain was detrimental to activity (**12** versus **13**, ID_{50} = 0.07 and 9.76 μM, respectively). Small substituents on the oxopyrimidine moiety were also well tolerated (R^1: **6**, **9**, ethyl and methyl; ID_{50} = 0.032 and 0.77 μM, respectively). Lastly, it was determined that substitution on the benzyl carbon (R^2) was well tolerated with a trend of exhibiting higher activity when substituents were present (**14**, **17**, ID_{50} = 0.03 and 0.003 μM, respectively). From this *S*-benzyl analog class, compound **17** was the most potent inhibitor: ID_{50} = 3 nM; EC_{50} = 25 pM in NL4−3 wild-type cells. This agent possessed submicromolar activity against three mutant strains (K103N, Y181C, Y188L; EC_{50} = 0.55, 0.3, and 0.95 μM, respectively).

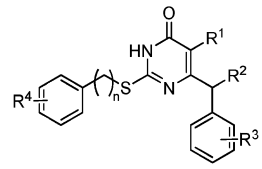
While changing the benzyl methylene unit for a vinyl unit was not favored (**20**, ID_{50} = 1.98 μM), an allyl group led to increased activity (**21**, ID_{50} = 0.007 μM). Among the 3-arylallylphenyl analogs (**21**−**28**) sharing many of the substituents present in **17**, analog **27** was found to exhibit optimal anti-HIV activity in both the enzymatic and cell-based assays (ID_{50} = 9 nM; EC_{50} = 0.4 nM). Interestingly, exchanging the allyl group in **27** for a propargyl group was detrimental to activity, particularly in NL4−3 wild-type cells.

Although compounds **29**−**31** having a *para*-methoxybenzyloxy ethyl group linked to the sulfur atom were potent enzyme inhibitors, it was only **30** that exhibited activity against the wild-type and the K103N, Y181C, and Y188L mutant strains (EC_{50} = 0.0011, 0.92, 0.65, and 0.32 μM, respectively). To rationalize these observations, the authors used molecular docking in conjunction with crystallographic data for reverse transcriptase (RT)-ligands of the K103N, Y181C, Y188L mutant strains. Docking studies with the Y188L mutant correctly predicted inhibitors **17**−**19** to be the most potent. The *R*-enantiomer of **17** adopted a similar orientation to **32**, where the pyrimidinone ring of **17** occupied the same region as **32**'s quinoxaline ring. Inhibitor **17** also formed two hydrogen bonding interactions with the CO and NH groups of Lys101 in the backbone, the same hydrogen bonds found in **32**. Moreover, the *para*-methoxybenzyl group was positioned in a large hydrophobic-reach pocket defined by Val106, Pro225, Pro236, and Phe227, justifying the role and interactions of the *para*-methoxybenzyl group with the protein. These docking parameters, however, could not fully explain the potent activity exhibited by compound **30**.

Tethering Dynamic Combinatorial Chemistry: Aurora A Kinase Inhibitors.[72] Aurora kinases are serine/threonine kinases involved in mitosis, particularly in chromosome segregation and cell division, and their functional deregu-

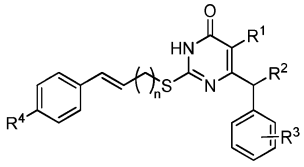


Antiviral activity and SAR (1)



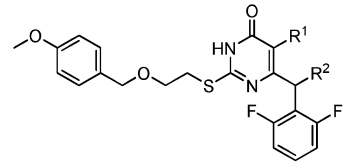
Hit	n	R^1	R^2	R^3	R^4	ID_{50} (μM) wt	EC_{50} (μM) NL4-3 wt
6	1	Et	H	2,6-diCl	4-OMe	0.032	0.0022
7	1	Et	H	2,6-diCl	4-CN	0.1	0.044
8	1	Et	H	2,6-diCl	4-NO_2	0.075	0.0666
9	1	Me	Me	2,6-diCl	4-OMe	0.77	0.0011
10	1	Me	Me	2,6-diCl	4-NO_2	0.408	0.019
11	1	Me	Me	2,6-diCl	4-CN	0.02	0.16
12	2	Et	H	2,6-diCl	4-OMe	0.07	0.0013
13	3	Me	Me	2,6-diCl	4-OMe	9.76	0.0002
14	1	Et	H	2,6-diF	4-OMe	0.03	0.012
15	1	Et	H	2,6-diF	4-CN	0.17	0.075
16	1	Et	H	2,6-diF	4-NO_2	0.07	0.074
17	1	Me	Me	2,6-diF	4-OMe	0.003	$2.5x10^{-5}$
18	1	Me	Me	2,6-diF	4-CN	0.01	0.0078
19	1	Me	Me	2,6-diF	4-NO_2	0.03	0.0033

Antiviral activity and SAR (2)



Hit	n	R^1	R^2	R^3	R^4	ID_{50} (μM) wt	EC_{50} (μM) NL4-3 wt
20	0	Me	H	2,6-diCl	4-OMe	1.98	> 57.74
21	1	Me	H	2,6-diCl	4-OMe	0.007	0.015
22	1	Me	Me	2,6-diCl	4-OMe	0.056	0.0015
23	1	Me	Me	2,6-diF	4-NO_2	0.283	0.14
24	1	Me	Me	2,6-diF	4-OMe	0.292	0.0002
25	1	Me	Me	2,6-diF	4-CN	0.161	0.14
26	1	Et	Me	2,6-diF	4-NO_2	0.016	0.0002
27	1	Et	Me	2,6-diF	4-OMe	0.009	0.0004
28	1	Et	Me	2,6-diF	4-CN	0.048	0.59

Antiviral activity and SAR (3)



Hit	R^1	R^2	ID_{50} (μM) wt	EC_{50} (μM) NL4-3 wt	K103N	Y181C	Y188L
29	Me	H	0.197	1.2	>55.87	>55.87	>55.87
30	Me	Me	0.0082	0.0011	0.92	0.65	0.32
31	Et	Me	0.741	3.89	>54.35	>54.35	>54.35

Y188L PDB 1BQN: Ligand

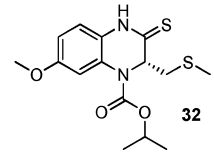


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Figure 1. HIV-1 nonnucleoside reverse transcriptase inhibitors.[277]

lation results in tumorigenesis. There are three known mammalian Aurora isozymes A, B, and C. Researchers at Sunesis Pharmaceuticals used site-specific dynamic combinatorial chemistry as an approach to the discovery of Aurora A kinase inhibitors. A unique tethering technology was developed in which a cysteine residue near a site of interest on a protein target is used to covalently bind with small thiol-containing molecular fragments via a disulfide bond in order to identify weak binding fragments. The second generation tethering technology incorporated the use of "extenders" or bifunctional molecular fragments containing an electrophilic unit and a thioacetate unit that are covalently linked to a protein's cysteine residue and can also interact reversibly with other fragments that bind at a neighboring site. A new third-generation tethering approach employs "dynamic extenders", which contain two disulfide units: one covalently binds with a cysteine residue (disulfide linkage), while the second disulfide unit reversibly captures other fragments. This third-generation tethering approach affords a combination of dynamic combinatorial chemistry with fragment-based lead discovery.

This new technology was used to identify novel binding fragments at the ATP catalytic site of Aurora A (Figure 2). The researchers first introduced a cysteine residue (T217C) near the ATP pocket via site-directed mutagenesis. A collection of approximately 4500 disulfide-containing fragments was screened in pools of 10 against the mutated Aurora A protein under partially reducing conditions in the presence of the diaminopyrimidine-based dynamic extender **33** (Library 2.2). Hits formed a stable complex with the T217C-mutated Aurora A kinase and were identified using electrospray ionization mass spectrometry. The extender-fragment combinations were elucidated and converted into the respective nondisulfide

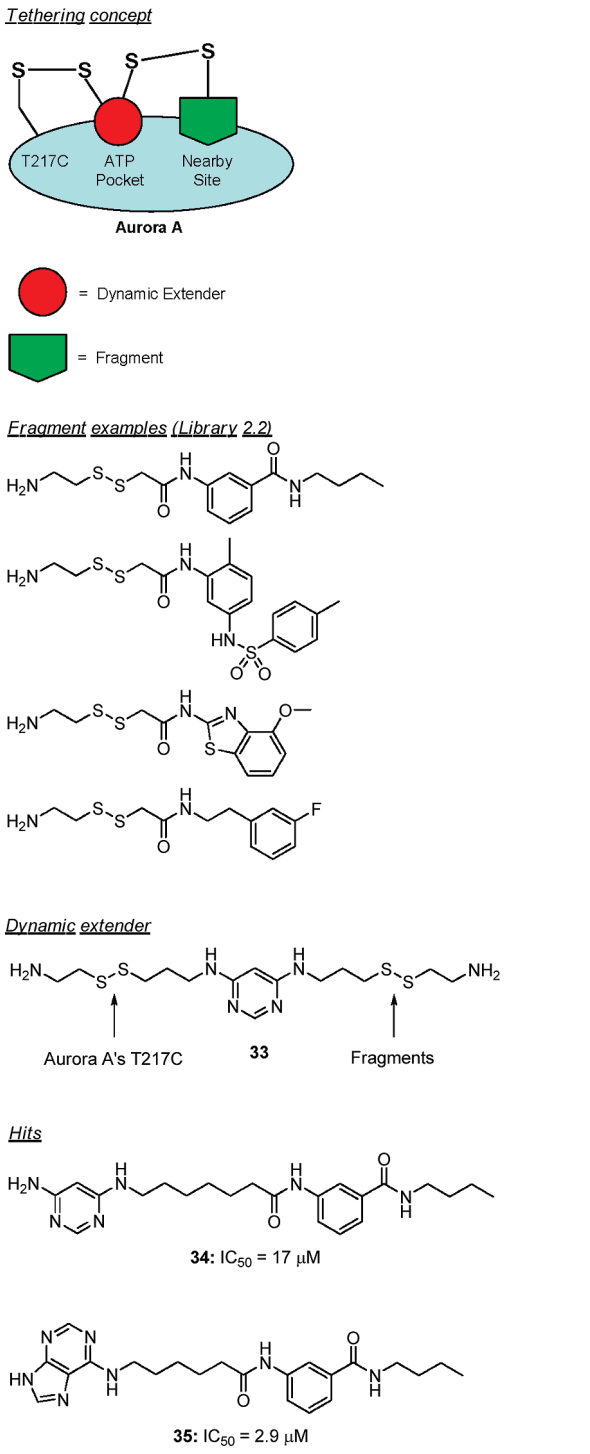


Figure 2. Sunesis' tethering dynamic combinatorial approach to Aurora A kinase inhibitors.[72]

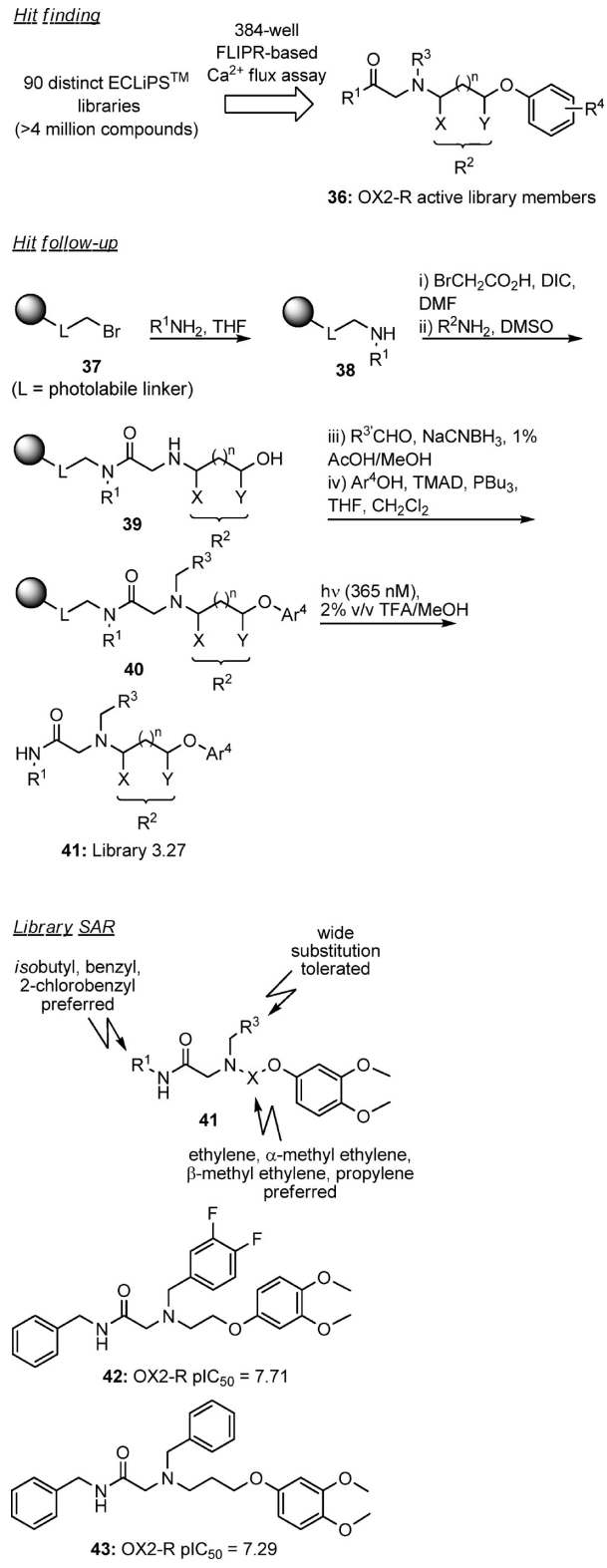


Figure 3. Orexin-2 receptor antagonists.[104]

small molecules, affording **34** (IC_{50} = 17 μM). Further experiments identified a purine-based dynamic extender affording **35** (IC_{50} = 2.9 μM), an analog 5-fold more potent than **34**. The results were validated by cocrystallizing **35** with nonmutated (wild-type) Aurora A kinase. As observed in the X-ray cocrystal structure, the purine unit of **35** is accommodated at the ATP binding pocket, the phenyl rings form a π-cationic interaction with the side chain nitrogen of residue Lys162 and the distal amide group interacts with the backbone of residue Phe144 via a hydrogen-bond interaction.

OX2 Receptor Antagonists.[104] The orexins (orexin A and orexin B, also named hypocretin 1 and 2, respectively) are hypothalamic peptides playing an important role in the regulation of the sleep-wake cycle, feeding behavior, regulation of gastric acid secretion, metabolic rate and

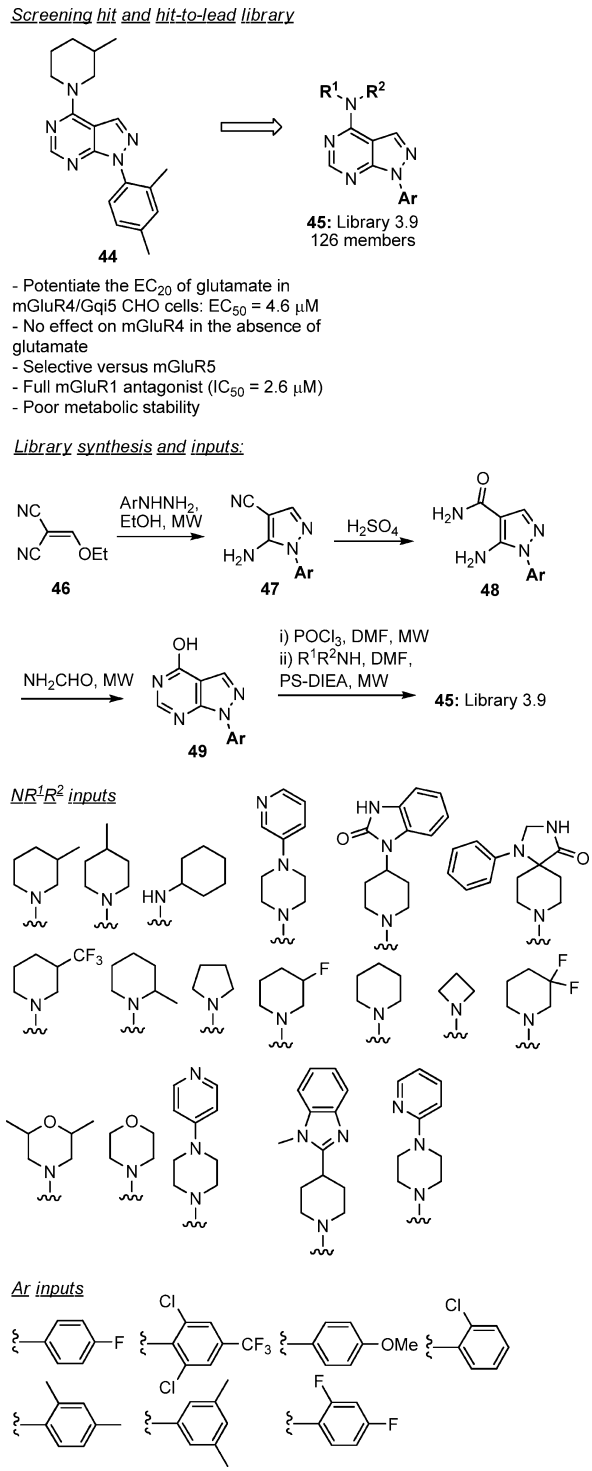


Figure 4. mGluR4 positive allosteric modulators.[285]

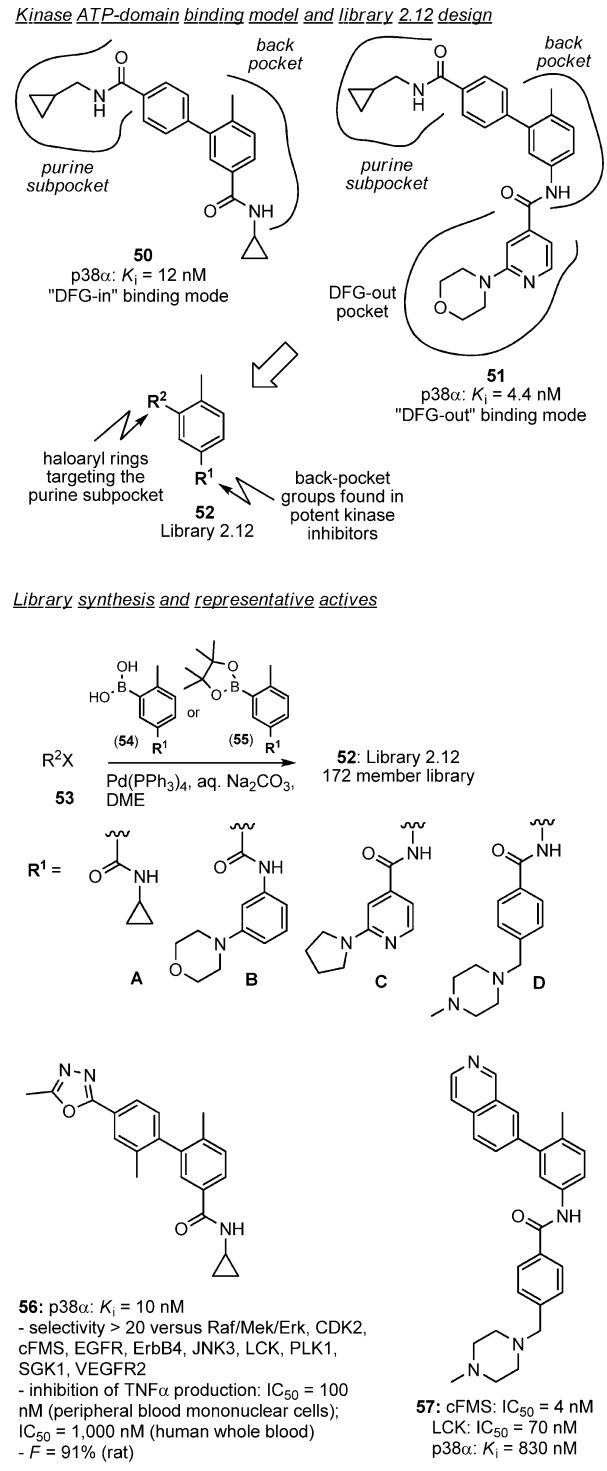


Figure 5. p38α kinase inhibitors.[35]

blood pressure. The orexins are endogeneous ligands of two receptors, OX1-R and OX2-R, which belong to the superfamily of G-protein coupled receptors (GPCRs). While OX2-R binds both neuropeptides with similar affinity, OX1-R binds orexin A with slightly higher affinity than orexin B. Recent data suggests that OX2-R is associated with the sleep/wake cycle and that mutations of this receptor are related to canine narcolepsy. Human narcolepsy also appears to be linked to deficient orexin signaling, most likely related to immune ablation of orexinergic neurons in the lateral hypothalamus. With these findings, the search for selective OX2-R antagonists for the treatment of sleep and neurological disorders has recently increased in intensity in the pharmaceutical industry. Researchers at Pharmacopeia conducted a high throughput screen of 90 distinct ECLiPS (Encoded Combinatorial Libraries on Polymeric Support) libraries to identify novel OX2-R antagonists (Figure 3). Libraries containing over four million compounds were screened at the human OX2-R using a Fluorescent Imaging Plate Reader (FLIPR)-based calcium assay. Active hits were

found from a subset library (~140 000 members) of general structure **36**. In particular, (3,4-dimethoxyphenoxy)-alkylaminoacetamides **41** were identified from this screening campaign as a novel chemical class of potent OX2-R antagonists. The combinatorial library synthesis of **41** (Library 3.27) is outlined in Figure 3. Condensation of primary amines (R^1NH_2) with resin **37**, prepared from Tentagel polymer support and a photolabile linker, provided the corresponding amine-bound resin **38**. This resin was converted to amino alcohol resin **39** by condensation with bromoacetic acids followed by addition of amines (R^2NH_2). Alkylation of the amine functionality of **39** under reductive amination conditions, followed by Mitsunobu coupling of the terminal alcohol with various phenolic derivatives, gave resin **40** which was cleaved by irradiation to release the desired library compounds **41**. SAR analysis in this series demonstrated that isobutyl, benzyl, and 2-chlorobenzyl groups were preferred at the R^1 position, while the R^2 position could accommodate a wide variety of substituents. For the more potent analogs, the α-aminoamide moiety of **41** was linked to the key 3,4-dimethoxyphenoxy pharmacophoric group by ethylene, α-methylethylene, *β*-methylethylene, or propylene linkers. From this work, compounds **42** and **43** were identified as potent OX2-R antagonists (pIC_{50} = 7.71 and 7.29, respectively).

mGluR4 Positive Allosteric Modulators.[285] The majority of drugs that target GPCRs interact with the receptor orthosteric site (i.e., the same domain recognized by the endogenous agonist for the receptor). Recently, several research groups identified ligands binding to allosteric sites of GPCRs (i.e., binding domains topographically distinct from the orthosteric sites). The binding of a ligand to an allosteric site causes a conformational change in the receptor protein that is transmitted to the orthosteric site (and vice versa). Allosteric ligands are also called allosteric modulators because they can alter the binding affinity or the signal produced to the cell by an orthosteric ligand. One of the main research interests in the Conn group at Vanderbilt University is to identify allosteric modulators of various proteins, including the metabotropic glutamate receptor subtype 4 (mGluR4). L-Glutamate, the major excitatory amino acid neurotransmitter in the CNS, binds to and activates several classes of receptors divided into two groups, the ionotropic (iGluR) and metabotropic glutamate receptors (mGluR). The metabotropic glutamate receptors, belonging to the family of GPCRs, have been divided into eight subtypes based on sequence homology (group I mGluR1, mGluR5; group II mGluR2, mGluR3; group III mGluR4, mGluR6, mGluR7, mGluR8). Preclinical data support the utility of mGluR4 agonists in various indications including anxiety, depression, and Parkinson disease. A high throughput screening campaign of Vanderbilt's compound collection against mGluR4 identified the pyrazolo[3,4-d]pyrimidine **44** as a positive allosteric modulator (Figure 4). Compound **44** produced an EC_{50} for potentiation of the agonist (glutamate) response of 4.6 *μ*M. Importantly, this compound did not produce any effect on mGluR4 activity in the absence of glutamate. Compound **44** also produced a much greater shift of the glutamate concentration−response curve when compared to a literature referenced mGluR4 positive allosteric modulator. To support the hit-to-lead campaign, a 126-member library of substituted pyrazolo[3,4-d]pyrimidines **45** (Library 3.9) was prepared. A general microwave-assisted protocol to this heterocyclic system was developed to support parallel synthesis. Hence, treatment of aryl hydrazines with ethoxymethylenemalonitrile **46** in ethanol (MW, 105 °C, 10 min) yielded 4-cyano-5-aminopyrazole **47** in 54−77% yields. Hydrolysis of the nitrile with aqueous H_2SO_4 gave the corresponding carboxamides **48** which were converted to the 1-aryl-*1H*-pyrazolo[3,4-d]pyrimidin-4-ols **49** in neat formamide (MW, 200 °C, 20 min). Microwave-assisted-conversion of **49** to the corresponding heteroaryl chloride with $POCl_3$ and subsequent S_NAr with various amines provided pyrazolo[3,4-*d*]pyrimidines **45**. A majority of the analogs prepared did not show any activity as mGluR4 positive allosteric modulators. The "flat" SAR observed in this series has also been an issue for other chemical series of mGluR positive allosteric modulators.

Kinase Inhibitors.[35] Protein kinases constitute one of the largest protein families in humans. These kinases regulate the majority of signal transduction pathways in cells, and thus play an important role in cell growth, metabolism, differentiation, and apoptosis. Deregulation of protein kinases is implicated in a number of diseases, including cancer, diabetes, and inflammation. For these reasons, targeted inhibition of protein kinases is an attractive therapeutic strategy. All kinase enzymes share a catalytic domain that contains a cleft where adenosine triphosphate (ATP) binds. This catalytic cleft is a major focus of small molecule drug design. Functional states of a typical protein kinase can be characterized by the position of a conserved DFG (aspartate, phenylalanine, glycine) motif in its activation loop. The majority of inhibitors target the ATP site of the kinase in its active "DFG-in" state. In contrast, the so-called type-II inhibitors induce a distinct "DFG-out" conformation and occupy an additional hydrophobic pocket created by this rearrangement. These type-II inhibitors possess several advantages over ATP-site compounds, including improved kinase selectivity and slower off-rates. Researchers at GlaxoSmithKline recently identified a series of biphenyl amides as p38α mitogen-activated protein (MAP) kinase inhibitors (Figure 5).[35] Representatives of these agents are compounds **50** and **51**, binding to the p38α MAP kinase in either the DFG-in (compound **50**) or DFG-out (compound **51**) conformation. To further explore the SAR in this series, a 172-member biaryl library **52** (Library 2.12) was prepared in one step (Suzuki coupling) and profiled in the p38α competitive binding assay. The R^1 substituents (**A**-**D**) targeting the lipophilic interior of the ATP-site (or back-pocket) were selected based on the structure of other potent kinase inhibitors. The R^2 substituents, designed to occupy the purine subpocket, were chosen based on information obtained from the crystal structures of **50** and **51** binding to p38α MAP kinase. A total of 87 compounds,

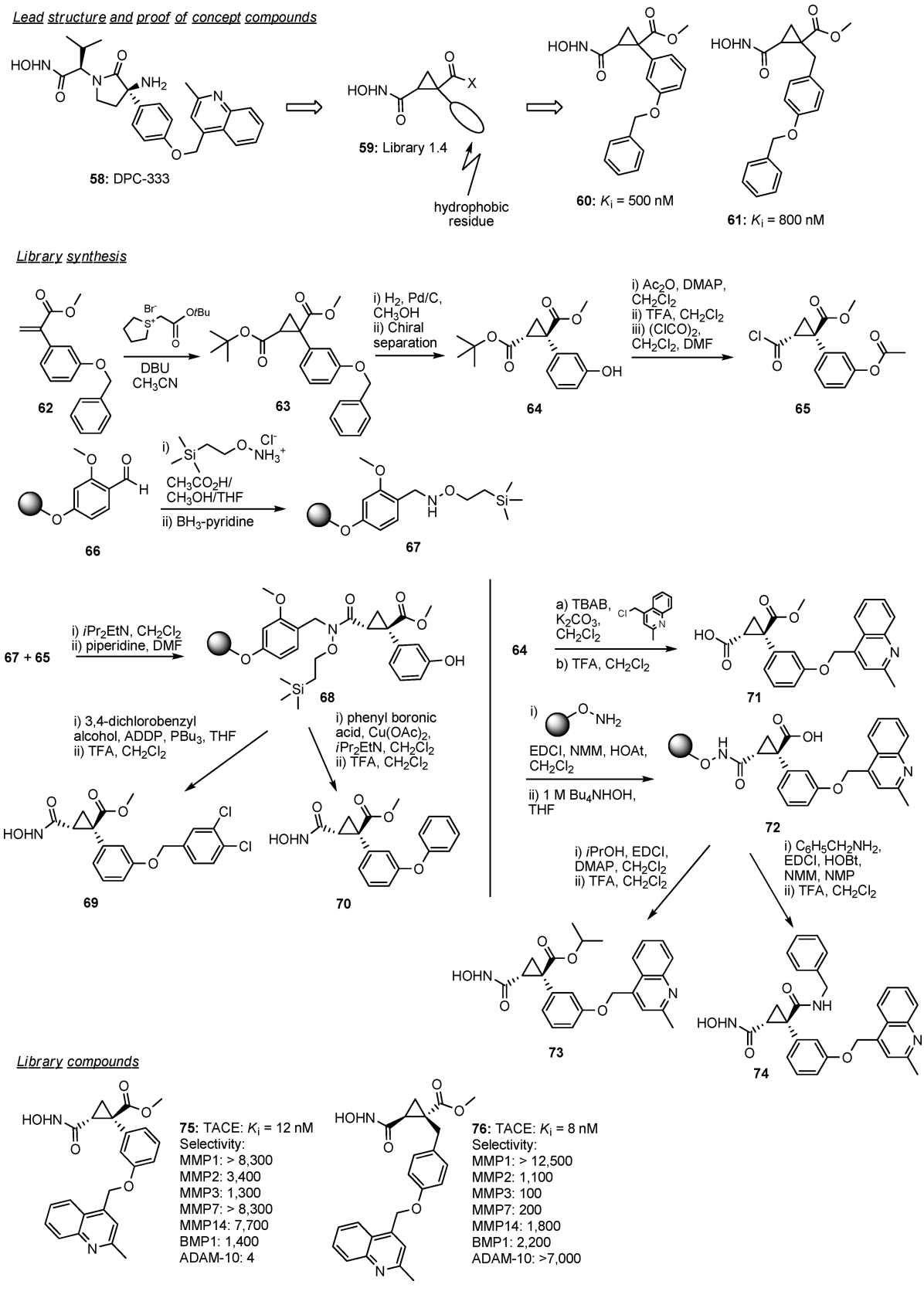


Figure 6. TACE inhibitors.[283]

including 60 different purine subpocket-binding groups, displayed K_i affinity at p38α of less than 100 nM. Selected compounds were also profiled against other kinases including Raf/Mek/Erk, CDK2, cFMS, EGFR, ErbB4, JNK3, LCK, PLK1, SGK1 and VEGFR2. This study led to the identification of compound **56**, a potent p38α MAP kinase inhibitor displaying >20-fold selectivity over the other kinases profiled. Additional studies showed that **56**

inhibited TNFα production in peripheral blood mononuclear cells (IC_{50} = 100 nM) and human whole blood (IC_{50} = 1000 nM). This compound also demonstrated favorable pharmacokinetic properties in rat. In contrast to compounds from arrays **A**−**C**, compounds from array **D**, such as **57** displayed potent affinity for cFMS and LCK, but weak affinity for p38α.

TACE Inhibitors.[283] The overexpression of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) has been implicated in numerous pathological conditions. The anti-TNF-α biological therapeutics entaneracept, infliximab, and adalimumab have demonstrated clinical success in treating inflammatory and autoimmune diseases validating the modulation of TNF-α as a drug discovery target. Inhibition of TNF-α converting enzyme (TACE) is considered an attractive mechanism to control the release of TNF-α and a viable therapy for the treatment of rheumatoid arthritis and Crohn's disease, as these conditions are caused by overexpression of TNF-α. TACE (also called ADAM-17) is a Zn-dependent metalloproteinase belonging to a subclass of the metzincin family. Because of structure similarities between the active sites of TACE and related matrix metalloproteinases (MMPs), early TACE inhibitors were derived from MMP inhibitors and suffered from broad spectrum activity against the MMP family. Nonselective TACE inhibitors have been shown to produce musculoskeletal side effects in clinical trials. Research efforts are currently concentrated on identifying TACE inhibitors with high selectivity over the other MMPs. Researchers at Schering-Plough designed a novel series of TACE inhibitors based on the information obtained from the X-ray crystal structure of the known TACE inhibitor **58** docked into the enzyme active site. In the newly designed structures **59** (Figure 6), the key hydroxamate moiety can coordinate the zinc atom of the enzyme in a bidentate fashion, while the carbonyl moiety can potentially participate in hydrogen-bonding interactions with the Leu348 and Gly349 amino acid residues of the enzyme. An additional lipophilic moiety is necessary to occupy the lipophilic S1′−S3′ binding pocket. Four compounds were prepared as proof of concept molecules for this study. Two of these compounds, **60** and **61**, were found to bind to TACE with submicromolar affinity (**60**: K_i = 500 nM; **61**: K_i = 800 nM). Based on these encouraging results, analogs of **60** and **61** were prepared using solution-phase and solid-phase synthesis (Library 1.4). The preparation of selected examples is shown in Figure 6. Cyclopropanation of the acrylate derivative **62** in the presence of *tert*-butyloxymethyltetrahydrothiophenium bromide provided the cyclopropane derivative **63**, which was converted to the chiral derivative **64** by hydrogenation, followed by chiral separation of the corresponding racemic mixture. Coupling of the acyl chloride **65** (obtained in three steps from **64**) to the resin-bound hydroxylamine **67**, followed by cleavage of the acetyl protecting group provided the resin-bound phenol **68**. Alkylation or arylation of the phenolic hydroxyl group of **68** followed by TFA cleavage and HPLC purification provided the desired compounds **69** and **70**. Loading of **71** (prepared in 2 steps from **64**) to the hydroxylamine resin provided the corresponding hydroxamate resin, which was converted to **72** by subsequent ester hydrolysis. Coupling of the carboxylic acid moiety of **72** with either isopropyl alcohol or benzyl amine followed by TFA cleavage afforded the corresponding isopropyl ester **73** and benzylamide **74**, respectively. Multiple derivatives from both series were identified as potent TACE inhibitors. In particular, compounds **75** and **76** displayed K_i values for TACE of 12 nM and 8 nM, respectively. Despite the close structural similarity between these two compounds, their selectivity profile for TACE versus other members of the MMP family was surprisingly quite different. Hence, while **75** displayed poor selectivity over ADAM-10, compound **76** was identified as a selective TACE inhibitor. X-ray crystallography of **75** and **76** binding to TACE revealed two different binding modes for these inhibitors. This could account for the difference in SAR trends and selectivity profiles among the two series of inhibitors.

Cannabinoid 2 Receptor Agonists.[412] There are three cannabinoid receptors linked to nociception and agonists of the receptors are thought to be potential analgesics. Worm and colleagues describe the synthesis of a series of sulfamoyl benzamides for use as CB_2 agonists. On the basis of the high-throughput screening hit **77**, the authors investigated three points of derivatization for the sulfobenzoic acid core (Figure 7) using a combination of parallel and solid-phase synthetic approaches. Coupling of amines **81a**−**h** with the commercially available sulfonyl chloride **79** gave the sulfonamides **80**. A diverse set of resin bound amines was prepared by reductive amination of amines to an aldehyde-based polystyrene resin. These were subsequently coupled to the sulfonamides. Cleavage of the resin with TFA gave the desired compounds **78** (Library 3.4). Approximately half of the compounds produced in this library led to retention or increased affinity for the CB_2 receptor when compared to **77**, while the remaining compounds exhibited reduced affinity for both CB receptors. In an effort to improve affinity for the CB_2 receptor, the authors then looked to introduce highly branched amines (**83a**-**h**) at the R^3 position. Initial attempts to prepare the amides using the resin bound strategy previously employed failed and these amides were subsequently prepared via solution phase methodology. Introduction of the *S*-fenchyl group (**84**) led to vastly improved affinity for the CB_2 receptor. Replacement of piperidine with morpholine at the R^2 position (**85**) led to a further increase in CB_2 receptor affinity. Substitution of the bromo substituent at R^1 with a methyl group (**86**) had no significant effect on binding affinity for the CB_2 receptor. However, inversion of the fenchylamine stereocenter at R^3 (**87**) led to a dramatic decrease in CB_2 receptor affinity. All compounds were then tested in a [^{35}S]GTPγS functional assay. All were found to be full agonists, with the exception of **90**, which exhibited inverse agonist activity.

CCR2b Antagonists.[275] In an extension of their previous research, Moree and co-workers report a new set of potent

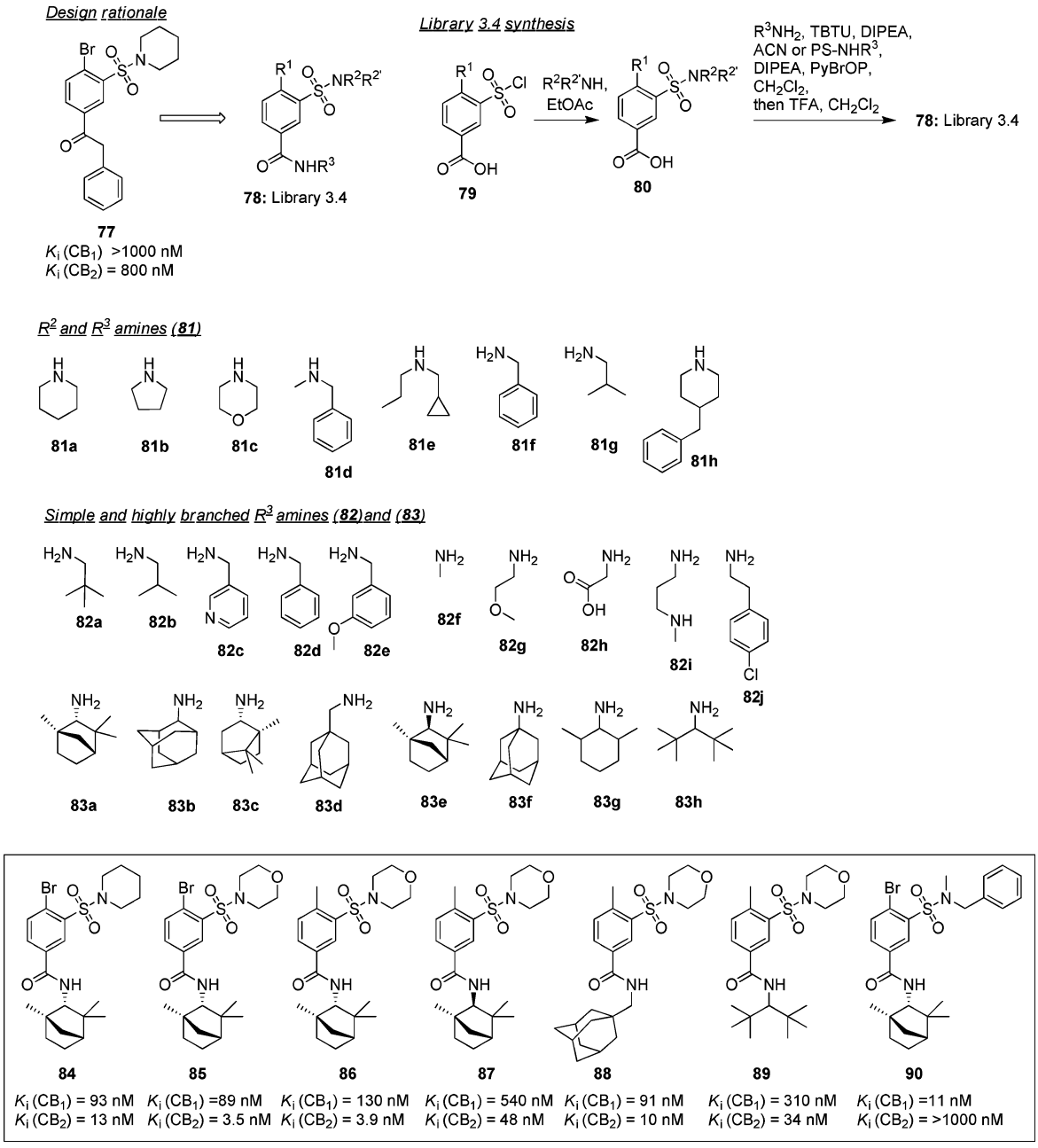


Figure 7. Adolor's CB2 agonists.[412]

CCR2b antagonists.[275] Based on lead compound **91**, the authors identified three areas of derivatization for SAR development (Figure 8). Initial research to investigate the R^1 functionality was performed in solution phase. Representative compounds include **95**−**100**. A clear preference for *para*-substituted benzyl substituents was established through comparison of the CCR2b affinity of compound **91** with compounds **96** and **97**. Expansion of the range of 4-benzyl substituents showed a preference for small electron donating groups (**98**) over electron withdrawing moieties (**99**). Interestingly, 2,3- or 2,4- disubstituted benzyl groups were also tolerated and in some instances led to enhanced affinity for the CCR2b receptor (**100**). Simultaneous modification of the R^2 and R^3 substituents was explored while holding the R^1 substituent (4-chlorobenzyl) constant. Representative compounds include **103**−**108**. Utilizing a variety of α and *β* amino acids, it was established that even small modifications to the amino acid residue (**103**, **104**) led to significantly reduced affinity for the receptor. Likewise, relocation of the R^2 substituent from the *meta* to the *ortho* (**105**) or *para* (**106**) positions led to decreased receptor affinity. However, 2,5-disubstitution of the benzyl ring led to compounds with much greater affinity for the CCR2b receptor. Following this finding, attention was refocused on the R^1 substituent to further optimize the ligands. Keeping the 2-amino-5-trifluoromethylbenzamide R^2 substituent constant, it was found that modification of the R^1 substituent through the use of mono substituted benzyl compounds offered very little improvement in receptor binding. However, disubstituted analogs (**109**, **110**) led to compounds with single digit nanomolar affinity for the CCR2b receptor and potent

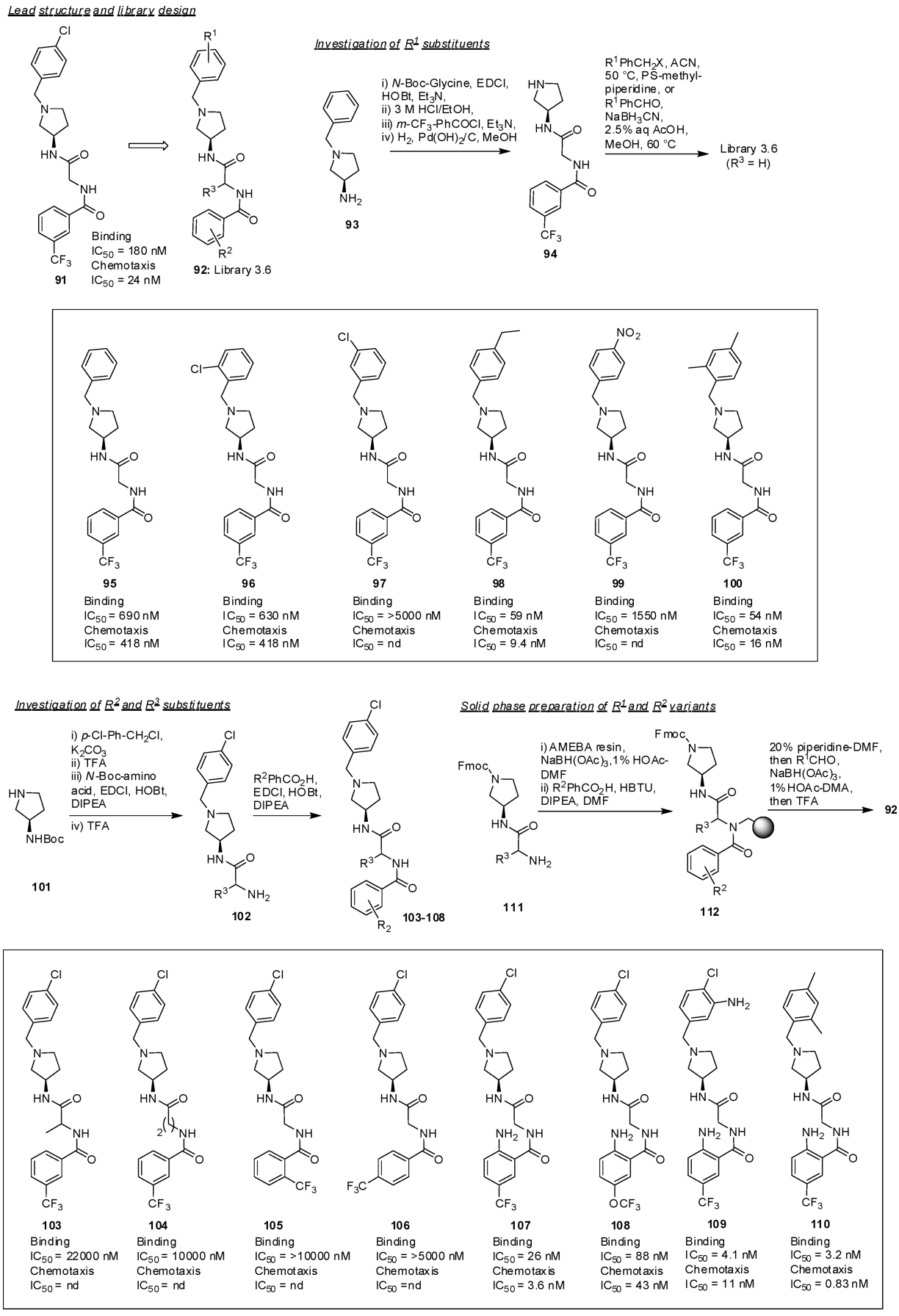


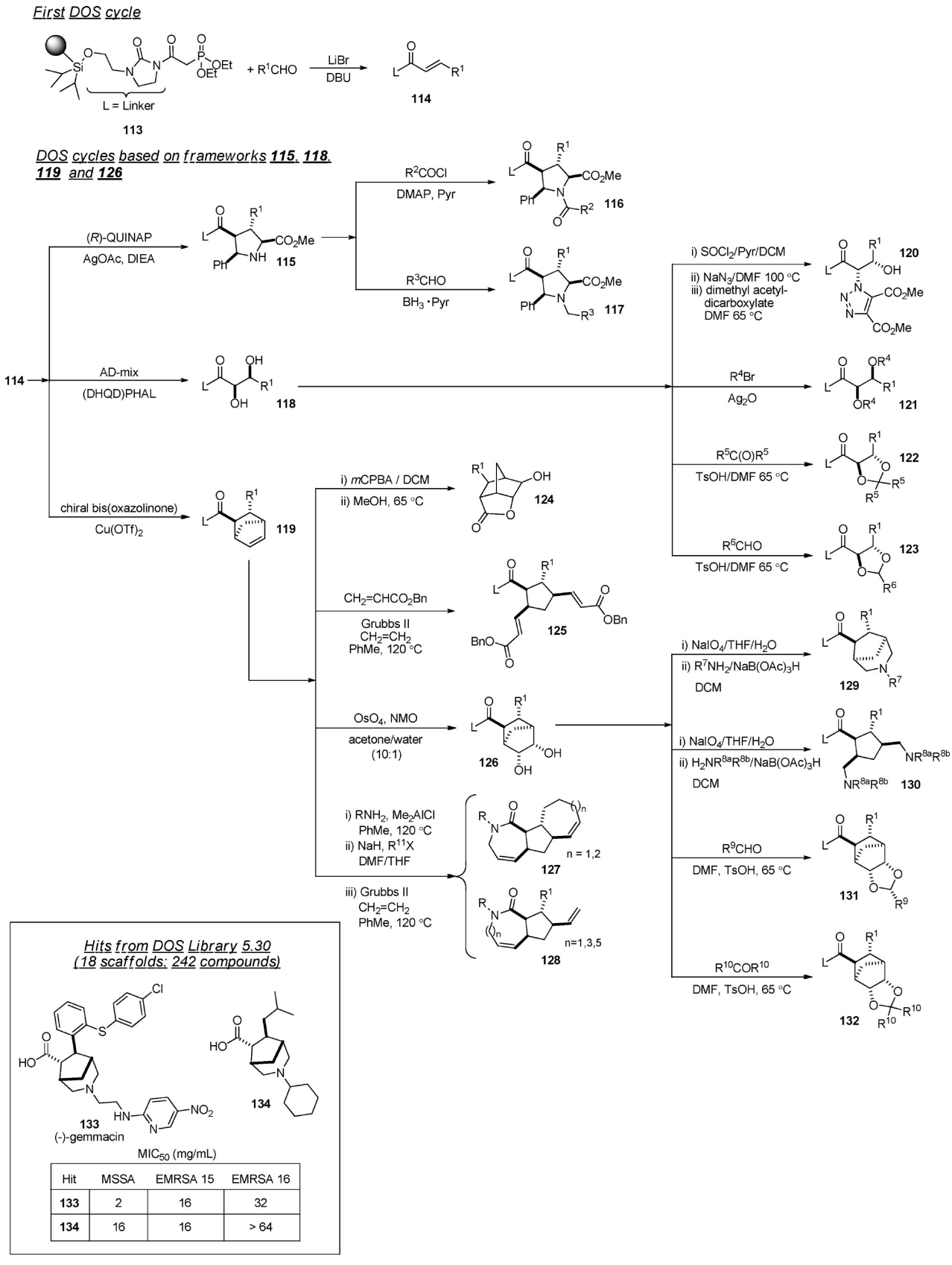
Figure 8. Lead optimization plan for CCR2b antagonists.[275]

MCP-1 induced chemotaxic activity. During the execution of the research, a solid-phase strategy for simultaneous derivatization of the R^1 and R^2 substituents was devised. Using the acid sensitive methoxybenzaldehyde (AMEBA) resin, the protected aminopyrrolidine was attached to the preloaded amino acid of interest. Introduction of the R^2 substituents was then achieved through amide formation with a benzoic acid. Removal of the Fmoc protection and reductive amination with a variety of benzaldehydes afforded the resin bound products. Cleavage of the resin using TFA gave the target compounds, which were then purified using ion exchange chromatography.

Anti-MRSA Agent Discovery Using Diversity-Oriented Synthesis (DOS).[377] Bacterial drug resistance is the cause of serious health problems. Of particular concern is the rise of nocosomial infections in patients exposed to drug-resistant bacteria in hospitals and day-care centers. Drug-resistant bacteria, also referred to as "superbugs", cannot be treated successfully with available antibacterials and may lead to mortality within a week of infection. One of the most devastating superbugs is methicillin-resistance *Staphylococcus aureus* (MRSA). MRSA is resistant to ~30 different antibiotics.

Thomas and colleagues employed DOS to generate Library 5.30 derived from 18 different natural-product-like scaffolds (**115**−**132**) to discover novel compounds with anti-MRSA activity (Figure 9). A silyl-based solid-phase synthesis strategy based on resin **113** was pursued for three reasons: (1) solid-phase simplifies optimization and workup procedures, (2) the phosphonate moiety in **113** allows for the stereoselective formation of α,β-unsaturated acyl imidazolidinones to introduce selected stereofunctionalities, and (3) the imidazolidinone linker can be hydrolyzed, esterified, reduced, and amidated to produce desired molecular diversity. Resin **113** was exposed to alkyl, aryl, and heteroaryl aldehydes in the presence of LiBr and DBU to afford a set of twelve α,β-unsaturated acyl imidazolidinones **114**. Building blocks **114** were subjected to three enantioselective skeletal diversification reactions creating three primary DOS spurs: [2 + 3] cycloaddition (**114** → pyrrolidines **115**); dihydroxylation (**114** → diols **118**); and the Diels−Alder cycloaddition (**114** → norbornenes **119**). Each spur was then submitted to further derivatization. Acylation and reductive amination of pyrrolidine spur **115** afforded **116** and **117**, respectively. Spur **118** was sequentially treated with (a) $SOCl_2$ (dioxathiolane formation), (b) NaN_3 (azido alcohol intermediate), and (c) dimethyl acetyldicarboxylate ([3 + 2] cyclization) yielding triazoles **120**. Alternatively, **118** was *O*-alkylated, condensed with ketones and aldehydes generating diether, ketal, and hemiacetal analogs (**119** → **121**, **122**, **123**). Utilizing oxidation and metathesis reactions, norbornene spur **119** was diversified to bicyclic and tricyclic scaffolds **124**−**128**. A secondary spur **126** was obtained through robust synthetic transformations furnishing five additional scaffolds **129**−**132**. After resin cleavage, 242 compounds were obtained in 1−20 mg quantities (purified as necessary to ensure >90% purity), and all characterized by ^1H NMR and LCMS. To determine its overall diversity, library 5.30 was evaluated against a series of "benchmark" collections including biologically active molecules in the MDL Drug Data Report database (MDDR). Diversity was assessed through principal component analysis (PCA). Library 5.30 was screened against three *S. aureus* strains: methicillin-susceptible *S. aureus* (MSSA), and the penicillin- and erythromycin-resistant U.K. epidemic methicillin-resistant strains EMRSA 15 and EMRSA 16. Compounds **133** and **134** were identified as hits derived from spur **119** → bicyclic amine family **129**. The nascent SAR (13 analogs) around the more potent compound **133** named (−)-gemmacin indicated that both carboxylic and nitro groups are essential for activity. (−)-Gemmacin exhibited higher selectivity toward Gram-positive over Gram-negative bacteria, low antifungal activity ($MIC_{50} > 64$ mg/mL in 7 *Candida* species) and low mammalian cell toxicity: $MIC_{50} > 64$ mg/mL in human epithelial cells.

Molecular Probe: SGLT2 Inhibitor Dapagliflozin.[486] A number of important molecules have recently joined in the fight against type 2 diabetes. Included among their ranks is dapagliflozin **137** (Figure 10), a recently reported inhibitor of renal sodium-dependent glucose cotransporter 2 (SGLT2).[486] The SGLTs regulate the reabsorption of plasma glucose and SGLT2 is responsible for this process in the kidney. Inhibition of SGLT2 is theorized to be a unique method for control of plasma glucose levels by promoting glucose excretion. Selective inhibitors of SGLT2 may minimize side effects associated with SGLT1 inhibition in the gastrointestinal tract including diarrhea and dehydration. Furthermore, controlling glucose levels via this mechanism would not alter the native regulatory machinery for glucose, thus avoiding issues of hypoglycemia. The natural product *O*-glucoside phlorizin **135** has been demonstrated to inhibit SGLTs in a nonspecific manner and is a well-known glucosuric agent. Given its lack of selectivity and poor bioavailability, researchers at Bristol-Myers Squibb Company opted to use the core structure of phlorizin as a starting point for the rational design of a novel, selective inhibitor of SGLT2. A key component of their efforts was the switch from *O*-glycosides to more robust *C*-glycosides. From these efforts they found the *C*-aryl glycoside **136** with modest activity versus SGLT2. Exploration of this scaffold eventually led to dapagliflozin **137**. Synthetically, the core *C*-aryl glycoside is established via lithium−bromine exchange on the appropriately substituted aromatic precursor and nucleophilic attack on a persilylated gluconolactone. This reaction gives a mixture of lactols that requires in situ conversion to the desilylated *O*-methyl lactol. Reduction of the anomeric methoxy was accomplished with triethylsilane and $BF_3 \cdot OEt_2$ and peracetylation allows a key crystallization which is necessary to ensure collection of the β-anomer. A final hydrolysis provided dapagliflozin. Biochemically, dapagliflozin inhibits SGLT2 with an EC_{50} of 1.1 nM and SGLT1 with an EC_{50} of 1.39 μM (1200 fold selectivity for SGLT2). In vivo analysis in rats (both glucosuric response and mean blood glucose levels) was promising and dapagliflozin was advanced for clinical



Hit	MSSA	EMRSA 15	EMRSA 16
133	2	16	32
134	16	16	> 64

Figure 9. DOS library of MRSA growth inhibitors.[377]

evaluation. Dapagliflozin **137**, a probe with a unique chemotype that cleverly incorporates a carbohydrate scaffold, represents an important new tool in the fight against type 2 diabetes.

Molecular Probe: BMP Signaling Inhibitor Dorsomorphin.[473] The use of small molecules to manipulate stem cells (adult and embryonic), reprogram lineage committed cells or revert defined cell types to a pluripotent state has

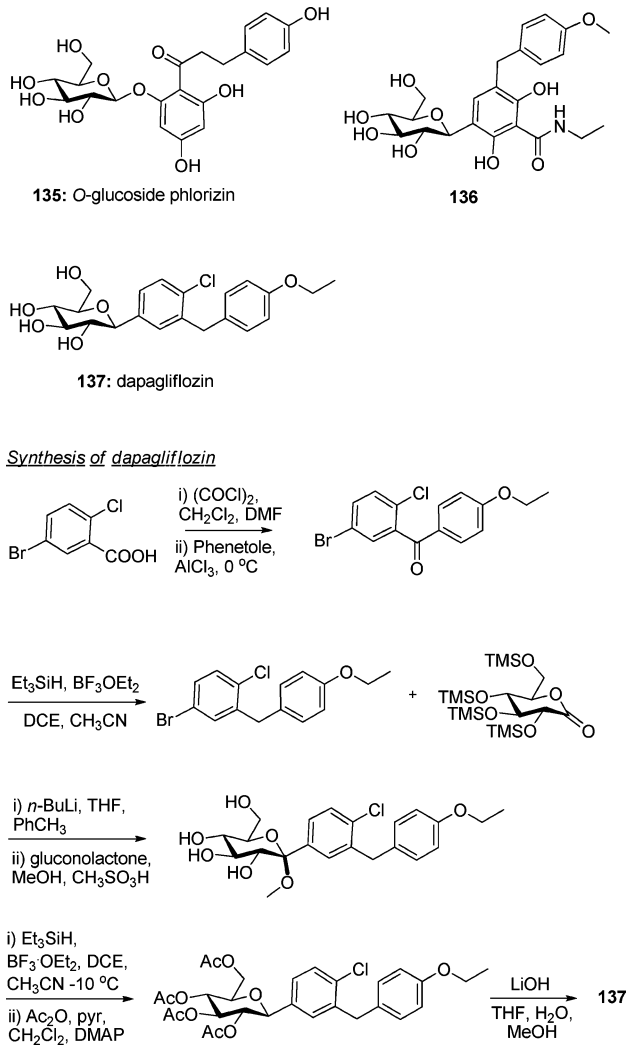


Figure 10. Discovery of dapagliflozin.[486]

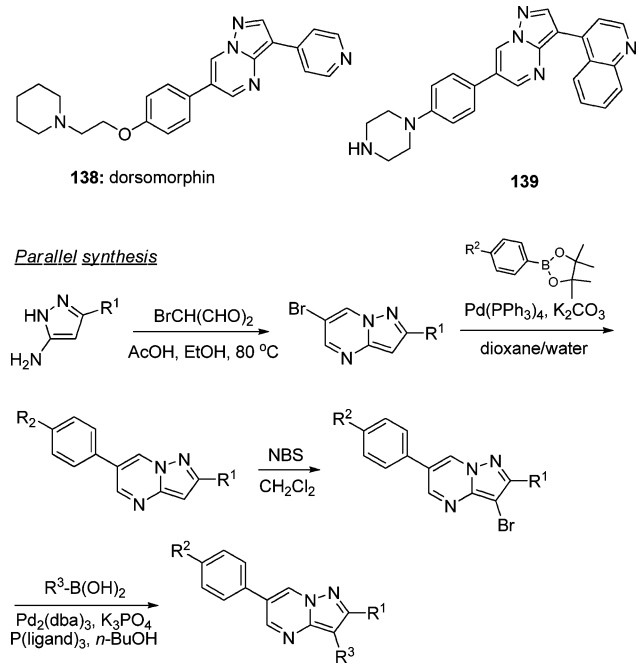


Figure 11. Discovery of dorsomorphin.[473,571]

been the focus of much effort in recent years.[568] Many of these studies are forward chemical genomics studies that define molecules with desired phenotypes without understanding the mechanism behind these actions. However, advances in the study of the endogenous signals that control and regulate the fate of multipotent cells during development has provided a plethora of new information regarding important targets that control cellular differentiation. These studies allow reverse chemical genomics screens aimed at defining potent and selective molecules that modulate important cellular targets and provide researchers novel tools for this rapidly advancing field. An impressive example of this is the discovery of dorsomorphin **138** (Figure 11), a small molecule inhibitor of bone morphogenetic protein (BMP) signaling. BMP signaling controls a number of developmental pathways including heart tissue, CNS development, and various aspects of bone maturity.[473] BMP receptors are a primary activator of the SMAD family and their associated transforming growth factors. In this contribution, Peterson and co-workers screened a focused library of compounds (7500) for the ability to affect dorsalization of zebrafish embryos from which dorsomorphin **138** was identified. This agent was previously shown to inhibit AMPK activity (K_i between 10 μM and 20 μM).[569] These authors subsequently demonstrated that the AMPK activity of **138** is unrelated to the phenotype of dorsalization and that **138** directly inhibits signaling through the BMP type 1 receptors ALK2, ALK3, and ALK6. A further link was found between BMP signaling and SMAD1/5/8 phosphorylation and ultimately iron-hepcidin homeostasis. A subsequent publication demonstrated the ability of **138** to promote differentiation of embryonic stem cells into cardiomyocytes.[570] With the target of dorsomorphin established, Peterson and co-workers initiated a program to explore the SAR of dorsomorphin in regard to BMP signaling inhibition.[571] Of particular importance in this study were examinations of the 6-, 3-, and 2-positions of the core pyrazolo[1,5-*a*]pyrimidine ring. Several synthetic sequences were presented, including the introduction of a diversity element at the 2-position through the choices of appendages at the 3-position of the 1*H*-pyrazol-5-amine starting material. Reaction of these intermediates with 2-bromomalonaldehyde resulted in the formation of the 6-bromopyrazolo[1,5-*a*]pyrimidine precursor. Entry of this brominated heterocycle into Suzuki−Miyaura couplings provided another diversity element at the 6-position. Bromination of this heterocyclic core was accomplished via treatment with NBS, and a subsequent coupling provided the final diversity element at the 3-position. From these efforts, DM-3189 (**139**) was identified as an optimized analog of dorsomorphin (IC_{50} = 4.9 nM for inhibition of BMP4-induced phosphorylation of SMAD 1/5/8) having good metabolic stability in mouse liver microsomes. These molecules represent important new probes of BMP signaling and may assist the further understanding of the complexities of cellular differentiation.

Molecular Probe: Neuregulin/ErbB4 Signaling Inhibitor (Compound 52).[474] The past decade has seen several advances in library design and manufacturing. Among

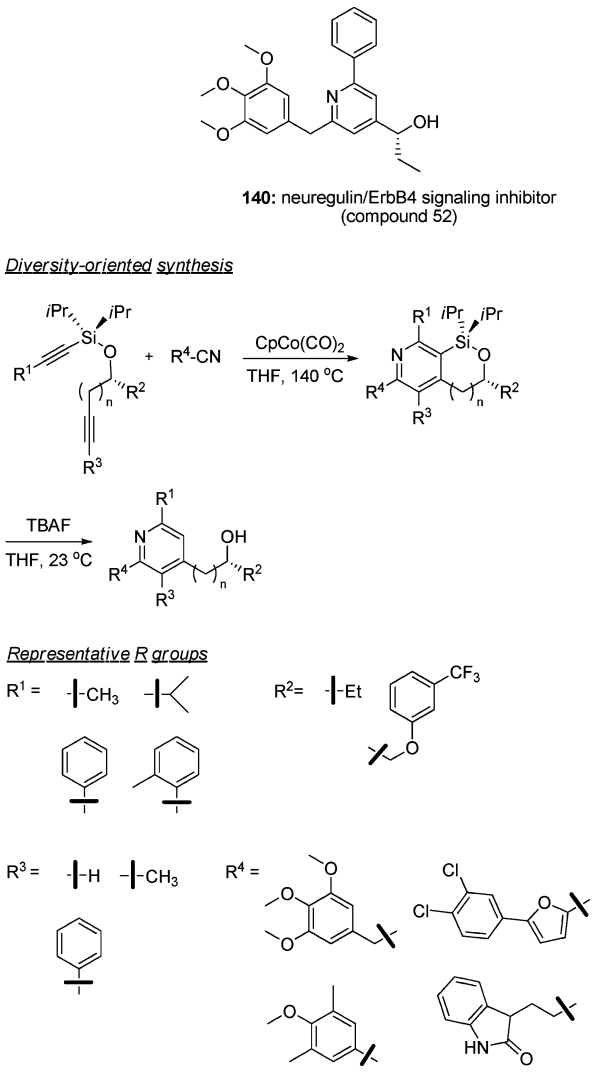


Figure 12. Discovery of neuregulin/ErbB4 signaling inhibitor (compound **52**).[474]

these are the establishments of diversity oriented synthesis (DOS) libraries and natural product inspired libraries. DOS libraries are composed of architecturally complex and stereochemically rich small molecules. Such libraries are a stark contrast to the more linear heterocyclic based libraries that dominated screening collections of the past decade. The Schreiber laboratory is the driver of the synthetic technologies behind DOS libraries. In this contribution, Schreiber and co-workers establish a novel Co(I)-catalyzed [2+2+2] cycloaddition between silyl ligated diynes and substituted nitriles in order to advance multifaceted bicyclic pyridines (Figure 12).[474] Cobalt catalysts have proven useful in several cycloaddition systems and the $CpCo(CO)_2$ catalyst is among the most useful as elevated temperature and irradiation are required to form the active Co(I) species. Selected silyl ligated diynes were reacted with numerous nitriles in the presence of $CpCo(CO)_2$ to provide substituted pyridines. The choice of THF as a solvent provided dramatically enhanced reaction yields and 25 mol % of $CpCo(CO)_2$ was found to be an optimized catalyst percentage. Interestingly, heat, but not irradiation, was required when using THF for this transformation. The regiochemistry of the resulting substituted pyridines was confirmed by NOE studies. Treatment of the products from this reaction with TBAF in THF afforded the facile removal of the diisopropylsilyl group. The output was a collection of bicyclic and monocyclic pyridines with various diversity elements interwoven to the structures. A selected number of these agents was screened for inhibition of neuregulin-induced neurite outgrowth via a high-content screen of ErbB4 expressing PC12 cells. One derivative (compound 52: **140**) was found to be a potent inhibitor of this pathway. Studies aimed at elucidating the cellular target of **140** are reported to be underway. It is noteworthy that **140** is more reminiscent of traditional library compounds rather than the unique and novel structures found in DOS libraries. This is the case too for (−)-gemmacin (**133**) discovered from DOS library 5.31 (Figure 9).[377]

Molecular Probe: Proteinase Activated Receptor-2 (PAR-2) Agonist AC-264613.[468] The G-protein coupled receptor (GPCR) proteinase activated receptor-2 (PAR-2) plays a critical role in numerous physiological processes, including the inflammatory response. This receptor is activated by proteolytic cleavage of exocyclic peptides on the amino-terminus of the protein by serine proteases (e.g., trypsin). Antagonists of the PAR class of GPCR's have long been sought as a means to circumvent the inflammatory response. Agonists are paradoxically thought to have a beneficial role in smooth muscle relaxation and as cytoprotective agents in the gastric system. Numerous peptide based agonists of PAR-2 have been reported; however, prior to this contribution by Burstein and co-workers[468] no potent, selective small molecule agonists of PAR-2 had emerged. A HTS campaign of over 250 000 small molecules was performed and two novel structures were found (Figure 13). The first was a relatively elaborate class of hydrazide/hydrazones (**141**) that displayed good potency and efficacy (6.7 nM and 81% efficacy). The second was a related class of hydrazide/hydrazones with specified chirality (**142**) that displayed good potency but only modest efficacy (5.2 nM and 30% efficacy). Efforts to expand upon the first chemotype were hindered by poor solubility and synthetic difficulties. Alignment of both lead compounds via a flexible overlay provided good evidence that only modest substituent changes to **142** may provide the necessary efficacy enhancement. Particularly, *meta*-substitutions on the aryl group attached to the hydrazone were considered important for both potency and efficacy. To explore this hypothesis the authors considered a synthesis utilizing commercially available chiral ethyl ester **144**.[572] Treatment of **144** with hydrazine in ethanol/acetic acid at elevated temperatures in a microwave reactor afforded hydrazide **145** in good yield. A microwave-accelerated condensation between **145** and the aryl ketone **146** provided AC-264613 (**143**). SAR exploration confirmed that the *meta*-bromo substitution was essential for both potency (7.5 nM) and efficacy (93%), as the corresponding *ortho*- and *para*-bromo substitutions had depressed efficacies (11% and 32%, respectively). The activity of AC-264613 was shown to be highly specific

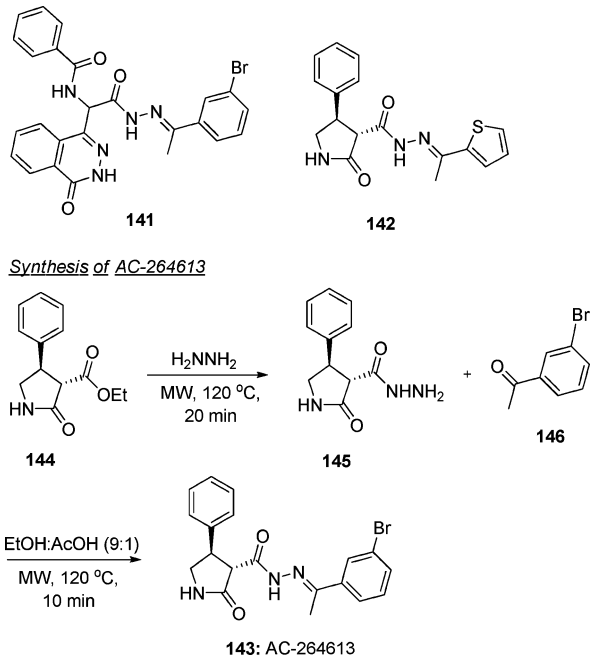


Figure 13. Discovery of proteinase activated receptor-2 (PAR-2) agonist AC-264613.[468]

for PAR-2 (no activity was noted at PAR-1 or PAR-4) and was confirmed in phosphatidyl inositol hydrolysis and Ca^{2+} mobilization assays. AC-264613 demonstrated efficacy in two divergent in vivo inflammatory assays. AC-264613 represents the first small molecule probe of PAR-2 agonism.

Fluorinating Cleavage of Solid-Phase Linkers.[408] Fluorine-containing compounds, although not abundantly found in nature, have found their place in modern drug discovery. Introduction of fluorine atoms can dramatically modify the physicochemical, reactivity and biological profiles of organic compounds. Organofluoro chemistry has produced several marketed drugs, including Lipitor, Advair, and Prozac. Recognizing the synthetic limitations to introducing fluorine via high throughput chemistry, Bräse and colleagues devised a solid-phase methodology for the synthesis of *gem*-difluoro compounds. This is based on the observation that the desulfurative fluorination of dithianes afford *gem*-difluoro analogs.[408] Their strategy centered on the immobilization of aldehydes and ketones with a polymer-supported dithiol-based linker **153** to afford dithiane intermediates **14,** then employing fluorinating cleavage to release the desired *gem*-difluoro analogs **148**. Commercially available 2-(bromomethyl)acrylic acid **149** was exposed to sodium thioacetate to form dithioacetate intermediate **150** which in turn was anchored onto aminomethyl polystyrene resin **151** under peptide coupling reaction conditions to give resin **152**. Since basic hydrolysis would lead to undesired disulfide formation, resin **152** was treated with a solution of HCl in MeOH at 50 °C for 24 h to quantitatively afford the dithiol resin **153**. The conversion of **152** to **153** was monitored by gel-phase ^{13}C NMR spectroscopy. Resin **153** was condensed with a selection of substituted benzaldehydes and phenyl-substituted methyl ketones **154** in the presence of $BF_3 \cdot Et_2O$ in chloroform at 40 °C for 24 h generating immobilized dithiane intermediates **147**. Fluorinating cleavage was carried out by treating a suspension of **147** in dichloromethane with *N*-iodosuccinimide (NIS) and HF·pyridine (70%) from −78 °C → 0 °C. The desired *gem*-difluoro products **148** were obtained in yields up to 81% starting from resin **153**. NIS was the optimal oxidizing agent since *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin gave brominated side products.

To determine the robustness and scope of the dithiane linker, solid-supported aniline analog **155** and iodide analog **156** were investigated. Immobilized aniline **155** was successfully acylated with acid chlorides, this was followed by fluorinating cleavage to give *gem*-difluoro amides **157** in good overall yields (40−60%). Immobilized iodide analog **156** was subjected to various carbon−carbon coupling reactions (e.g., Suzuki, Heck, Horner−Wadsworth−Emmons, olefination, Sonogashira) where it was observed that not only the efficiency of the carbon coupling reactions was low (15−35% yields) but also the fluorinating cleavage conditions further halogenated products derived from olefin (**160**) and Sonogashira coupling (**161**). Immobilized analogs **147** (R^1 = H) could be alkylated with *n*-BuLi/1-bromobutane affording the corresponding pentane analog (**147**: R^1 = n-Bu; ∼16% yield).

Traceless Solid-Phase Synthesis: Thiomorpholin-3-ones and 1,4-Diazepan-2-ones.[333,334] Saruta and Ogiku reported the traceless solid phase synthesis of thiomorpholin-3-ones[334] and 1,4-diazepan-2-ones[333] via dibenzylation of sulfonium and quaternary ammonium salts, respectively. Thiomorpholin-3-ones are ligands for a wide range of receptors such as 5-HT1B and EP4. There are scant reports on the synthesis of these compounds via solid-phase and the reported methodologies use highly toxic cleavage reagents (e.g., HF) or produce desired products with low purities. A traceless solid-phase approach for the synthesis of thiomorpholin-3-ones was devised where a thiobenzyl linker undergoes intramolecular sulfur alkylation to form benzyl sulfonium intermediates **162** which, upon CsI-mediated debenzylation, releases the desired thiomorpholin-3-ones **163** in a traceless manner (Figure 15). Sulfanyl-ethanols **165** were coupled to Merrifield resin **164** in the presence of DBU to afford thioether-linked alcohols **166**. Immobilized alcohols **166** were aminated with *N*-monosubstituted 2-nitrobenzenesulfonamides **167** under Mitsunobu reaction conditions, followed by removal of the 2-nitrobenzenesulfonyl group with 2-mercaptoethanol. The polymer-supported secondary amines **168** obtained were coupled to chloroacetic acids **169**, and the resulting amides **170** underwent intramolecular sulfur-driven cyclization forming benzyl sulfonium intermediates **162**. Upon treatment with CsI (dioxane/water (4:1); 95 °C) the benzyl moiety of **162** undergoes an iodine-mediated S_N2 reaction releasing the thiomorpholin-3-ones **163** in high purities (>95%). This methodology offers the advantage that only desired products **163** are afforded, as potential byproducts derived from either S_N2 reaction at the α-position of the carbonyl group or

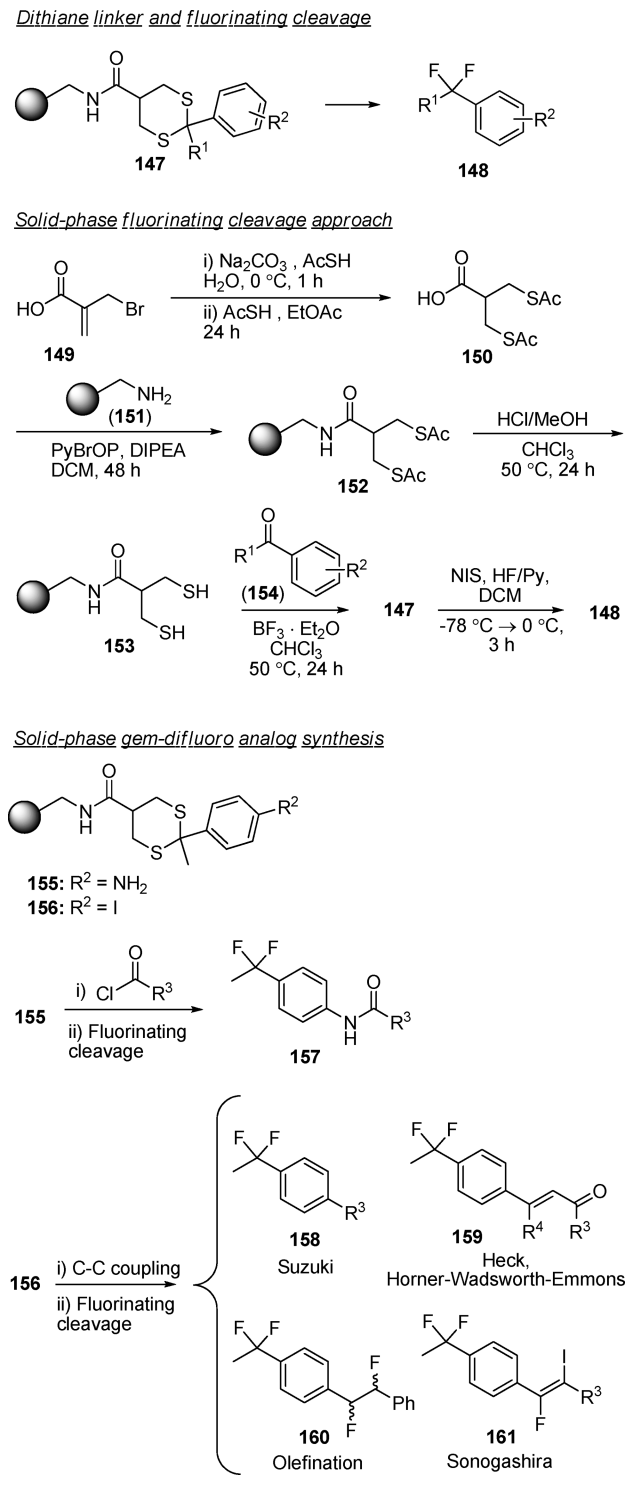


Figure 14. Fluorinating cleavage of immobilized dithianes.[408]

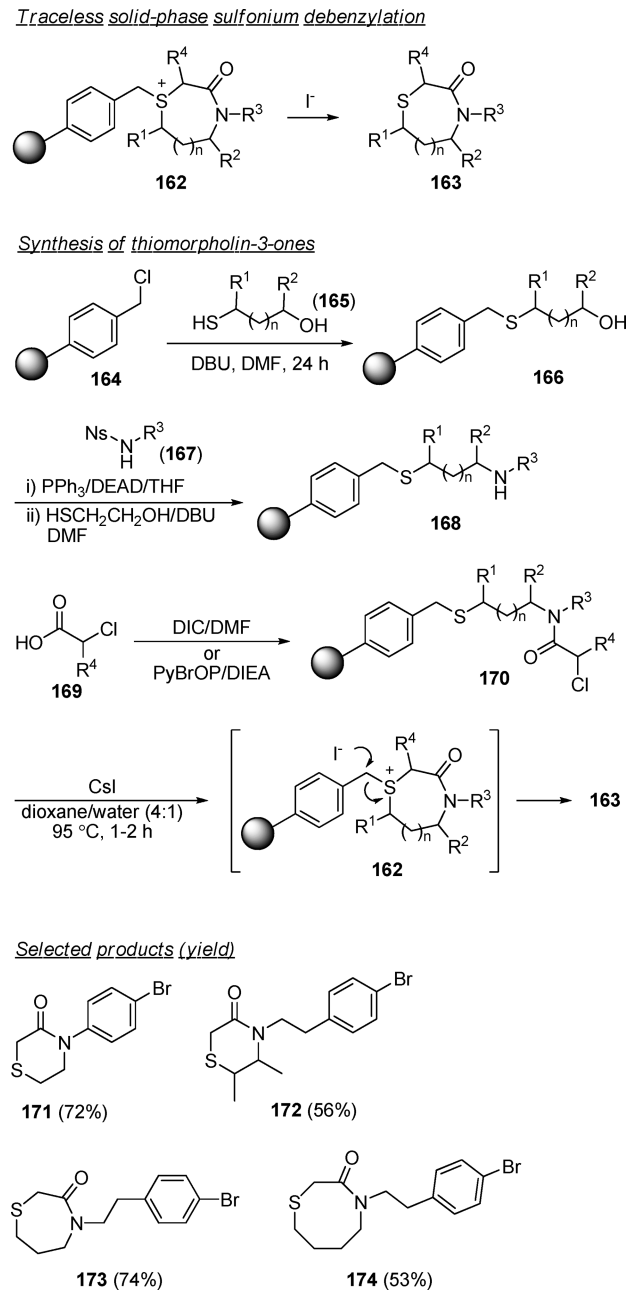


Figure 15. Traceless solid-phase synthesis of thiomorpholin-3-ones.[334]

β-elimination of acyclic sulfides remain anchored to the polymer support. Thiomorpholin-3-ones represented by **171** and **172**, where three out of the four diversity sites (R^1 through R^4) were substituted, afforded products with overall yields of 47−72%. The methodology was extended to construct 7- and 8-membered ring analogs **173** and **174**.

Saruta and Ogiku also developed a traceless solid-phase synthesis approach for biologically active 1,4-diazepin-2-ones **176** (Figure 16).[333] Analogous to the thiomorpholin-3-one synthesis, the traceless route was based on the dibenzylation of quaternary ammonium salts **175** to afford 1,4-diazepin-2-ones **176**. In this approach 4-hydroxymethyl polystyrene resin **177** was aminated with *N*-monosubstituted 2-nitrobenzenesulfonamides **178** under Mitsunobu reaction conditions followed by removal of the 2-nitrobenzenesulfonyl group with 2-mercaptoethanol. The resulting polymer-supported secondary amines **179** were alkylated with alkyl vinyl ketones **180** via Michael addition to afford amino ketones **181** which were then further converted to their corresponding diamines **183** via reductive amination. The polymer-supported diamines **183** were subsequently acylated with chloroacetic acids **169**. Exposure to CsI (dioxane/water (4:1); 95 °C) led to cyclized resin-bound intermediates **175**, which upon final treatment with 2-mercaptoethanol furnished the desired

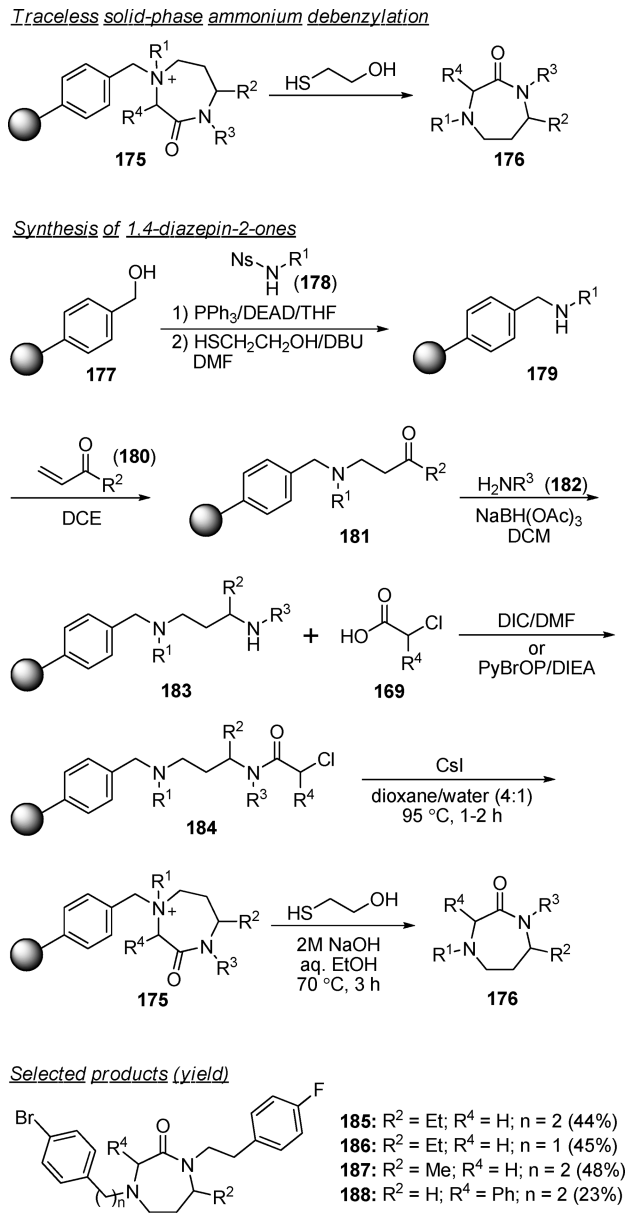


Figure 16. Traceless solid-phase synthesis of 1,4-diazepin-2-ones.[333]

1,4-diazepin-2-ones **176**. Representative compounds **185**−**188** were obtained in modest yields (23−48%) and high purity (>91%). The authors demonstrated that substituents at all 4 diversity points were well tolerated in the reaction. The reaction fails with acrolein (**188** R^2 = H) in place of vinyl ketones (**188** R^2 = carbon radical).

MCR to 1,4-Diazepin-5-ones.[150] Fenster and co-workers describe the preparation of an extensive library of 1,4-diazepin-5-ones as potential tools for the investigation of γ-turn peptidomimetic processes (Figure 17). During the course of the research the authors derived a novel three component synthesis of the diazepinone scaffold. In the first part of the study, diazepinone cores were prepared from piperidone in gram quantities using the ring-expansion protocol developed within their laboratories. Reaction of the *N*-benzyl piperidone **189** with substituted azidoethanols **190a**−**d** gave the iminium ethers **191a**−**d** which were subsequently treated with aqueous bases to give lactams **192a**−**d**. Use of benzylated piperidone allowed for subsequent deprotection (**192a**−**d** → **193a**−**d**) and diversification of the secondary amine. Various libraries were prepared from the four synthesized diazepinones (**193a**–**d**). For example, reductive amination of the four amines (**193a**–**d**) with twelve aldehydes generated a 48-member library of *N*-substituted diazepinones (**194**). Alternatively the amines **193a**–**d** were treated with various benzoic acids or tosyl chloride to give an 18-member library of amides (**195**) or the sulfonamides (**196**) respectively. Further diversification of **195** and **196** was conducted via *O*-alkylation with a variety of benzyl bromides to produce a 76-member library of compounds (**197**, **198**). A 26-member carbamate library (**199**) was generated through treatment of compounds **192c** and **198a** with various isocyanates. In the second part of the study, the susceptibility of the imine intermediate to attack by nucleophiles was exploited. As an extension of previous research conducted by Fenster and colleagues where the electrophilic property of the *N*-alkyloxazilinium bicyclic ring system (**191**) was investigated, the authors combined the nucleophilic addition step, in a single-pot fashion, to the ring expansion reaction. In a 2 × 2 × 2 approach, an eight compound library was prepared as a rehearsal using substituted thiophenoxides (R^3-C_6H_4SH; **203**) as the nucleophile: **201a/b** + **202a/b** + **203a/b** → **204a**−**h**. Initially the eight reactions were performed in a Bohdan Miniblock XT. In an effort to automate the process, the same reactions were then carried out using a Chemspeed SLT100 synthesizer. Comparative results were obtained for the library preparation. Polymeric scavengers were used in the purification of the libraries and the products were isolated with purities ≥90%. Having established the viability of the chemistry and using four *N*-substituted piperidones, four aldehydes and eight nucleophiles, a 128-member library was generated. Out of the 128 attempted reactions, 117 reactions provided more than 20 mg of product and 113 reactions yielded the products with purities ≥85%.

Spiroquinolines via One-Pot Multicatalytic and Multicomponent Cascade Reaction.[40] Multicomponent reactions (MCRs) are highly efficient reactions where three or more reactants can react in a one-pot approach providing a broad range of compound classes that are structurally, electronically, stereochemically, and chemically diverse. These reactions are also very attractive due to their operational simplicity, high atom economy, and high catalytic efficiency. Inspired by the Povarov reaction where activated olefins and aromatic imines react to produce quinolines, Barluenga and co-workers[40] devised a one-pot multicatalytic-driven multicomponent reaction to synthesize spiroquinolines **210** (Figure 18). One limitation of the Povarov cyclization is the availability of enol ether substrates. This limitation was circumvented in the new cascade reaction by generating enol ethers in situ through catalysis. Thus, a reaction mixture of alkynols **205**, aldehydes **206**, and anilines **207** was treated with catalytic [$PtMe_2$(cod)] (cod = cyclooctadiene) and HBF_4. Under these reaction conditions, alkynols **205** suffer

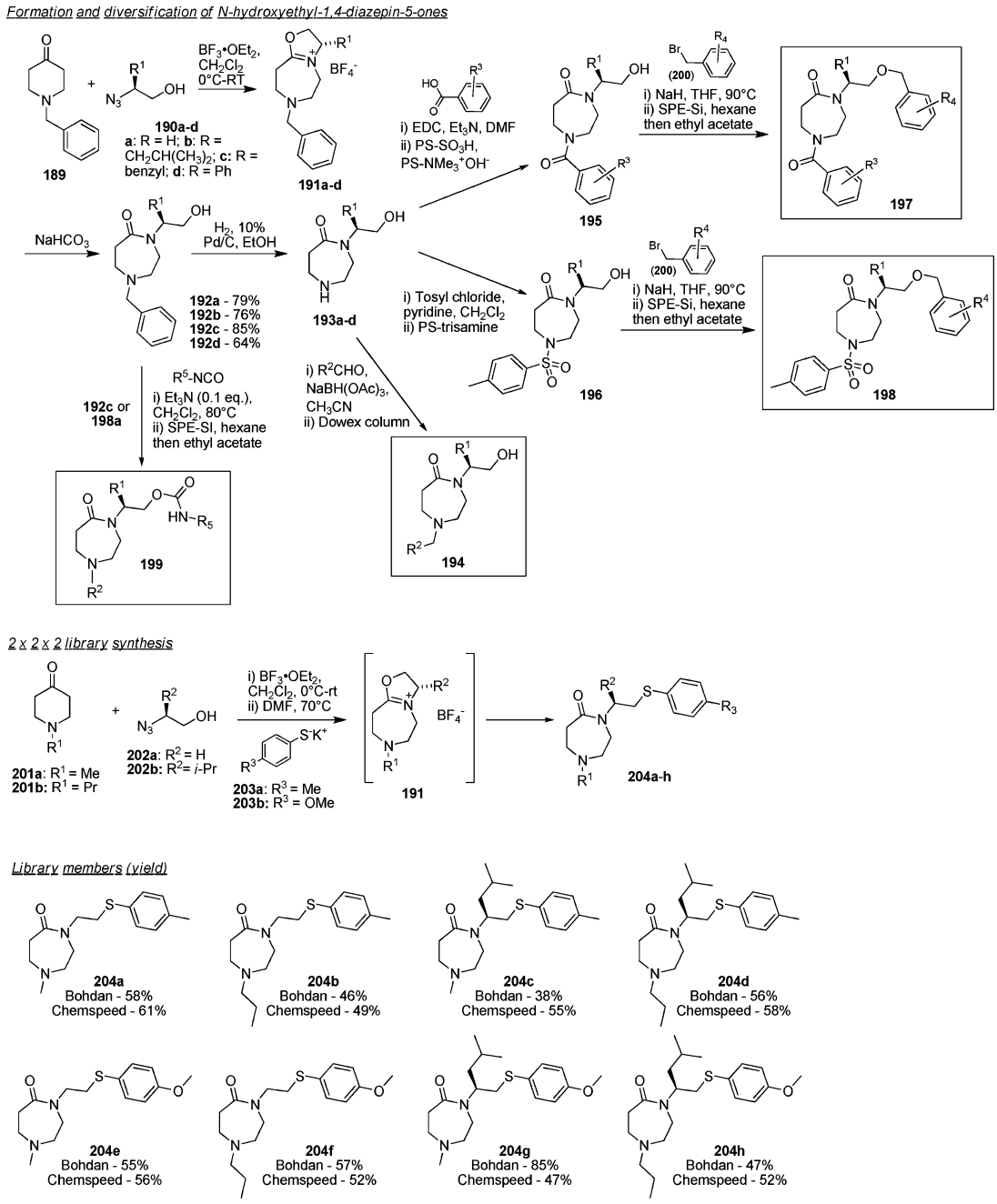


Figure 17. Synthesis of *N*-hydroxyethyl-1,4-diazepin-5-one scaffold.[150]

intramolecular hydroalkoxylation to form the corresponding exocyclic enol ethers **208**, which in turn, react with in situ generated aromatic imines yielding spiroquinolines **210**. The reaction generally proceeds in high yield (72−89%) giving 1:1 diasteromeric mixtures of spirocyclic products. The cascade reaction appears to have wide scope, accommodating a range of substrate combinations yielding unsubstituted (**211**, **212**), substituted (**213**, **214**), and spirotetrahydro-substituted (**215**, **216**) spiroquinolines. In some instances, single diastereomers are formed (**217**, **218**). When pent-4-yn-1-ol was used, furo[3,2-*c*]quinolines (**219**) were obtained.

Amines Directly from Catalytic Three-Component Ugi Reaction.[296] The Ugi four-component reaction has been more widely studied and used than any other MCR. The process consists of reacting a carbonyl compound, an amine, an isocyanide and a carboxylic acid to yield α-amino acid derivatives **225** (Figure 19). According to the proposed mechanism for this reaction, the addition of the isocyanide to the protonated imine (formed by condensation of the amine with the aldehyde) leads to the nitrilium ion intermediate **224**. Nucleophilic addition of carboxylate to **224** yields an acylimidate derivative, which after an irreversible Mumm rearrangement forms the classical *N*-carbamoyl α-amino acid amide product **225** and water. Researchers at the Max Plank Institute demonstrated that the nitrilium ion **224** can react with the water generated during the imine formation to provide directly α-amino amides **226**. Using benzaldehyde, *p*-anisidine, and *tert*-butyl isocyanide as model substrates, this new

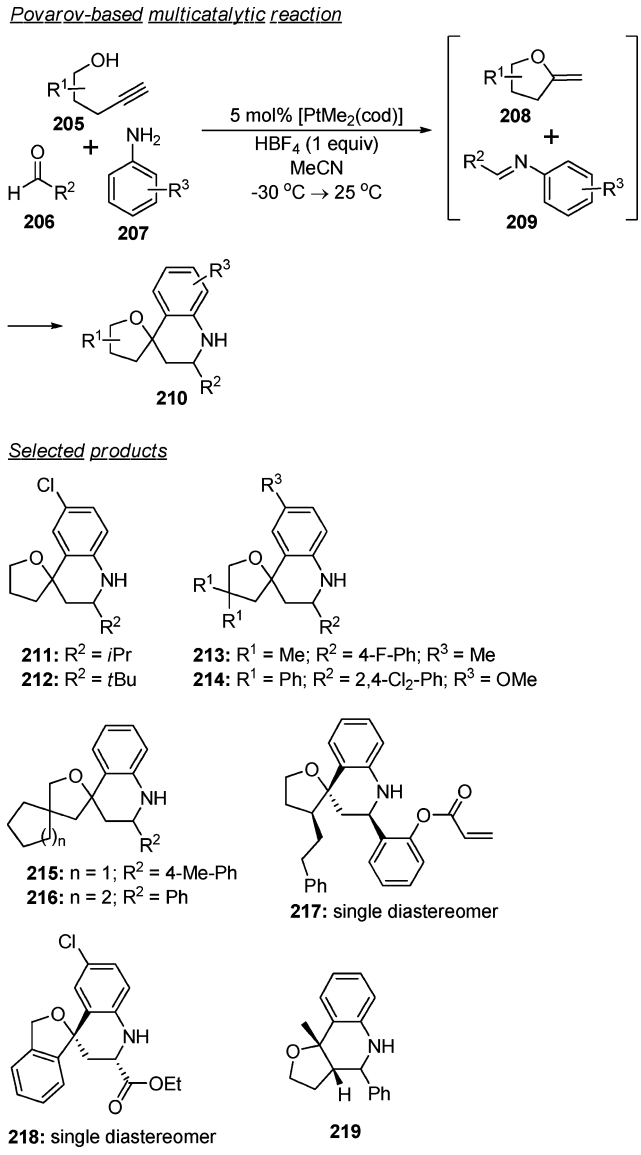


Figure 18. Multicatalytic MCR spiroquinoline synthesis.[40]

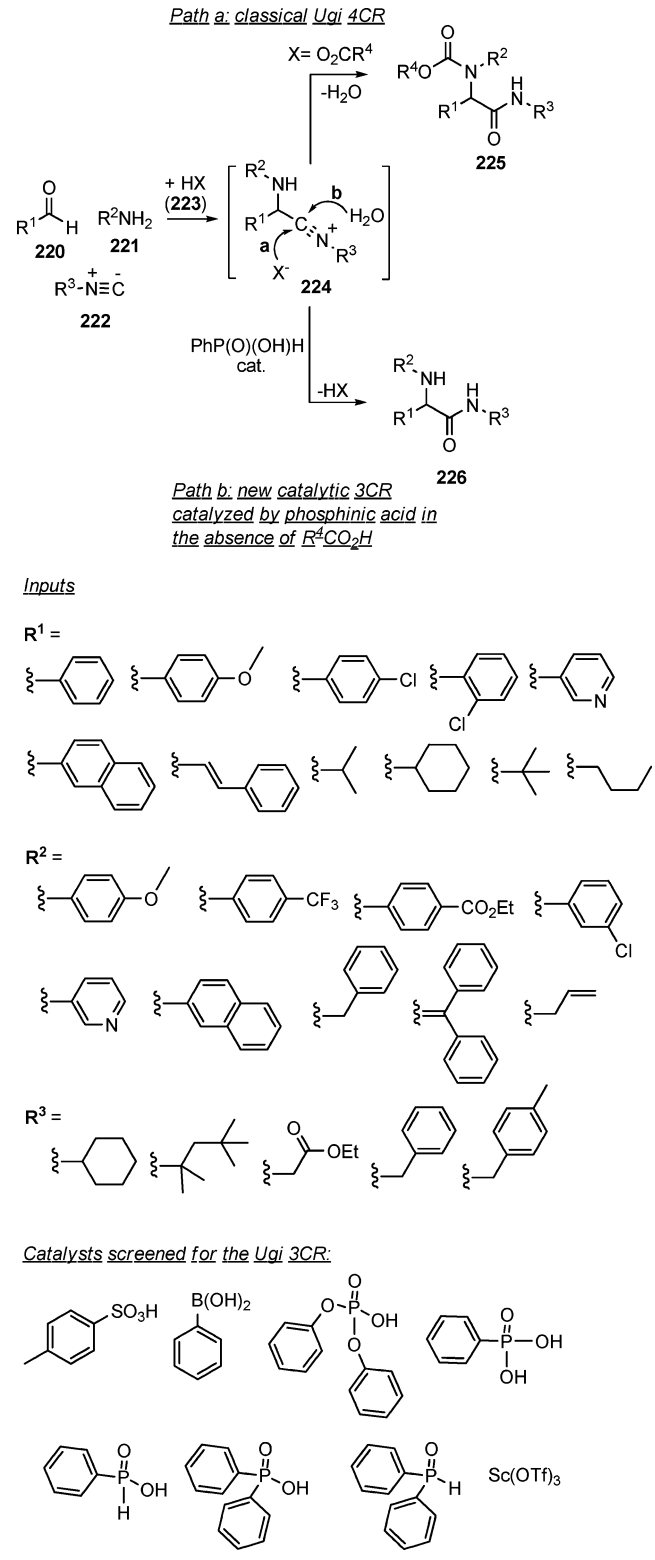


Figure 19. Catalytic three-component Ugi reaction.[296]

three component Ugi reaction is conducted efficiently at 80 °C in toluene in the presence of phenylphosphinic acid (10 mol %). Other catalysts were screened, but phenylphosphinic acid provided the best results in terms of rate of conversion to the desired product. The scope of this reaction was extended using various amines, aldehydes and isocyanides. In all cases reported, the desired products were formed in moderate to good yield demonstrating the broad utility of this new MCR.

Tricyclic Scaffolds via Palladium-Catalyzed 3CR.[117] Scientists at Lundbeck identified a novel synthesis of the phenothiazine template **230** using a one-pot reaction consisting of a simultaneous formation of C−S and C−N bonds in the presence of a palladium catalyst (Figure 20). With the use of this new methodology and after optimization of the reaction conditions, the antipsychotics promazine **230a**, chlorpromazine **230b**, flupromazine **230c**, triflupromazine **230d**, and methylpromazine **230e** were all prepared in good yields (50−76%) by condensing 2-bromobenzenethiol, 1-bromo-2-iodobenzene derivatives, and *N*,*N*-dimethylpropane-1,3-diamine in toluene under microwave or conventional heating conditions in the presence of $Pd_2(dba)_3$ (2.5 mol %), dppf (10 mol %), and sodium *tert*-butoxide (4 equiv). Various benzyl amine and aniline derivatives were also efficient substrates for this novel three component reaction. The utility of this reaction was demonstrated by the one step preparation of promazine **230a** in multigram quantity.

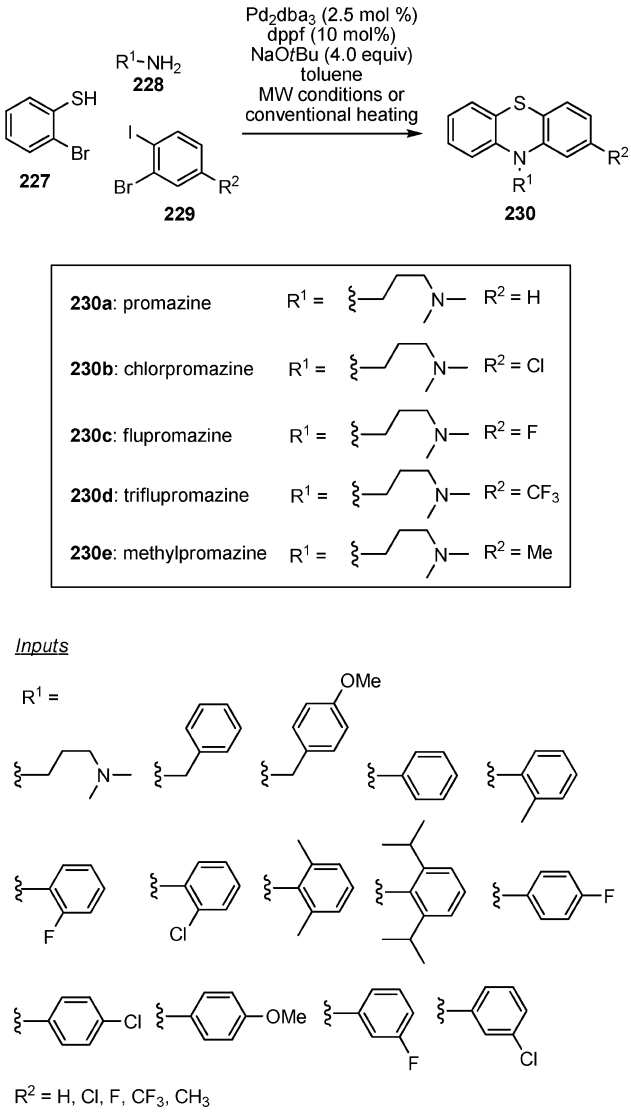


Figure 20. Tricyclics via Pd-catalyzed three-component reaction.[117]

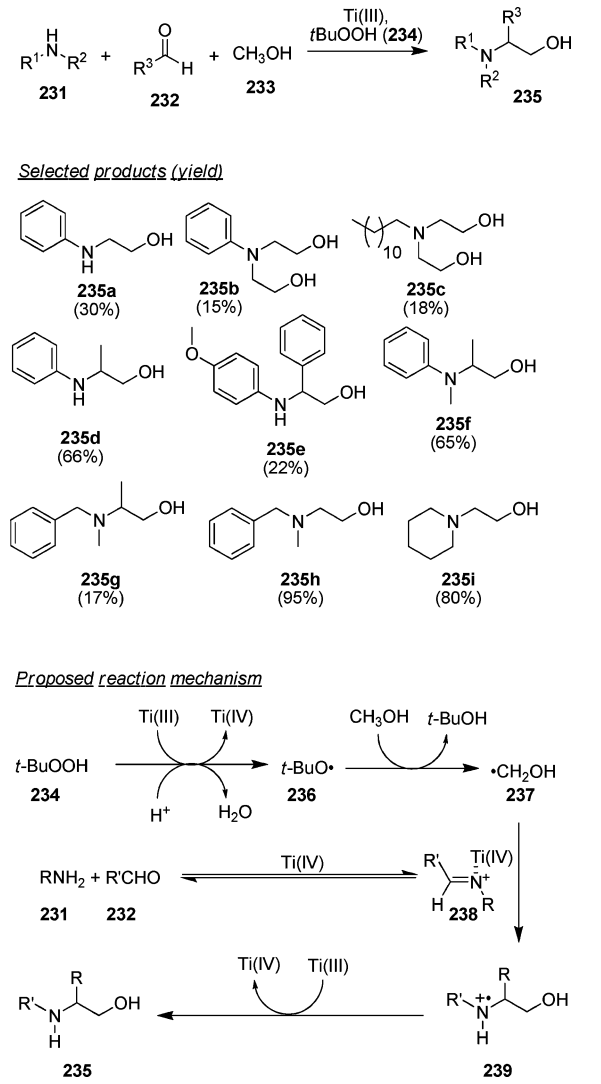


Figure 21. One-pot, four component synthesis of 1,2-amino alcohols.[101]

Radical Domino 4CR to Amino Alcohols.[101] Clerici and colleagues described a new four component, one-pot procedure for the generation of β-amino alcohols **235** (Figure 21). Previous research performed by the authors demonstrated the utility of a titanium chloride/hydroperoxide system to perform radical versions of the Mannich reaction and Strecker synthesis. A similar titanium III chloride/peroxide system was developed to promote the synthesis of 1,2-amino alcohols via a radical domino multicomponent reaction (e.g., **235a**−**i**). The general applicability of the procedure was established with various aldehydes, and selected primary and secondary amines. The reaction of primary amines with formaldehyde led to a mixture of mono- and disubstituted products (**235a**,**b**). When undecamine was used only the disubstituted product was isolated (**235c**). The authors attribute this to competition between the starting amine and product in the imine formation step. Use of substituted aldehydes, however, resulted in only monosubstituted products. The multiple roles of the titanium and a mechanism for the reaction was proposed. Decomposition of the *tert*-butylhydroperoxide (**234**) is induced by oxidation of Ti(III) to Ti(IV). This resulting alkoxy radical (**236**) then generates the hydroxymethyl radical (**237**) through hydrogen abstraction from methanol. Simultaneously the Ti(IV) species acts as a Lewis acid in the promotion of the imine formation (**238**) between the aldehyde and amine. Addition of the hydroxymethanol to the imine generates the radical intermediate (**239**) which is then reduced by Ti(III) to give the desired products **235**.

1,2,4-Oxadiazoles via a Flow Reaction.[167] In a remarkably simple approach, using a single continuous microreactor, Grant and co-workers prepared a series of 1,2,4-oxadiazoles **244** in moderate to good yields (Figure 22). Utilizing an unbroken three-step microreactor sequence, the "in flask" reaction sequence was re-engineered, converting a multistep, multiday synthesis of oxadiazoles into a highly efficient procedure taking <30 min. The utility of the procedure was demonstrated through the use of a variety of aryl and heteroaryl nitriles with various acid chlorides to give products **244a**−**d** in 45−63% yields. When substituted succinic anhydride was used in place of the acid chloride, propanoic acid analogs **247a**−**c** were generated.

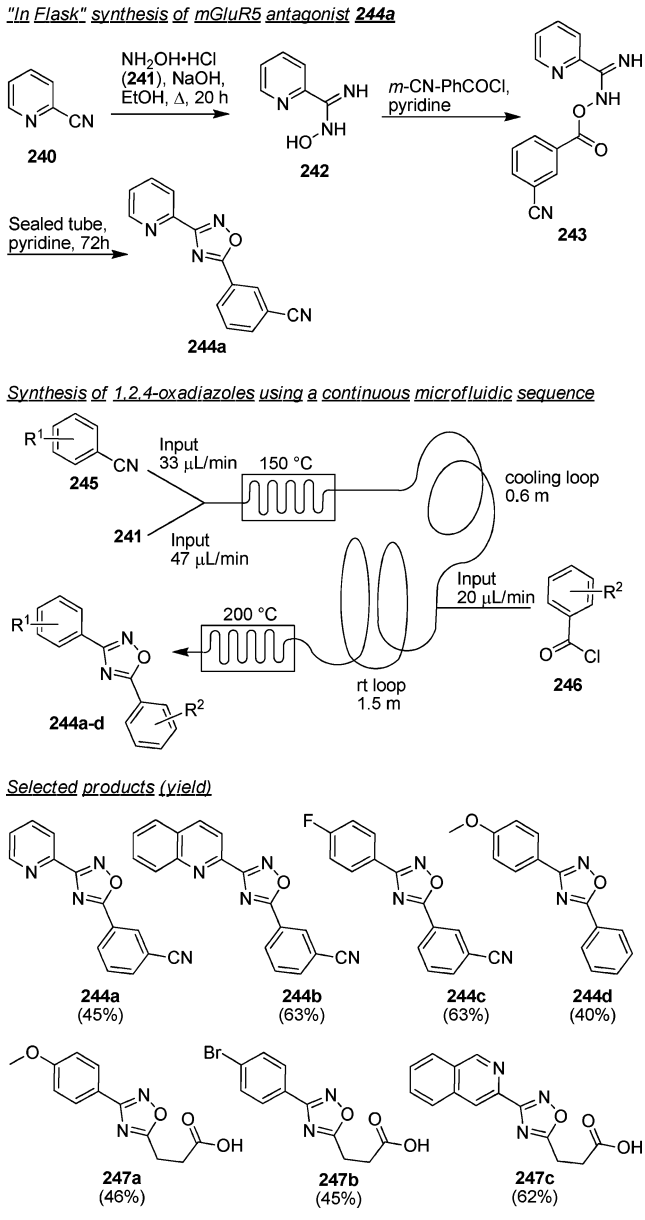


Figure 22. Flow reaction to 1,2,4-oxadiazoles.[167]

Fluorous Mixture Synthesis of (+)-Cytostatin and Its Stereoisomers.[205] Since the introduction of fluorous mixture synthesis (FMS) by the Curran group in 2001, this new solution phase technique has been applied to the synthesis of libraries of drug-like compounds and natural product analogs. One of the most recent examples of FMS is related to the preparation of (+)-cytostatin (**248a**) and its stereoisomers **248b**−**d** (Figure 23).[205] Cytostatin was isolated from the cultured broth of *Streptomyces sp.*[573] This compound is a potent and selective inhibitor of protein phosphatase 2A. It inhibits metastasis of lung melanoma cells in mice and also has potent cytotoxic activity toward leukemia cell lines (IC_{50} = 42−65 nM). Cytostatin has six chiral centers and its configuration was previously determined by comparison of spectroscopic, physical, and biological properties of a synthetic sample and the natural product. To confirm the structure of cytostatin, the Curran group employed the FMS technique to synthesize two pairs of enantiomerically pure isomers which were believed to be the most likely candidates for cytostatin. One of the key steps in this work was the coupling of fluorous quasi-racemic mixtures M-**252** and M-**255**. Compounds M-**252** each contains three chiral centers and the enantiomeric configurations were encoded by C_6F_{13} and C_8F_{17} tags, respectively. Compound M-**255** contains two chiral centers and the enantiomeric configurations were encoded by a regular alkyl (zero fluorines) and C_4F_9 tag, respectively (Figure 23). Horner−Wadsworth−Emmons reaction of M-**252** and M-**255**, followed by sequential 1,4-reduction using the Stryker reagent and ketone reduction using $LiAl(tBuO)_3H$, generated the sixth chiral center and gave M-**257** as a mixture of two pairs of quasi-racemic mixtures, which were then converted to M-**258** after several reactions. Since four compounds from two pairs of quasiracemic mixtures of M-**258** each has a different fluorine content, they were demixed by the tag-based fluorous HPLC to give four individual fluorous compounds **259a**−**d**. Each of these four separated compounds underwent further transformations followed by fluorous tag cleavage to give four stereoisomers **248a**−**d**. After ^1H NMR comparison and the TLC study of these four compounds and the natural sample, it was concluded that compound **248a** has the same configuration as cytostatin and thus confirmed the original structure characterization. This work demonstrated the power of FMS for making natural stereoisomers for structure determination. Since the preparation of four stereoisomers was carried out in one-pot, significant effort was saved in this multistep natural product synthesis.

Fluorous Diastereoselective Synthesis of Cyclic β,β-Difluorinated α-Amino Acid Derivatives.[458] Incorporation of fluorine into biologically active compounds to alter drug metabolism and enzyme substrate recognition has become a common practice in medicinal chemistry. One of the applications is to prepare fluorinated amino acid-based peptides and other derivatives. Using a fluorous tag to facilitate product purification, the Fustero group developed a new protocol to synthesize chiral cyclic quaternary α-amino acids for potential biological property studies.[458] As shown in Figure 24, the fluorous linker was introduced to chiral imidoyl iodide **260** by alkoxycarbonylation to form imino ester (−)-**261**. After an easy fluorous solid-phase extraction (F-SPE), compound (−)-**261** was isolated and subjected to diastereoselective addition of allylzinc bromide generating (−)-**262**, followed by ring-closing metathesis to afford (−)-**263**. Transesterification with TBAF in the presence of benzyl bromide cleaved the silylated fluorous tag to yield fluorous chiral cyclic quaternary α-amino ester (−)-**264**. The same research group previously developed similar approaches for both solution-phase and solid-phase synthesis of chiral cyclic quaternary α-amino esters. After side-by-side comparison of these methods with the fluorous method, the authors concluded that fluorous synthesis is more advantageous. It is faster and more cost efficient since it does not require excess reagents to push the reaction to completion as the solid-phase synthesis does. In addition, the fluorous reaction is easy to follow using conventional analytical tools and the product purification by F-SPE is straightforward. Synthetic procedures

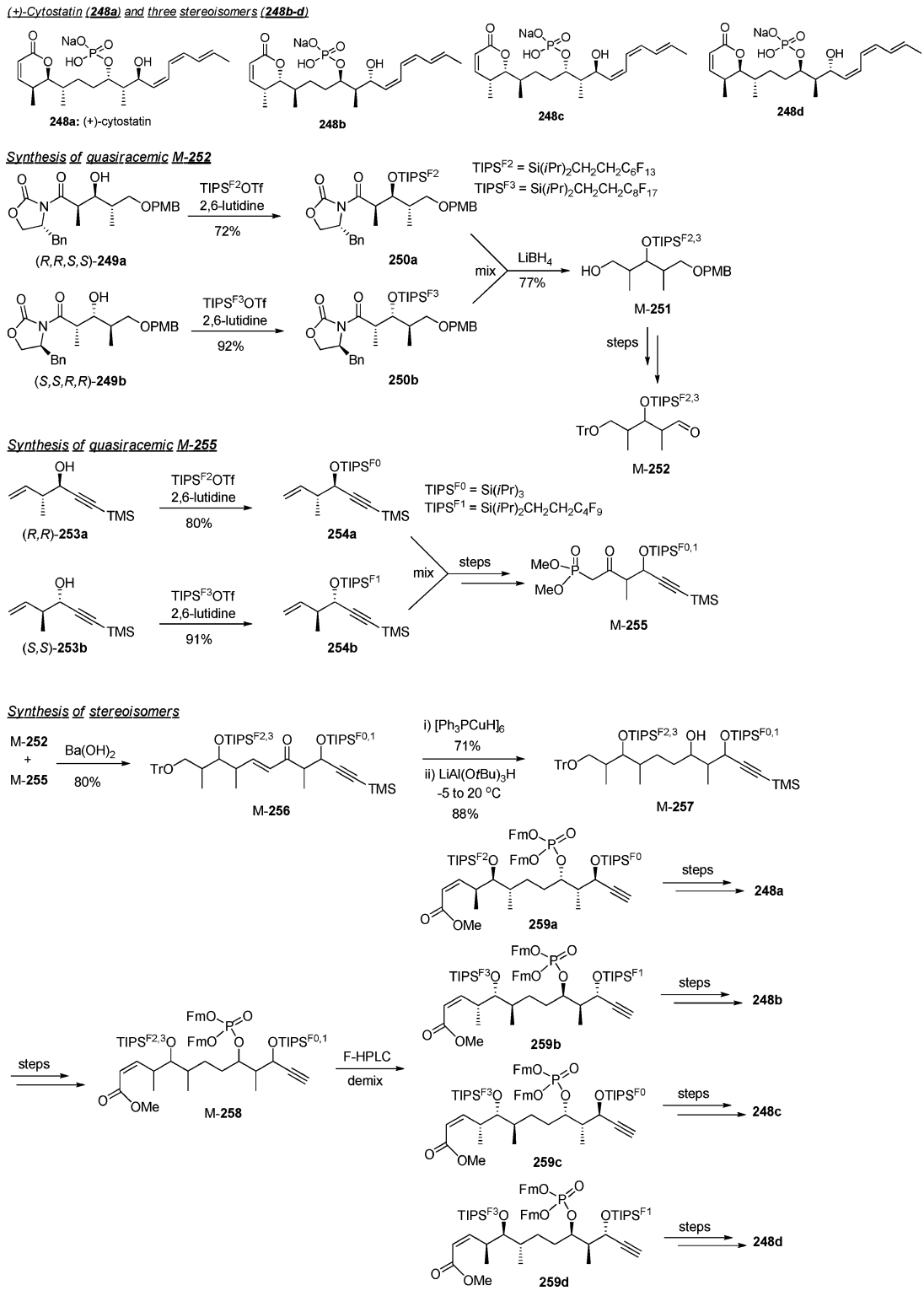


Figure 23. Fluorous mixture synthesis of (+)-cytostatin stereoisomers.[205]

highlighted in Figure 24 have been applied to the preparation of 5-membered ring analogs.[155]

Fluorous Synthesis of Structurally Diverse Cyclic Silaketals and Related *Z*-Alkenes.[459] Using silaketal to tether allylic or homoallylic alcohols for cross-metathesis is a new strategy for selective synthesis of the *Z*-isomer of dihydroxyalkenes. This approach has been employed in the target and library synthesis of attenol A, mucocin, and epothilones. The Nelson group recently reported a fluorous protocol to improve the separation efficiency of unsymmetrical silaketal tethered ring-closing metathesis reactions (Figure 25).[459] In this work, an allylic alcohol with fluorous-linker **265** was tethered to another allylic alcohol derivative **266** to form silaketal **267**. Ring-closing metathesis of the silaketal generated the desired cyclic product **268** and simultaneously released the fluorous

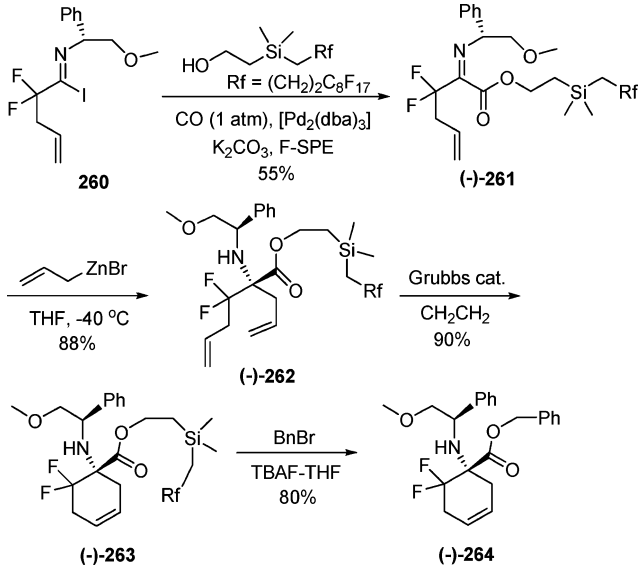


Figure 24. Fluorous synthesis of chiral cyclic β,β-difluorinated α-amino acid derivative.[458]

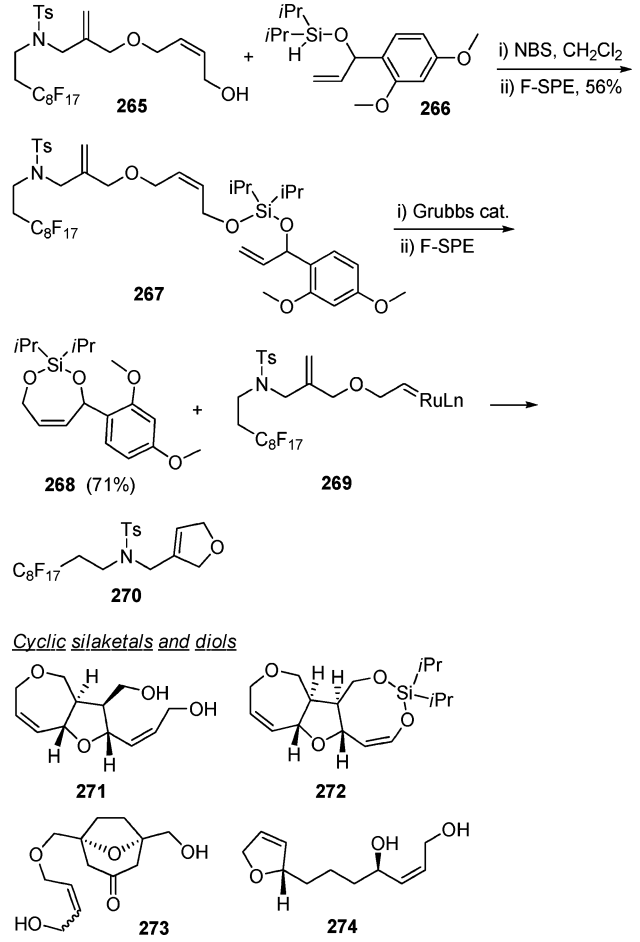


Figure 25. Fluorous synthesis of cyclic silaketals.[459]

component **269**. Subsequent ring-closing metathesis of **269** regenerated the fluorous linker **270** as a substituted 2,5-dihydrofuran. The feature of this new protocol is that both silaketal **267** and fluorous linker **270** can be easily purified by F-SPE. Structurally diverse cyclic silaketals **271**−**274** and related ring-opened diols were prepared by ring-closing metathesis. The same research group has also used a fluorous Grubbs catalyst for the ring-closing metathesis reactions. In this case, both the cleaved fluorous linker and the catalyst were collected in the fluorous fraction after F-SPE.[457]

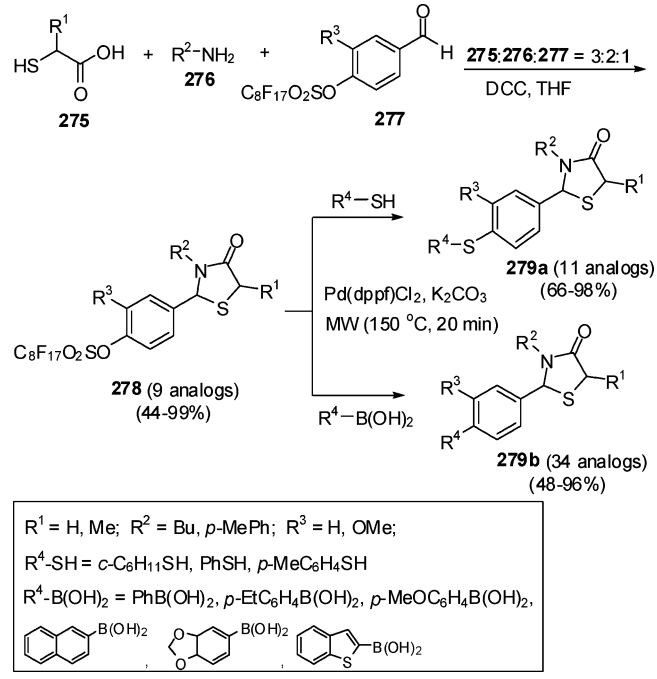
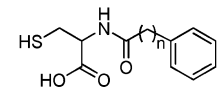


Figure 26. Fluorous benzaldehyde-based synthesis of 2-arylsubstituted 4-thiazolidinones.[440]

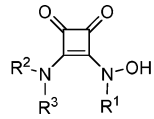
Microwave-Assisted Fluorous Synthesis of Substituted Thiazolidinones.[440] Substituted thiazolidinones possess a wide range of biological activities. Among them, the 2-imine-substituted 4-thiazolidinones have shown selective cytotoxicity to both paclitaxel sensitive and resistant lung cancer cells and are nontoxic to normal human fibroblast.[573] The Yan and Zhang groups developed a microwave-assisted fluorous method and synthesized a 2-arylsubstituted 4-thiazolidinone library for quantitative structure activity relationship (QSAR) studies (Figure 26).[440] The three-component reaction for the preparation of 4-thiazolidinones **278** involved reaction of fluorous benzaldehydes **277** with excess amounts of the nonfluorous components mercaptoacetic acids **275** and amines **276**. Thus, no fluorous starting material was left over and the condensed products containing the fluorous tag were easily isolated from the reaction mixture by F-SPE. The purified compounds **278** were then subjected to Pd-catalyzed fluorous tag cleavage reactions with thiols and boronic acids to form compounds **279a** and **279b**, respectively. The reaction mixtures were also purified by F-SPE and gave final product purities between 74−100%. To ensure the quality of compounds for cell-based screening, all 60 final products were further purified by semipreparative HPLC. This fluorous tag-facilitated synthetic method has been extended for a small library of the structurally related 2-aryl-substituted 4-thiazinanones.

Table 1. Chemical Libraries Targeting Proteases[a]

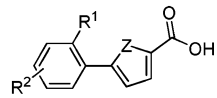
Metallo proteases



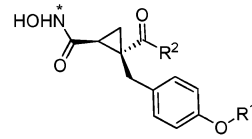
• Library 1.1
• Lienard [245]
• BcII metallo-β-lactamase inhibitors from a dynamic combinatorial library of thiols/disulfides



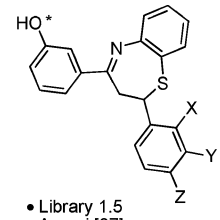
• Library 1.2
• Charton [85]
• zinc metalloenzyme ADAMTS-5 inhibitors



• Library 1.3
• Vedantham [391]
• methionine amino-peptidase inhibitors

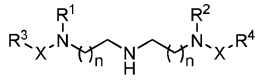


• Library 1.4
• Zhu [283]
• tumor necrosis factor-α converting enzyme inhibitors

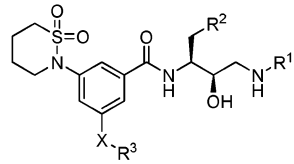


• Library 1.5
• Ansari [27]
• butyrylcholinesterase inhibitors

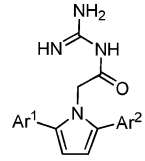
Aspartyl proteases



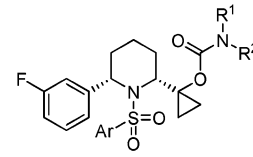
• Library 1.6
• Blum [52]
• HIV, plasmepsin II and IV, renin, BACE-1, pepsin inhibitors



• Library 1.7
• Beswick [49]
• BACE-1 inhibitors

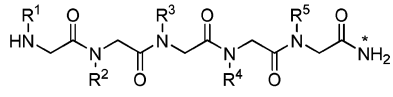


• Library 1.8
• Cole [105]
• β-secretase inhibitors

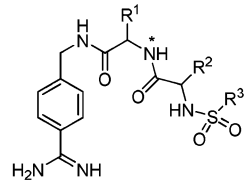


• Library 1.9
• Vaccaro [389]
• γ-secretase inhibitors

Serine proteases

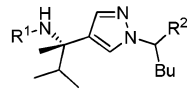


• Library 1.10
• Messeguer [267]
• trypsin inhibitors

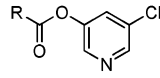


• Library 1.11
• Shiraishi [358]
• factor VIIa inhibitors

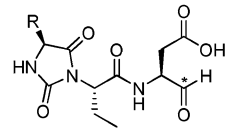
Cysteine proteases



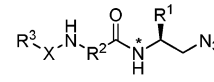
• Library 1.12
• Brak [60]
• cruzain inhibitors; R^2 = vinyl sulfone or aryloxyketone



• Library 1.13
• Huitema [189]
• hepatitis A virus 3C proteinase inhibitors



• Library 1.14
• Vazquez [390]
• caspase-3 inhibitors

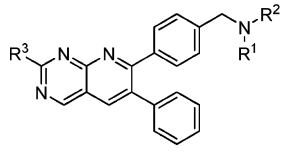


• Library 1.15
• Yang [427]
• caspase-1 inhibitors

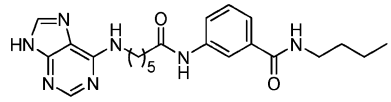
[a] Asterisk is the point of attachment to resin.

Table 2. Chemical Libraries Targeting Nonproteolytic Enzymes[a]

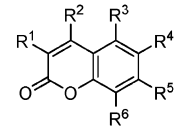
Kinases and Phosphatases



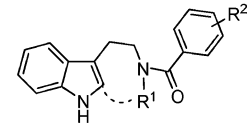
• Library 2.1
• Wu [414]
• dual Akt1/2 inhibitors



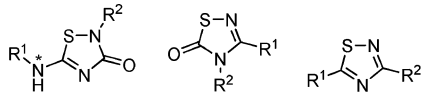
• Library 2.2
• Cancilla [72]
• aurora kinase inhibitor derived from site -specific dynamic combinatorial chemistry



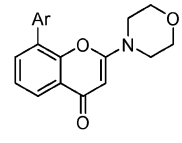
• Library 2.3
• Chilin [94]
• casein kinase 2 (CK2) inhibitors



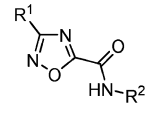
• Library 2.4
• Jenkins [196]
• CDK4 inhibitors



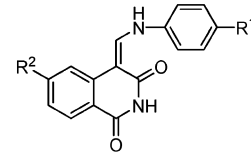
• Library 2.5
• Castro [78]
• glycogen synthase kinase 3β (GSK-3β) inhibitors



• Library 2.6
• Murr [279]
• DNA-dependent protein kinase inhibitors

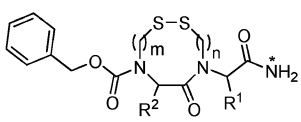


• Library 2.7
• Koryakova [214]
• GSK-3 inhibitors

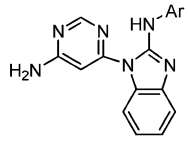


• Library 2.8
• Mayer [264]
• insulin-like growth factor receptor (IGF-1R) inhibitors

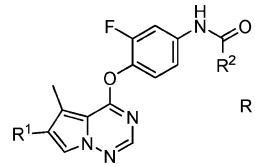
Table 2. Continued



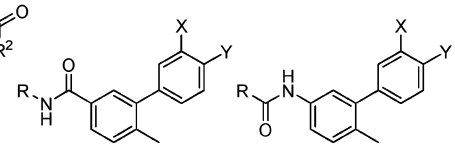
• Library 2.9
• Qvit [313]
• insulin-like growth factor-1 (IGF-1) receptor (IGF-1R) tyrosine kinase inhibitors



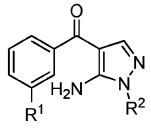
• Library 2.10
• Zhang [433]
• Lck inhibitors



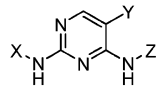
• Library 2.11
• Schroeder [339]
• Met kinase inhibitors



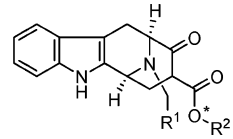
• Library 2.12
• Baldwin [35]
• p38 MAP kinase inhibitors



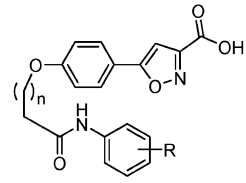
• Library 2.13
• Bagley [33]
• p38 MAPK inhibitors



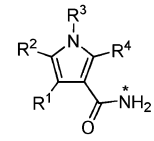
• Library 2.14
• Walker [399]
• proline-rich tyrosine kinase 2 (PYK2) and focal adhesion kinase (FAK) inhibitors



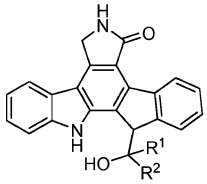
• Library 2.15
• Noeren-Muller [286]
• *M. tuberculosis* protein tyrosine phosphatase B inhibitors



• Library 2.16
• Srinivasan [367]
• protein tyrosine phosphatase inhibitors

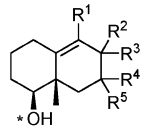


• Library 2.17
• Bang [38]
• Wip 1 phosphatase inhibitors

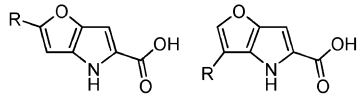


• Library 2.18
• Tripathy [382]
• TrkA kinase inhibitors

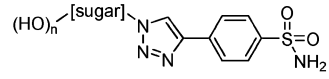
Alphabetical order



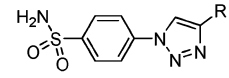
• Library 2.19
• Scheck [337]
• acetylcholinesterase inhibitors



• Library 2.20
• Sparey [365]
• D-amino acid oxidase (DAO) inhibitors

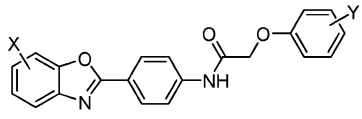


• Library 2.21
• Wilkinson [410]
• carbonic anhydrase II inhibitors

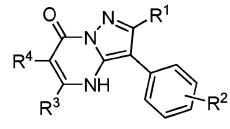


• Library 2.22
• Poulsen [308]
• dual human mitochondrial carbonic anhydrase VA and VB inhibitors

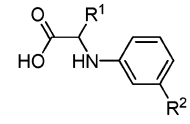
• Library 2.23
• Krungkrai [216]
• *P. falciparum* carbonic anhydrase inhibitors



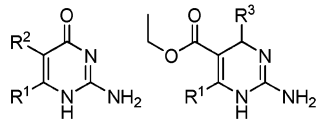
• Library 2.24
• Harikrishnan [180]
• cholesteryl ester transfer protein inhibitors



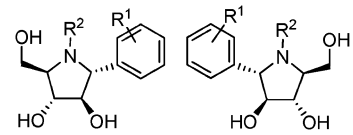
• Library 2.25
• Mao [259]
• *Mycobacterium tuberculosis* 1-deoxy-D-xylulose 5-phosphate synthase inhibitors



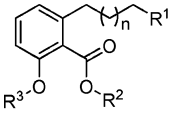
• Library 2.26
• Nordqvist [288]
• *Mycobacterium tuberculosis* glutamine synthetase inhibitors



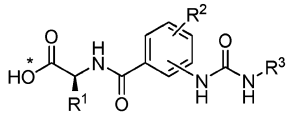
• Library 2.27
• Wyatt [415]
• anti-MRSA dihydrofolate reductase inhibitors derived from DOS



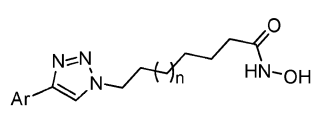
• Library 2.28
• Tsou [384]
• α-glucosidase inhibitors



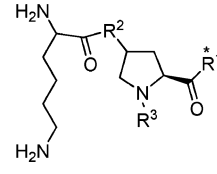
• Library 2.29
• Pereira [299]
• *T. cruzi* glyceraldehyde-3-phosphate dehydrogenase inhibitors



• Library 2.30
• Evans [143]
• glycogen phosphorylase inhibitors

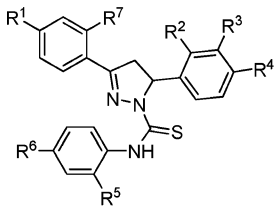


• Library 2.31
• Pirali [303]
• histone deacetylase inhibitors

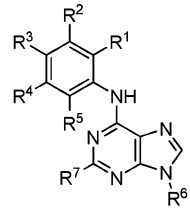


• Library 2.32
• Farrera-Sinfreu [149]
• lysyl-tRNA synthetase inhibitors

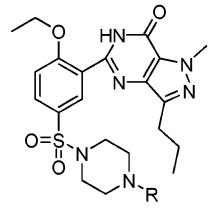
Table 2. Continued



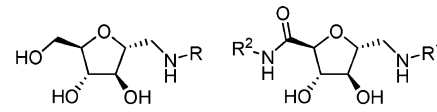
- Library 2.33
- Jayaprakash [194]
- MAO inhibitors



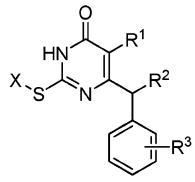
- Library 2.34
- Zatloukal [431]
- *A. thaliana* cytokinin oxidase/dehydrogenase inhibitors



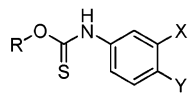
- Library 2.35
- Toque [152]
- PDE5 inhibitors



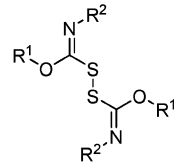
- Library 2.36
- Nowicki [289]
- dual *Trypanosoma brucei* phosphofructokinase (PFK) and *Leishmania mexicana* pyruvate kinase (PyK) inhibitors



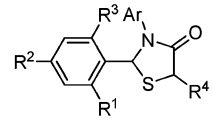
- Library 2.37
- Mugnaini [277]
- reverse transcriptase inhibitors



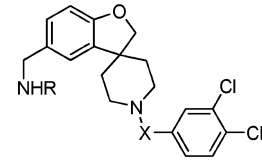
- Library 2.38
- Cesarini [80, 81]
- non-nuleoside HIV-1 reverse transcriptase inhibitors



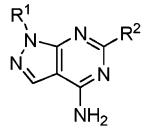
- Library 2.39
- Cesarini [82]
- non-nuleoside HIV-1 reverse transcriptase inhibitors



- Library 2.40
- Rawal [315]
- hepatitis C virus (HCV) NS5B RNA polymerase inhibitors



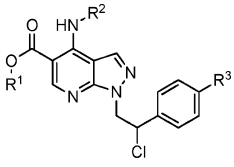
- Library 2.41
- Costanzo [110]
- human mast cell tryptase inhibitors



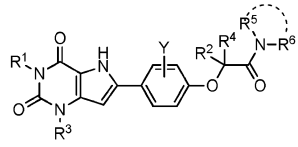
- Library 2.42
- Oliveira-Campos [294]
- xanthine oxidase inhibitors

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

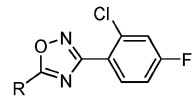
Table 3. Chemical Libraries Targeting G-Protein Coupled Receptors[a]



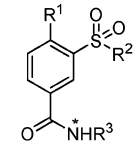
- Library 3.1
- Tuccinardi [386]
- A_1 adenosine receptor antagonists



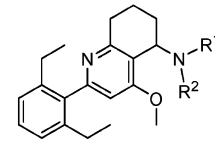
- Library 3.2
- Stefanachi [369]
- human A_{2B} adenosine receptor antagonists



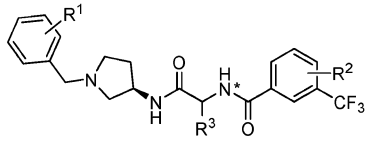
- Library 3.3
- DiMauro [130]
- cannabinoid-2 (CB2) receptor agonists



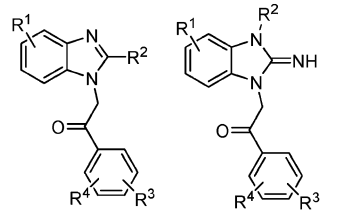
- Library 3.4
- Worm [412]
- CB_2 cannabinoid receptor agonists



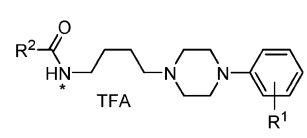
- Library 3.5
- Barbay [39]
- C5a receptor antagonists



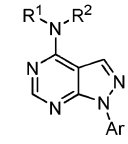
- Library 3.6
- Moree [275]
- CCR2b receptor antagonists



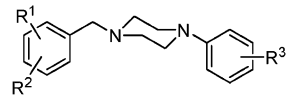
- Library 3.7
- Hayes [182]
- chemokine receptor CXCR3 antagonists



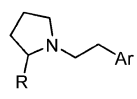
- Library 3.8
- Jean [195]
- dopamine D_3 receptor ligands



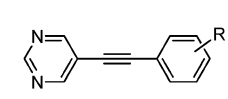
- Library 3.9
- Niswender [285]
- mGluR4 positive allosteric modulators



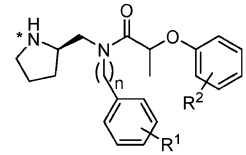
- Library 3.10
- Tietze [380]
- dopamine D4 selective ligands



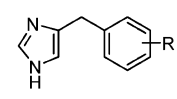
- Library 3.11
- Nersesian [282]
- histamine H_3 receptor antagonists



- Library 3.12
- Sharma [353]
- mGluR5 allosteric partial antagonists

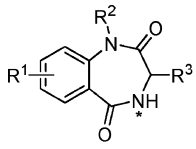


- Library 3.13
- Zhai [432]
- growth hormone secretagogue receptor (GHSR) agonists

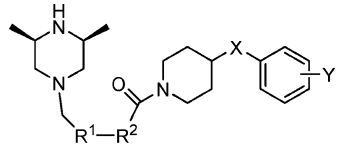


- Library 3.14
- Wijtmans [409]
- histamine H_3 receptor agonists

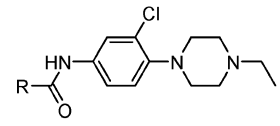
Table 3. Continued



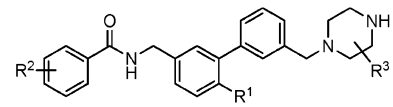
- Library 3.15
- Joseph [204]
- melanocortin receptor agonists



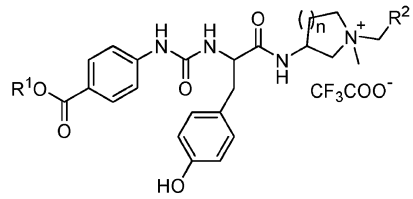
- Library 3.16
- Westaway [406]
- motilin receptor agonists



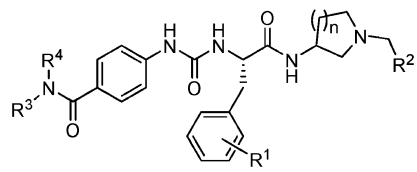
- Library 3.17
- Lewis [237]
- muscarinic acetylcholine receptor subtype 1 (M_1 mAChR) antagonists



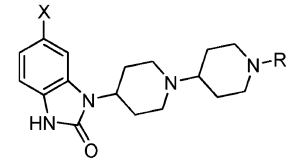
- Library 3.18
- Jin [200]
- long acting muscarinic acetylcholine receptor antagonists



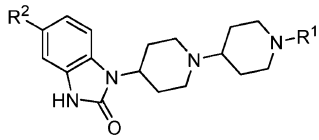
- Library 3.19
- Jin [201]
- long acting muscarinic acetylcholine receptor antagonists



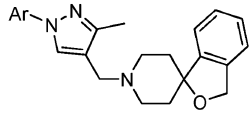
- Library 3.20
- Jin [202]
- muscarinic acetylcholine receptor antagonists



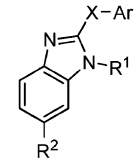
- Library 3.21
- Miller [271]
- M_1 receptor allosteric agonists



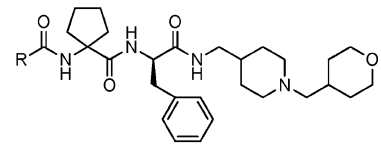
- Library 3.22
- Bridges [62]
- M_1 receptor allosteric agonists



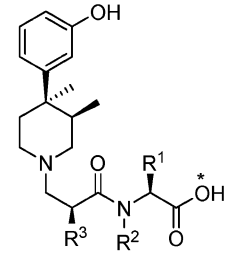
- Library 3.23
- Yoshizumi [430]
- ORL1 receptor antagonists



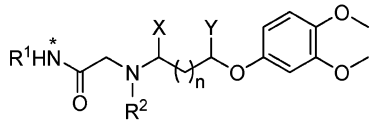
- Library 3.24
- Micco [269]
- α7 neuronal nicotinic acetylcholine receptors (nAChRs) agonists



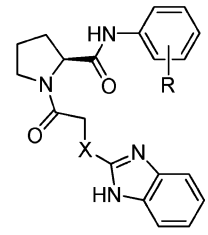
- Library 3.25
- Porcelloni [306]
- hNK_2 receptor antagonists



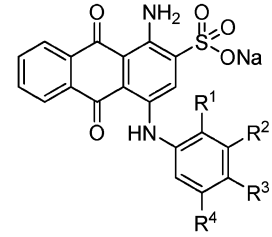
- Library 3.26
- Le Bourdonnec [228]
- μ opioid receptor antagonists



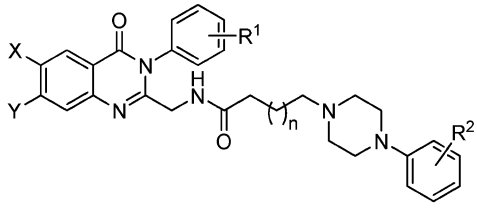
- Library 3.27
- Cole [104]
- orexin-2 receptor antagonists



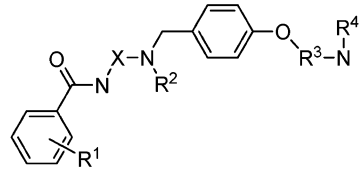
- Library 3.28
- Bergman [48]
- orexin receptor antagonists



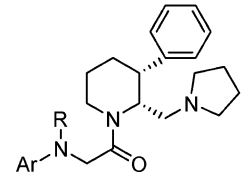
- Library 3.29
- Weyler [407]
- P_2Y_2 receptor antagonists



- Library 3.30
- Na [280]
- 5-HT_7 receptor antagonists



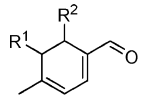
- Library 3.31
- Jin [199]
- urotensin-II receptor antagonists



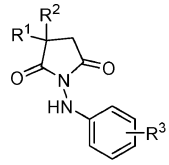
- Library 3.32
- Jin [203]
- urotensin-II receptor antagonists

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

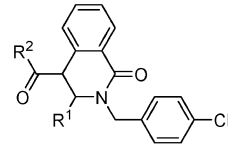
Table 4. Chemical Libraries Targeting Non-G-Protein-Coupled Receptors[a]



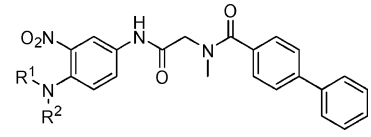
- Library 4.1
- Bench [47]
- activators of neurite outgrowth



- Library 4.2
- Kaminski [207]
- anticonvulsant activity in electrical (MES) and/or pentylenetetrazole induced seizure (*sc*PTZ) models

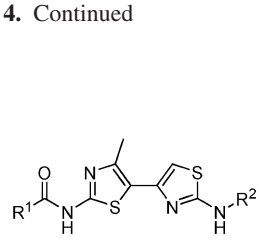


- Library 4.3
- Gitto [165]
- anticonvulsant activity against audiogenic seizures in DBA/2 mice

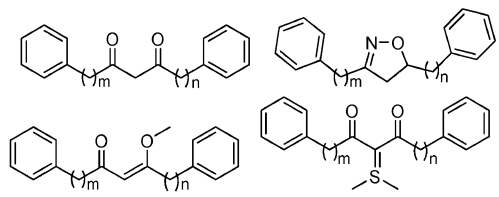


- Library 4.4
- Domling [134]
- Bcl-2 family protein-protein disruptor

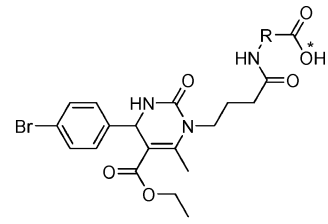
Table 4. Continued



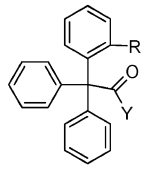
- Library 4.5
- Yoo [428]
- ΔF508-CFTR corrector activity



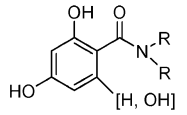
- Library 4.6
- Pulkkinen [311]
- dual estrogen receptor α (ERα) and estrogen receptor β (ERβ) ligands



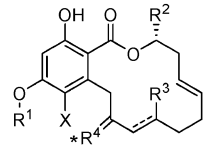
- Library 4.7
- Wisen [411]
- heat shock protein 70 (Hsp70) modulators



- Library 4.8
- McNaughton-Smith [265]
- Gardos channel blockers

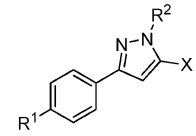


- Library 4.9
- Kung [223]
- Hsp90 molecular chaperone inhibitors

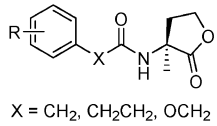


- Library 4.10
- Barluenga [42]
- Hsp90 inhibitors

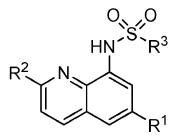
- Library 4.11
- Fanto [147]
- myeloid differentiation factor 88 inhibitors



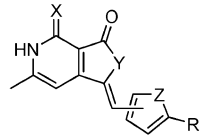
- Library 4.12
- Cocconcelli [102]
- neuroprotective activity in NMDA toxicity assay



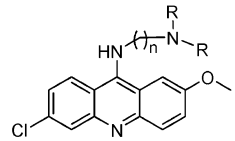
- Library 4.13
- Geske [163]
- quorum sensing receptor modulators against *P. aeruginosa* and *V. fischeri*



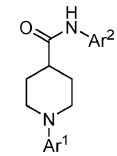
- Library 4.14
- Xie [420]
- down-regulators of NFκB activity



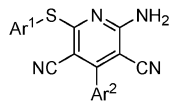
- Library 4.15
- Lena [236]
- inhibitors of the cytolytic effects of the pore-forming glycoprotein perforin



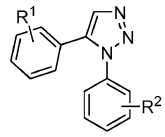
- Library 4.16
- Thi [376]
- antiprion activity (reduction of PrP^{Sc} in ScN2a cells)



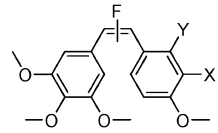
- Library 4.17
- Cheung [93]
- TRPV1 antagonists



- Library 4.18
- Guo [175]
- inhibition of cell-surface glycosylphosphatidylinositol (GPI)-anchored protein PrP^{C} to a partially protease resistant protein isoform PrP^{Sc}



- Library 4.19
- Cafici [70]
- tubulin aggregation inhibitors

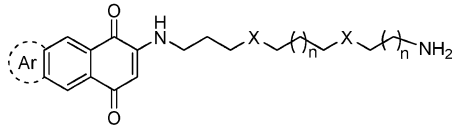


- Library 4.20
- Alloatti [24]
- tubulin aggregation inhibitors

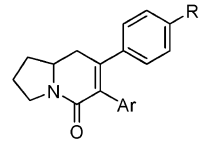
[a] Asterisk is the point of attachment to resin.

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

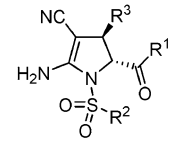
Cytotoxic agents



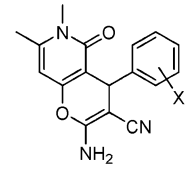
- Library 5.1
- Bolognesi [55]
- HT29 cell proliferation inhibitors



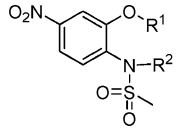
- Library 5.2
- Kimball [213]
- HCT-116 colon cancer cell proliferation inhibitors



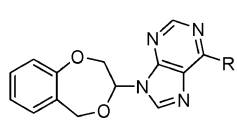
- Library 5.3
- Magedov [256]
- apoptosis inducers in Jurkat cells



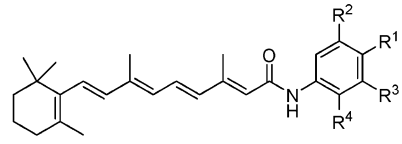
- Library 5.4
- Magedov [257]
- cell cycle arresters in Jurkat cells



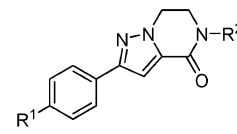
- Library 5.5
- Su [371, 372]
- suppression of aromatase activity in SK-BR-3 cells



- Library 5.6
- Conejo-Garcia [107]
- MCF-7 cell proliferation inhibitors

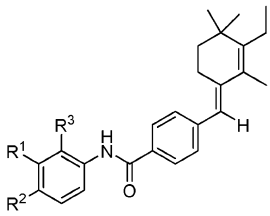


- Library 5.7
- Das [122]
- rhabdoid cell proliferation inhibitors

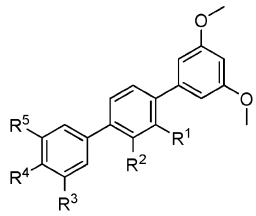


- Library 5.8
- Zhang [434]
- A549 lung cancer cells

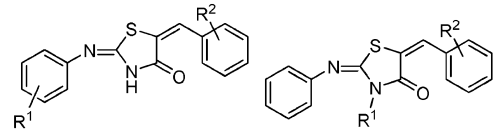
Table 5. Continued



• Library 5.9
• Das [121]
• rhabdoid cell proliferation inhibitors

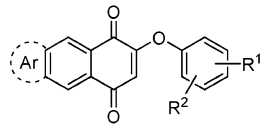


• Library 5.10
• Pizzirani [305]
• inhibition of cell-cycle progression at the G1 to S transition, acting on retinoblastoma phosphorylation and inducing cell differentiation

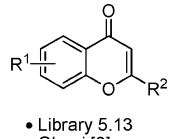


• Library 5.11
• Zhou [441]
• drug-resistant lung cancer cells

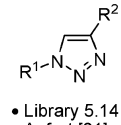
Antiinfective agents



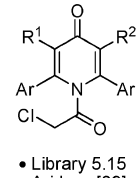
• Library 5.12
• Bolognesi [56]
• blood trypomastigote form of *Trypanosoma brucei rhodesiense*



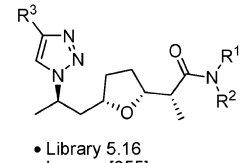
• Library 5.13
• Ghani [2]
• *A. niger*



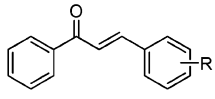
• Library 5.14
• Aufort [31]
• *S. aureus*



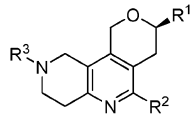
• Library 5.15
• Aridoss [29]
• *S. aureus, P. aeruginosa*



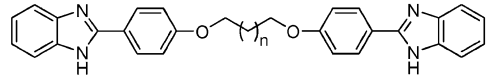
• Library 5.16
• Luesse [255]
• *E. coli*



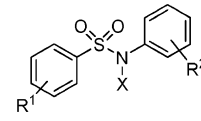
• Library 5.17
• Liu [250]
• *S. aureus*



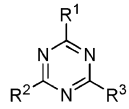
• Library 5.18
• Zhou [375]
• *M. tuberculosis*



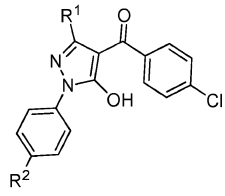
• Library 5.19
• Mayence [263]
• *L. donovani*



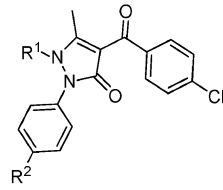
• Library 5.20
• Namba [281]
• methicillin-resistant *S. aureus* and vancomycin -resistant *Enterococcus*

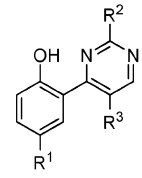


• Library 5.21
• Melato [266]
• D10 (CQ-sensitive) and W2 (CQ-resistant) strains of *P. falciparum*

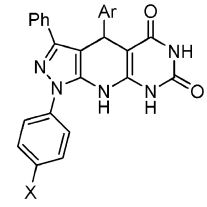


• Library 5.22
• Castagnolo [77]
• *M. tuberculosis*

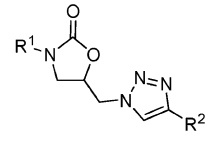




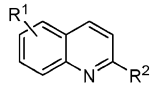
• Library 5.23
• Cheng [91]
• *Influenza A* virus



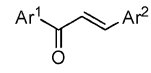
• Library 5.24
• Bazgir [45]
• *S. aureus*



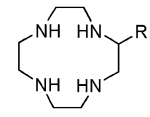
• Library 5.25
• Demaray [127]
• *Enterococcus faecalis* ATCC 29212



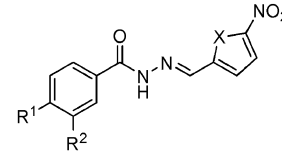
• Library 5.26
• Schramm [338]
• *P. falciparum* and other parasites



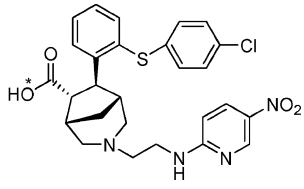
• Library 5.27
• Reichwald [317]
• inhibition of axenic *L. donovani* amastigotes

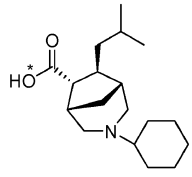


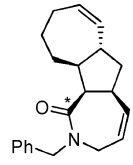
• Library 5.28
• Reid [318]
• *P. falciparum* and other parasites



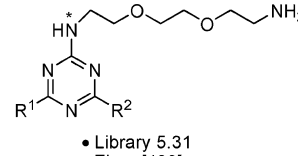
• Library 5.29
• Rando [314]
• *L. donovani*



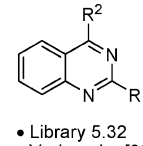




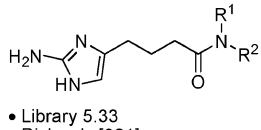
• Library 5.30
• Thomas [377]
• MR-*S. aureus* (MRSA); representative compounds from DOS library



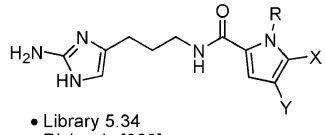
• Library 5.31
• Zhou [439]
• *S. aureus*



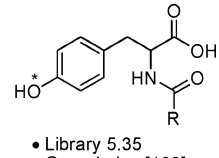
• Library 5.32
• Verhaeghe [395]
• *Plasmodium falciparum*



• Library 5.33
• Richards [321]
• *Pseudomonas aeruginosa* biofilms



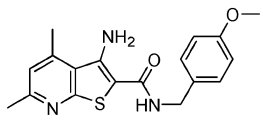
• Library 5.34
• Richards [320]
• *P. aeruginosa* biofilms



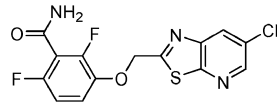
• Library 5.35
• Georgiades [162]
• *P. aeruginosa* biofilms

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

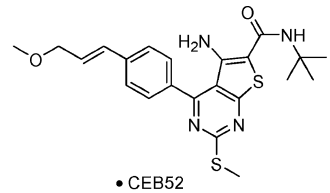
Table 6. Selected Molecular Probes



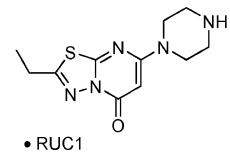
- VU0152100
- Vanderbilt University
- Brady [462]
- M4 receptor allosteric potentiator



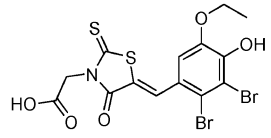
- PC190723
- Prolysis
- Haydon [463]
- FtsZ inhibitor



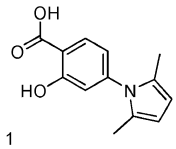
- CEB52
- NIDDK/NCGC
- Neumann [464]
- TSHR antagonist



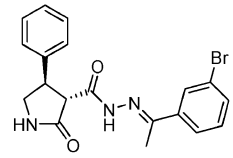
- RUC1
- Rockefeller University
- Blue [465]
- αIIbβ3 specific inhibitor



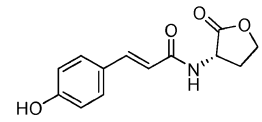
- RU7
- Rockefeller University
- Georgescu [466]
- DNA Pol III sliding clamp inhibitor



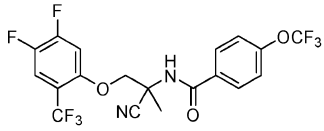
- Cmpd 1
- Burnham Institute for Medical Research
- Noberini [467]
- EphA4/EphA2 receptor inhibitor



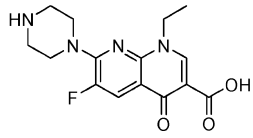
- AC-264613
- ACADIA Pharmaceuticals
- Gardell [468]
- PAR 2 agonist



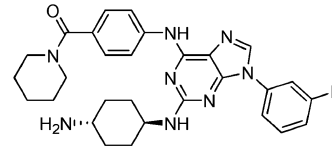
- pC-HSL
- University of Washington
- Schaefer [470]
- quorum-sensing signaling agent



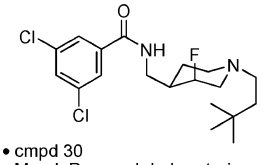
- AAD1470
- Novartis and University of Bern
- Kaminsky [469]
- anthelmintic (possible AchR activator)



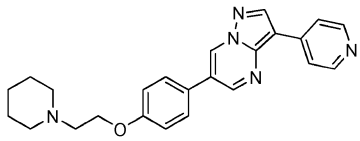
- Enoxacin
- Emory University
- Shan [471]
- RNAi and mRNA modulator



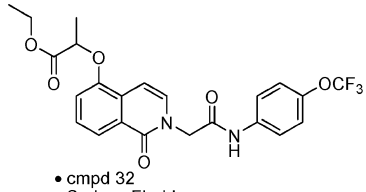
- Purfalcamine
- The Scripps Research Institute/GNF
- Kato [472]
- PfCDPK1 inhibitor



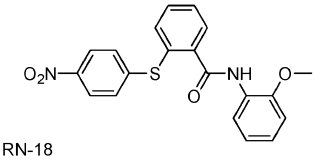
- cmpd 30
- Merck Research Laboratories
- Yang [478]
- T-type calcium channel inhibitor



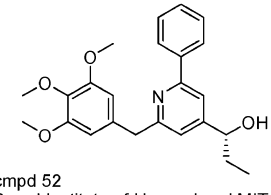
- Dorsomorphin
- Harvard Medical School
- Yu [473]
- BMP signaling inhibitor



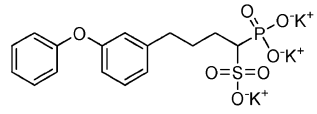
- cmpd 32
- Scripps Florida
- Roth [477]
- steroidogenic factor-1 inhibitor



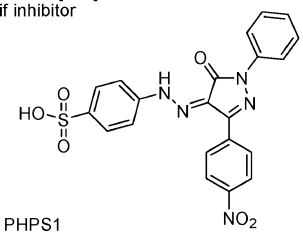
- RN-18
- University of Massachusetts Medical School
- Nathans [479]
- Vif inhibitor



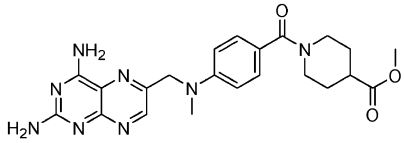
- cmpd 52
- Broad Institute of Harvard and MIT
- Gray [474]
- Neuregulin/ErbB4 signaling inhibitor



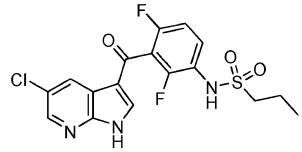
- BPH-652
- Academia Sinica/Cedars-Sinai Medical Center
- Liu [475]
- *S. aureus* dehydrosqualene synthase inhibitor



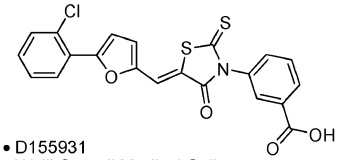
- PHPS1
- Max Delbrück Center for Molecular Medicine
- Hellmuth [482]
- Shp2 (PTPN11) inhibitor



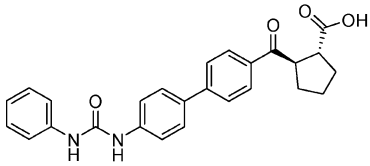
- cmpd 6b
- Università di Modena e Reggio Emilia
- Cavazzuti [480]
- pteridine reductase inhibitor



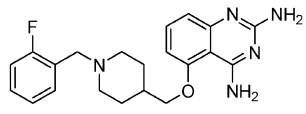
- PLX4720
- Plexxikon
- Tsai [481]
- B-RafV600E inhibitor



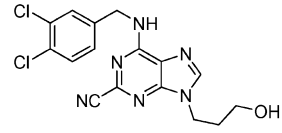
- D155931
- Weill Cornell Medical College
- Bryk [476]
- dihydrolipoamide acyltransferase inhibitor



- cmpd 4a
- Abbott Laboratories
- Zhao [483]
- DGAT-1 inhibitor

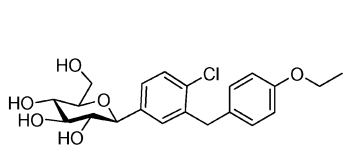


- cmpd 11a
- deCODE Chemistry, Inc.
- Thurmond [484]
- SMN2 promoter activator

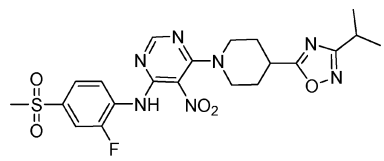


- cmpd 3{12, 2}
- University of California, San Francisco
- Mallari [485]
- TbcatB inhibitor

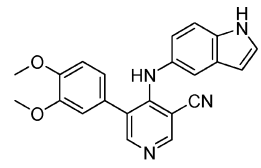
Table 6. Continued



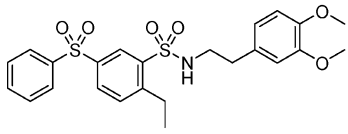
- Dapagliflozin
- Bristol-Myers Squibb Company
- Meng [486]
- SGLT2 inhibitor



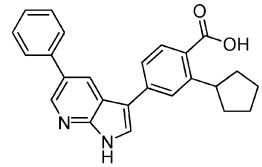
- cmpd 8g
- Arena Pharmaceuticals
- Semple [487]
- GPR119 agonist



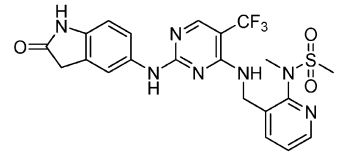
- cmpd 4p
- Wyeth Research
- Cole [488]
- PKCθ inhibitor



- cmpd 17
- Wyeth Research
- Gopalsamy [489]
- sFRP-1 inhibitor



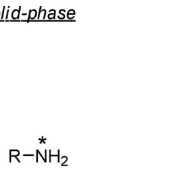
- GSK650394
- GlaxoSmithKline/Duke University
- Sherk [490]
- SGK1 inhibitor



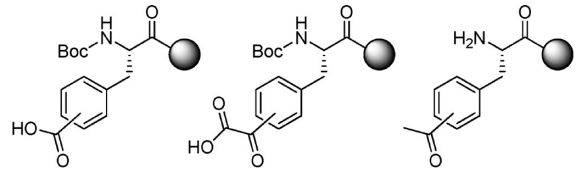
- PF-562,271-26
- Pfizer Oncology
- Roberts [491]
- FAK inhibitor

Table 7. Scaffold Derivatization and Acyclic Synthesis[a]

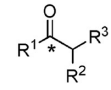
Solid-phase



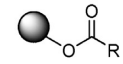
- Ayesa [32]
- from resin-bound Ph_3P, R^1N_3 and R^2CH_2X



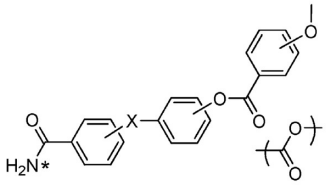
- Le Quement [230]
- divergent pathway for the solid-phase conversion of aromatic acetylenes to carboxylic acids, α-ketocarboxylic acids, and methyl ketones



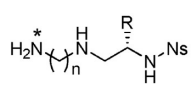
- Lazny [227]
- asymmetric alkylation of ketones immobilized via SAMP hydrazone



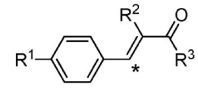
- Laborde [224]
- immobilization of RCO_2H using $(t\mathrm{BuCO})_2O$ as coupling reagent



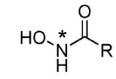
- Doi [133]
- sequential palladium-catalyzed coupling reactions



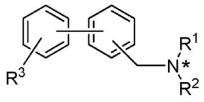
- Crestey [112]
- MW-assisted ring-opening of hindered aziridines and a resin-bound secondary amine



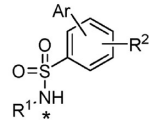
- Chang [84]
- alkylation of resin-bound benzyl sulfinate with allylbromide, ozonolysis and traceless sulfinate elimination



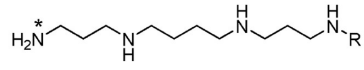
- Choi [97]
- cleavage of Marshall resin-bound caboxylic acids with NH_2OH



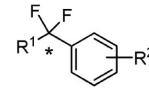
- Severinsen [341]
- multistep sequence using safety catch linker



- Gutierrez [177]
- $ClTi(O\mathit{i}Pr)_3$-promoted reductive amination, sulfonylation of the resin-bound amine, Suzuki cross-coupling, and acid-mediated cleavage

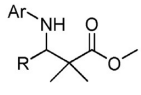


- Hahn [178]
- multistep sequence

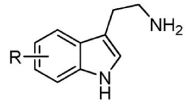


- Wiehn [408]
- fluorinating cleavage of resin-bound dithianes with NIS/HF

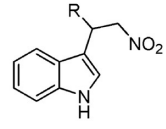
Solution-phase



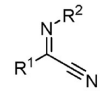
- Alaimo [14]
- In-catalyzed domino reaction of $ArNO_2$, RCHO and Danishefsky's diene or silyl ketene acetal



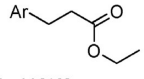
- Nicolaou [284]
- cascade sequence initiated by regioselective base-induced deprotonation of spiro carbamates



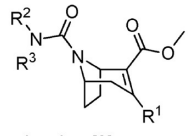
- Arai [28]
- 3CR via asymmetric tandem Friedel-Crafts/Henry reaction of indoles, nitroalkenes, RCHO and chiral CuOTf catalyst



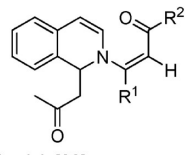
- Fontaine [153]
- 3CR of R^1CHO, R^2NH_2, and TMSCN then IBX oxidation



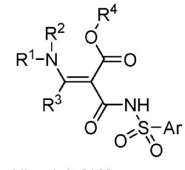
- Alacid [13]
- Heck reaction of acrolein diethyl acetal with aryl halides catalyzed by Kaiser oxime resin derived palladacycle



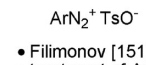
- Agarkov [8]
- multistep sequence from tropinone



- Alizadeh [22]
- 4CR of isoquinoline, electron -deficient acetylene compounds, diketene and water

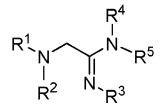


- Alizadeh [18]
- 3CR of amine, acetylenic compound, and $ArSO_2NCO$

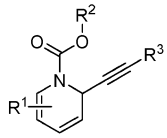


- Filimonov [151]
- treatment of $ArNH_2$ with polymer-supported nitrite

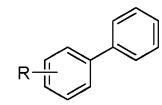
Table 7. Continued



• Kim [212]
• Cu-catalyzed 3CR of sulfonyl of phosphoryl azides and amines



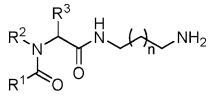
• Black [51]
• Cu-catalyzed coupling of pyridines and quinolines with alkynes



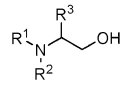
• Lee [231]
• Suzuki reaction of aryl chlorides with macroporous polystyrene-supported palladium catalyst

• Lehmann [235]
• MW-assisted reductive *N*-alkylation of methyl carbamate with aldehydes then hydrolysis

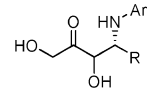
• Li [238]
• 3CR of benzylic and allylic alcohols, acyl chlorides, and HMDS



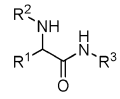
• Liu [249]
• Ugi 4CR of R^1COOH, R^2NH_2, R^3CHO and $BocNH(CH_2)_{11}CH_2NC$



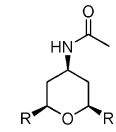
• Clerici [101]
• 4CR of R^1R^2NH, R^3CHO, MeOH and $TiCl_3$/*t*-BuOOH



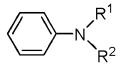
• Dziedzic [137]
• 3CR of dihydroxyacetone, $ArNH_2$ and RCHO



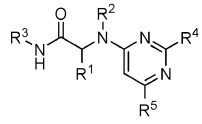
• Pan [296]
• Ugi 3CR of R^1CHO, R^2NH_2, R^3NC catalyzed by $PhHPO_2H$



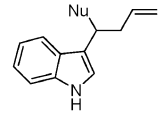
• Sabitha [327]
• Sakurai-Prins-Ritter reaction of RCHO and allylTMS



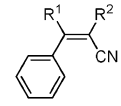
• Chen [89]
• MW-assisted Cu-promoted *N*-arylation of amines with arylboronic acids



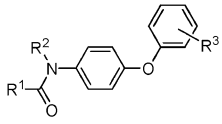
• Barthelon [43]
• Ugi/Smiles 4CR of pyrazinone or quinoxalinone derivatives with R^1CHO, R^2NH_2, and R^3NC



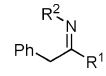
• Colombo [106]
• 3CR In-mediated Domino allylation of 1*H*-indole-3-carbaldehyde with electron-rich (hetero)arenes



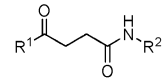
• Cheng [92]
• 3CR of aryl bromides, internal alkynes, and $K_4[Fe(CN_6)]$



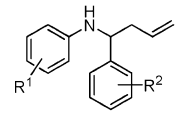
• Chen [90]
• Cu-catalyzed 3CR of phenols, amines, and 4-bromophenyl iodide



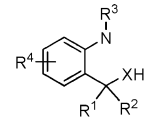
• Cho [96]
• 3CR of alkyne, sulfonyl azide, and heterocycle



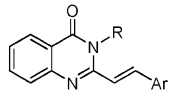
• Mittag [272]
• SmI_2/H_2O mediated coupling of *N*-peptidyl oxazolidinones with electron-deficient alkenes



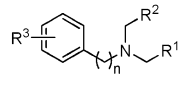
• Das [120]
• In-catalyzed 3CR of $ArNO_2$, ArCHO, $allylSn(Bu)_3$



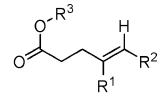
• Morishita [276]
• 3CR of arynes with aminosilanes and carbonyl compounds



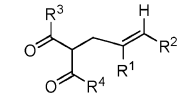
• Dabiri [115]
• tandem condensation of isatoic anhydride, a primary aniline or ammonium acetate, and triethylorthoacetate in the presence of ionic liquid



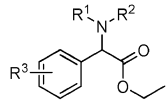
• Desforges [128]
• multistep sequence from heteroarylamines



• Herath [184]
• Ni-catalyzed 3CR of R^3OH, alkynes, and enals

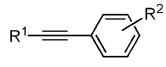


• Herath [184]
• Ni-catalyzed 3CR of R^4CHO, alkynes, and enals

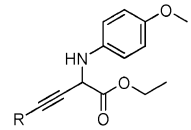


• Haurena [181]
• 3CR of in situ-generated aromatic or benzylic organozinc reagents, primary or secondary amines and ethyl glyoxylate

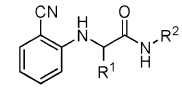
• Huang [187]
• Cu-promoted *N*-arylations of aryl halides with amines



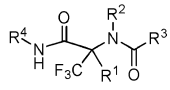
• Huang [186]
• MW-assisted Pd -catalyzed Sonogashira coupling of aryl chlorides



• Shao [352]
• Cu-catalyzed 3CR of ethyl glyoxylate, *p*-anisidine, and terminal alkynes

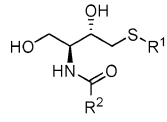


• Shaabani [343]
• 3CR of 2-aminobenzamide, R^1CHO, and R^2NC

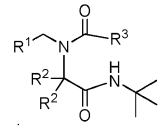


• Gulevich [174]
• Ugi 3CR of $F_3C(R^1)C{=}NR^2$, R^3CO_2H, and R^4NCO

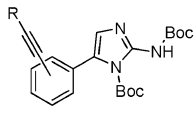
• Grzyb [173]
• DOS of ureas, carbamates, thiocarbamates, and amides using carbamoylimidazolium salts



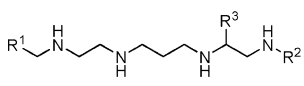
• Grijalvo [171]
• multistep sequence using polymer-supported scavengers



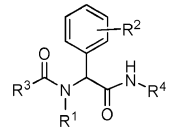
• Simila [360]
• Ugi 4CR of $R^1CH_2NH_2$, R^2COR^2, R^3CO_2H, and *t*-BuNC



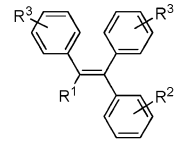
• Richards [322]
• Sonogashira coupling of *o*-, *m*-, and *p*-substituted iodobenzoic acid derivatives



• Pirali [302]
• 4CR of diamines, R^3CHO, R^2NCO, and $R^1CONHCH_2COOH$

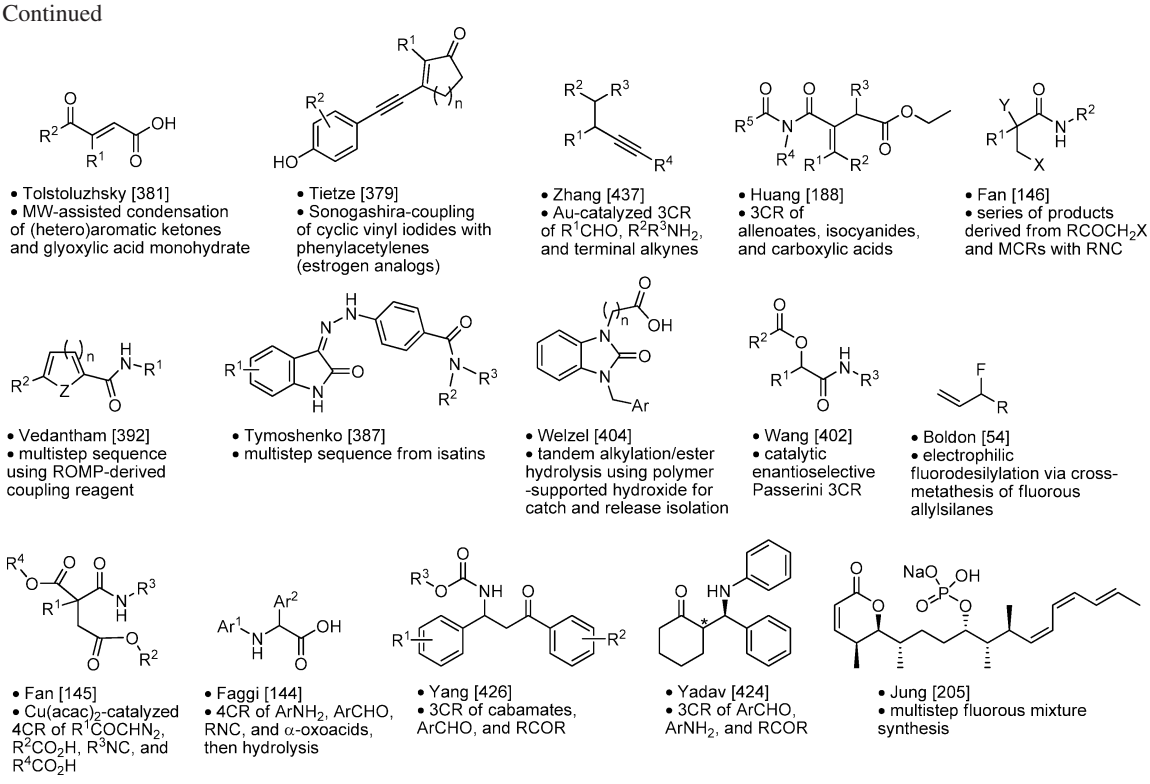


• Okandeji [292]
• Ugi 4CR of R^1NH_2, ArCHO, R^3COOH, R^4NC by $Sc(OTf)_3$ or $Yb(OTf)_3$



• Prokopcova [310]
• MW-assisted one-pot diboration/Suzuki cross -couplings of alkynes

Table 7. Continued



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

Table 8. Monocyclic Synthesis[a]

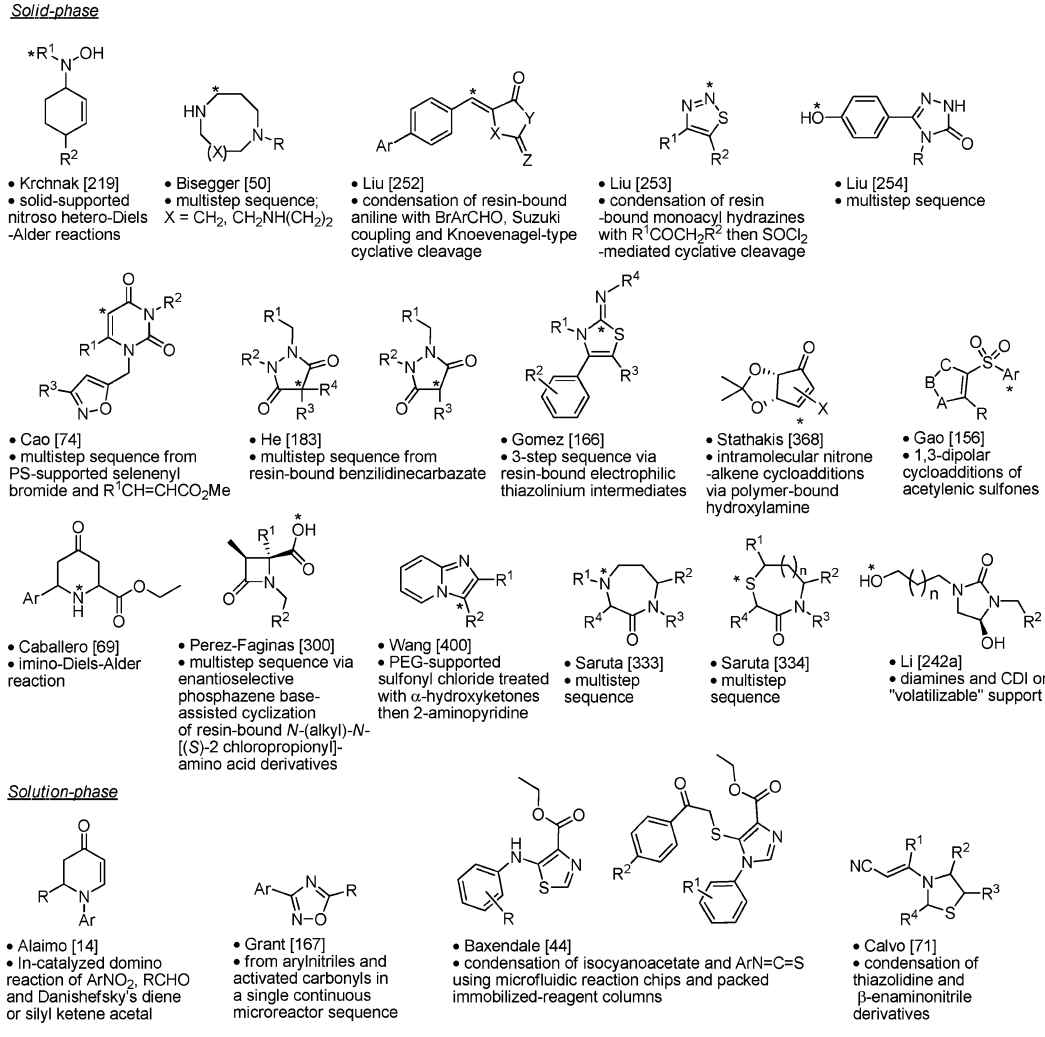
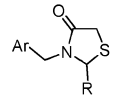
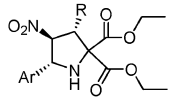


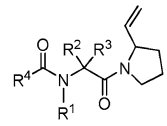
Table 8. Continued



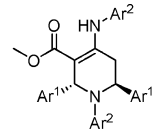
• Cunico [114]
• MW-assisted 3CR of ArCHO, amino acid and mercaptoacetic acid



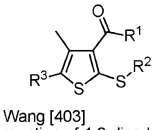
• Crovetto [113]
• 3CR of RCHO, aminomalonates, and nitroalkenes



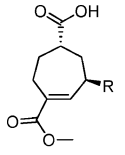
• Banfi [36]
• 4CR then palladium -mediated S_N2' cyclization

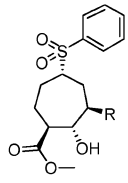


• Clarke [100]
• 5CR of methyl acetoacetate, 2 equiv Ar^1CHO, 2 equiv Ar^2NH_2

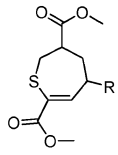


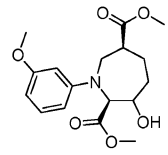
• Wang [403]
• reaction of 1,3-dicarbonyl compounds with CS_2 followed by stepwise addition of alkyl bromides and methylene active bromides

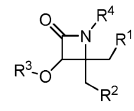




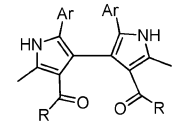
• Coquerel [108]
• Michael-aldol-retro-Dieckmann cascade



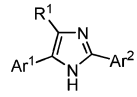




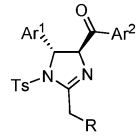
• Cariou [75]
• 4CR of methylene -aziridines, R^1MgCl, R^2X, and $R^3OCH{=}C{=}O$



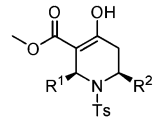
• Dey [129]
• In-catalyzed 3CR of diaroyl acetylene, 1,3-dicarbonyls, and NH_4OAc



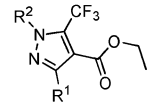
• Das Sharma [123]
• 3CR of benzil, Ar^2CHO and NH_4OAc



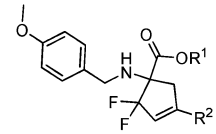
• Han [179]
• from terminal alkynes, sulfonyl azides, and *N*-unsubstituted aziridines



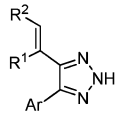
• Clarke [99]
• 4CR of diketene, tosyl imine, and R^1CHO



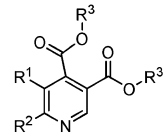
• Shen [355]
• $Yb(PFO)_3$-catalyzed 3CR of $ArNHNH_2$, RCHO, and $CF_3COCH_2CO_2Et$



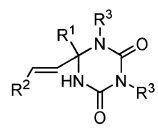
• Fustero [155]
• multistep sequence using fluorous synthesis



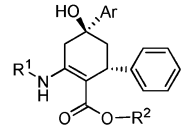
• Sengupta [340]
• 3CR of nitro olefins, ArCHO and NaN_3



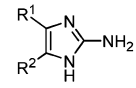
• Sasada [335]
• MeSiCl-promoted 3CR of a functionalized enamine, an acetal, and an alkyne



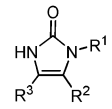
• Zho [172]
• MCR of phosphonates, nitriles, aldehydes, and isocyanates



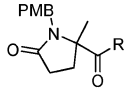
• Sridharan [366]
• 3CR of R^1NH_2, β-ketoesters, and chalcones



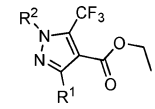
• Soh [361]
• MW-assisted condensation of α-haloketones and *N*-acetylguanidine, followed by deacetylation



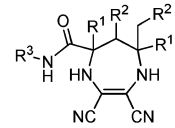
• Siamaki [359]
• Pd-catalyzed 4CR of imines, chloroformates, organostannane reagents, and carbone monoxide



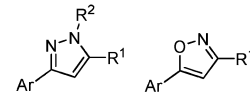
• Gilley [164]
• Ugi reaction of levulinic acid and 2-nitrophenyl isocyanide, hydrogenation (NO_2 to NH_2), then treatment with *i*-amylONO and Nu addition



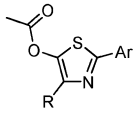
• Shen [355]
• $Yb(PFO)_3$-catalyzed 3CR of $ArNHNH_2$, RCHO, and $CF_3COCH_2CO_2Et$



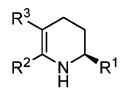
• Shaabani [345]
• 5CR of 2,3-diamino -maleonitrile, 2 equiv. cyclic or acyclic ketone, isocyanide and water



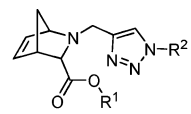
• Stonehouse [370]
• Pd-catalyzed 4CR of a halide, terminal alkyne, molybdenum hexacarbonyl and either a hydrazine or amidine



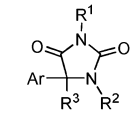
• Qiao [312]
• multistep sequence from $ArCO_2Me$: (1) ester to thionoester conversion, (2) coupling with an amino acid, (3) acetic anhydride mediated cyclization



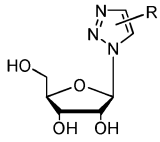
• Rueping [326]
• cascade sequence comprising a Michael addition, isomerization, cyclization, elimination, isomerization, and transfer hydrogenation



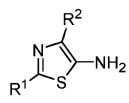
• Rodriguez-Borges [324]
• 3CR of cyclopentadiene, propargylamine, and glyoxylates then 1,3-dipolar cycloaddition with R^2N_3



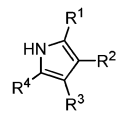
• Olimpieri [293]
• 3CR of R^1N_3, R^2NCO, and α-Br(Cl) -aryl acetic acids



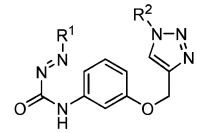
• Pradere [309]
• Cu-catalyzed azide -alkyne cycloaddition (CuAAC) or Ru-catalyzed azide-alkyne cycloaddition (RuAAC)



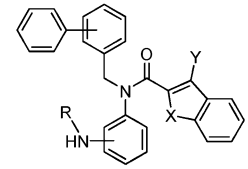
• Thompson [378]
• cyclization of diamide adducts, prepared using the Ugi reaction, in the presence of Lawesson's reagent



• Veitch [393]
• cyclocondensation of 1,4-dicarbonyl compounds with magnesium nitride as ammonia source

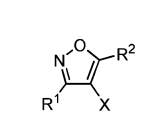


• Urankar [388]
• multistep sequence

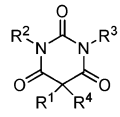


• Wang [401]
• DOS

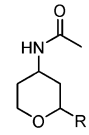
Table 8. Continued



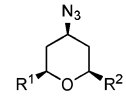
• Waldo [398]
• iodocyclization of *O*-methyloximes of 2-alkyn-1-ones then various Pd-catalyzed reactions



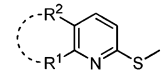
• Volonterio [397]
• condensation of carbodiimides with malonic acid monoethylesters, cyclization of the resulting *N*-acylureas, and the *C*-alkylation with R^4X



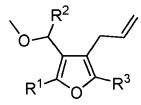
• Yadav [422]
• 3CR of carbonyl compounds, homoallylic alcohols, and nitriles



• Yadav [421]
• 3CR of RCHO, homoallylic alcohols, and trimethylsilyl azide

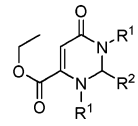


• Yadav [423]
• 3CR of acyclic or cyclic active methylene ketones

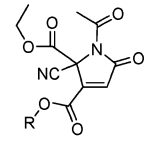


• Xiao [419]
• $[PdCl_2(CH_3CN)_2]$-catalyzed 3CR Michael addition/cyclization /cross-coupling of various 2-(1-alkynyl)-2-alken-1-ones with MeOH and allyl chloride

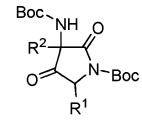
• Wypych [416]
• 3CR of aldimine anions, vinamidinium chloride, and NH_4OAc



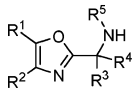
• Zhang [436]
• 3CR of DMAD, R^1NH_2, and R^2CHO



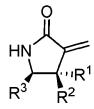
• Asghari [30]
• 3CR of ethyl acetamido-cyanoacetate, dialkyl acetylenedicarboxylate, and Ph_3P



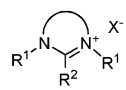
• Farran [148]
• treatment of bis-Boc protected 2,5-diketo-piperazines with LiHMDS and RCH_2Br



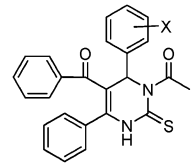
• Elders [140]
• 3CR of amines, aldehydes/ketones, α-acidic isocyano amides or esters



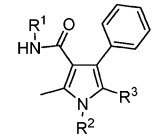
• Elford [141]
• 3CR of 2-alkoxycarbonyl allylboronate, ArCHO, and NH_4OAc



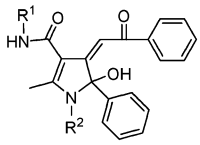
• Aidouni [9]
• MW-assisted cyclization of *N,N'*-dialkyl or diaryl ethane-1,2-diamines or propane-1,3-diamines with inorganic ammonium salts and orthoesters



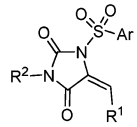
• Akbas [11]
• Biginelli 3CR of β-diketone, RCHO, and thiourea



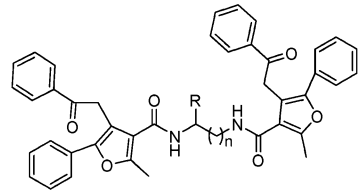
• Alizadeh [19]
• 4CR of R^1NH_2, R^2NH_2, diketene, and nitrostyrene



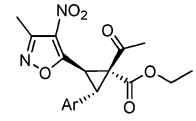
• Alizadeh [20]
• 4CR of R^1NH_2, diketene, R^2NH_2 and dibenzoylacetylene



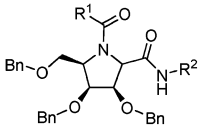
• Alizadeh [16]
• 3CR of RNH_2, $ArSO_2NCO$, and dialkyl acetylenedicarboxylate



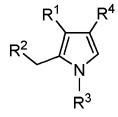
• Alizadeh [17]
• 5CR of 1,n-diamines, diketene, dibenzoylacetylene in the presence of Ph_3P



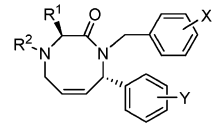
• Adamo [4]
• 3CR of 3,5-dimethyl-4-nitroisoxazole, ethyl 2-chloroacetoacetate and ArCHO



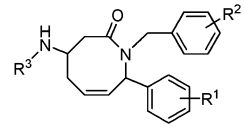
• Bonger [58]
• tandem Staudinger/aza-Wittig/Ugi 3CR on a L-ribose-derived 4-azido aldehyde



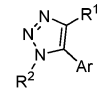
• Bremner [61]
• one-pot domino aldehyde/amine condensation, [3,3]-aza-Claisen rearrangement, imine-allene cyclization of propargylamines and RCHO



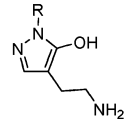
• Brown [65]
• multistep sequence



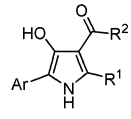
• Brown [66]
• multistep sequence via RCM



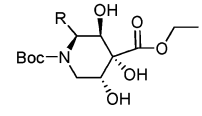
• Ackermann [3]
• Cu-catalyzed MCR of alkyne, NaN_3 and R^2X, followed by triazole arylation



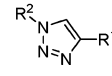
• Kralj [215]
• reaction of *N*-protected α-enamino lactams derived from 2-pyrrolidinone with $RNHNH_2$



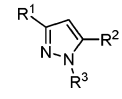
• Khalili [210]
• 3CR of β-dicarbonyl compounds with arylglyoxals in the presence of NH_4OAc in water



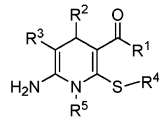
• Krishna [222]
• from L-amino acids via diastereoselective Baylis-Hillman reaction of *N*-allyl-Boc α-aminal, followed by RCM and dihydroxylation



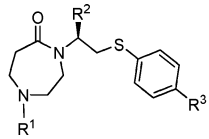
• Lee [232]
• Cu-catalyzed one-pot synthesis from cyclic enones, azides, and alkynes



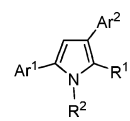
• Liu [248]
• 3CR of acid chlorides, terminal alkynes and hydrazines



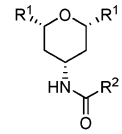
• Li [240]
• 4CR of β-aroylthioamides, aldehydes, acetonitrile derivatives, and 1,4-dihydropyridines followed by *S*-alkylation



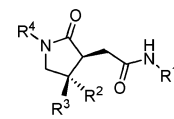
• Fenster [150]
• 3CR of 4-ketopiperidine, β-azido alcohol, and ArSK



• Dou [135]
• 3CR of 1,3-diketones, aldehydes, and amines induced by $TiCl_4/Sm$

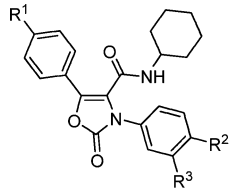


• Reddy [316]
• 3CR of allylsilanes, R^1CHO and R^2CN

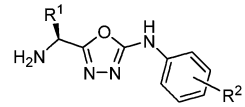


• Noth [287]
• 3CR of maleimides, aldehydes, and amines

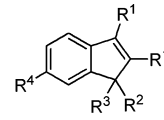
Table 8. Continued



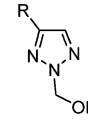
• Garcia-Valverde [160]
• Ugi reaction between arylglyoxals, anilines, cyclohexyl isocyanide and trichloroacetic acid



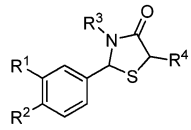
• Gavrilyuk [161]
• reaction of Boc-protected amino acid hydrazides with arylisothiocyanates in the presence of either $HgCl_2$, Mukaiyama's reagent or polymer supported Mukaiyama's reagent

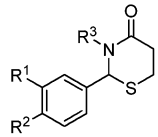


• Guo [176]
• Zr-mediated 3CR of alkynes, aldehydes/ketone, and aryl iodides then intramolecular Friedel-Crafts reactions of these allylic alcohol intermediates

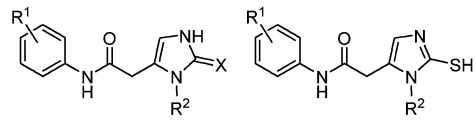


• Kalisiak [206]
• Cu-catalyzed 3CR of alkynes, NaN_3, and aq. HCHO





• Zhou [440]
• 3CR of fluorous ArCHO with amines and mecaptoacetic/propanoic acids using MW-assisted Pd-coupling

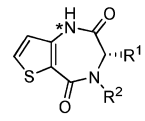


• Lee [233]
• from γ-aminoacetoacetanilides with R^2NCX

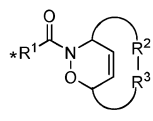
[a] Asterisk is the point of attachment to resin.

Table 9. Bicyclic and Spirocyclic Synthesis[a]

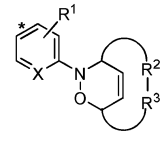
Solid-phase



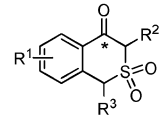
• Brouilletter [64]
• from resin-bound thiaisatoic anhydrides



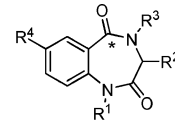
• Krchnak [220, 221]
• solid-supported nitroso hetero Diels-Alder reactions



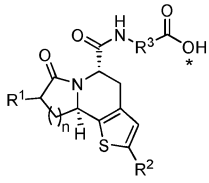
• Krchnak [218]
• immobilized arylnitroso dienophiles used in hetero Diels-Alder reactions

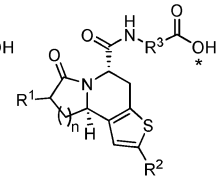


• Jeon [197]
• multistep sequence from resin-bound anthranilic acid

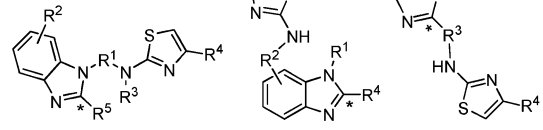


• Jeon [198]
• multistep sequence from resin-bound anthranilic acid

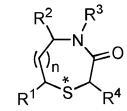




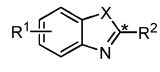
• Le Quement [229]
• intramolecular Pictet-Spengler reaction, bromination of the thiophene ring, and Suzuki cross-coupling



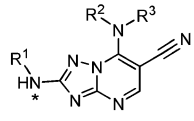
• Soural [364]
• multistep sequence from resin-bound 1,2-phenylenediamines



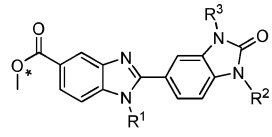
• Saruta [334]
• multistep sequence via intromolecular alkylation of sulfides



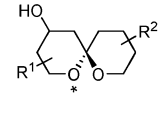
• Lim [246]
• MW-assisted condensation of resin-bound esters with 1,2-phenylenediamines, 2-aminophenols and 2-aminothiophenols



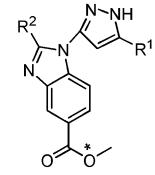
• Cavallaro [79]
• multistep sequence from resin-bound amines and diphenoxycyanoimidate



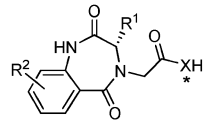
• Chen [87]
• multistep sequence from PEG-bound dianilino intermediate



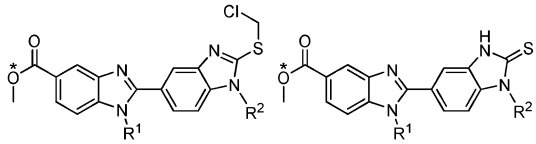
• Sommer [362]
• multistep sequence via double intramolecular hetero-Michael reaction to resin-bound alkynones



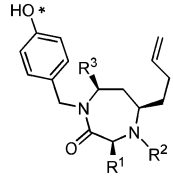
• Portilla [307]
• multistep sequence from 4-F-3-NO_2-benzoic acid



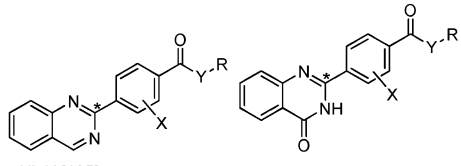
• Verdie [394]
• multistep sequence



• Chang [83]
• multistep sequence from PEG-bound dianilino intermediate



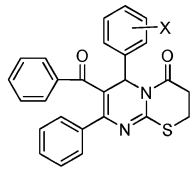
• Iden [190]
• multistep sequence



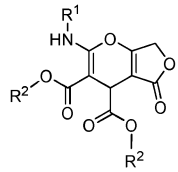
• Hioki [185]
• oxidative release from azomethine linkage on a solid-support by 2-aminobenzylamine or 2-aminobenzamide with air

Table 9. Continued

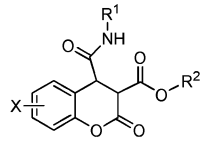
Solution-phase



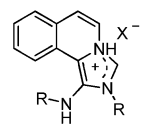
• Akbas [11]
• Biginelli 3CR of β-diketone, RCHO, and thiourea



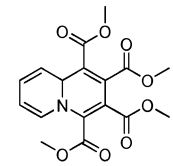
• Shaabani [350]
• 3CR of RNC, dialkyl acetylenedicarboxylate, and tetronic acid



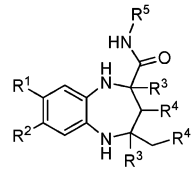
• Shaabani [349]
• 4CR of 2-hydroxybenzaldehyde, Meldrum's acid, isocyanide, and aromatic or aliphatic alcohol



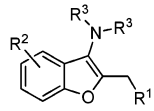
• Shaabani [348]
• 4CR of 2 equiv R^1NC, isoquinoline, and sulfonic or bromic acids



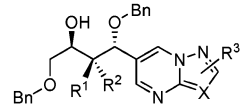
• Shaabani [346]
• 3CR of pyridine derivatives, dialkylacetylenedicarboxylate, and tetracyanoethylene



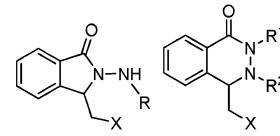
• Shaabani [342]
• 4CR of aromatic diamine, linear or cyclic ketone, isocyanide, and water



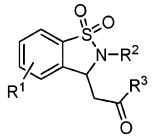
• Sakai [329]
• Cu-catalyzed 3CR of alkynylsilane, *o*-hydroxy-benzaldehyde derivative, and secondary amine



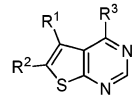
• Sagar [328]
• MW-assisted condensation of glycols and aminoheterocycles



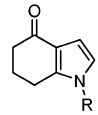
• Grigg [170]
• hydrazine nucleophiles in a Pd-catalyzed 3CR cascade from 2-I-PhCH=CHX



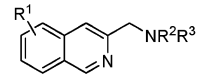
• Rolfe [325]
• domino Heck-Aza-Michael reaction of *o*-bromophenyl-sulfonylchloride and $H_2C{=}CHCOR^3$



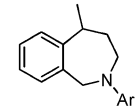
• Phoujdar [301]
• MW-assisted chlorination of 2-unsubstituted-thieno-[2,3-*d*]-pyrimidin-4-ones, followed by the nucleophilic displacement with $ArNH_2$



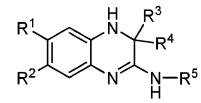
• Piras [304]
• MW-assisted aminolysis of 4-oxo-4,5,6,7-tetrahydro-benzofuran with RNH_2



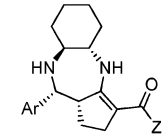
• Ohta [291]
• Cu-catalyzed domino 4CR coupling-cyclization using 2-ethynylbenzaldehydes, paraformaldehyde, secondary-arylamine, and *t*-$BuNH_2$



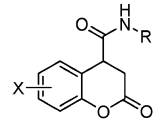
• Vieira [396]
• Rh-catalyzed 3CR of 2-vinylbenzaldehydes, $ArNH_2$ and CO



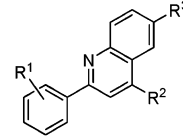
• Shaabani [344]
• 3CR of *o*-phenylenediamine, diverse carbonyl compounds, and isocyanides



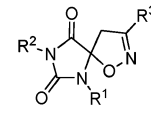
• Sotoca [363]
• 3CR between 1,2-diamines, 1,3-dicarbonyls, and aromatic aldehydes



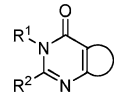
• Shaabani [347]
• 3CR of 2-hydroxy-benzaldehydes, Meldrum's acid, isocyanides



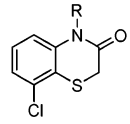
• Xiao [418]
• Au-catalyzed 3CR of aldehydes, amines, and alkynes



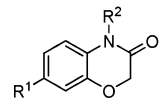
• Shih [357]
• multistep sequence from *N*-substituted methyl ester serine



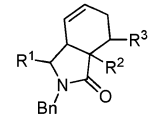
• Yang [425]
• 3CR of $ArNH_2$, ArCOCl, and heteroaromatic amino ester



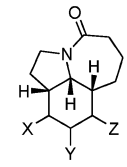
• Zuo [172]
• MW-assisted 3CR of 2-chloro-benzenethiols, chloroacetyl chloride, and primary amines via Smiles rearrangement



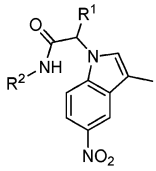
• Zuo [15]
• MW-assisted 3CR of 2-chlorophenols, chloro-acetylchloride, and R^2NH_2



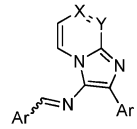
• Zhang [435]
• Cu-catalyzed 3CR and Diels-Alder reaction



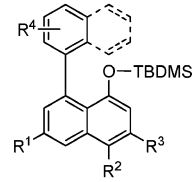
• Frankowski [154]
• tandem Diels-Alder/Schmidt reaction then skeletal diversification



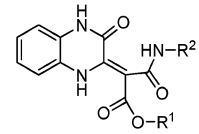
• El Kaim [139]
• *o*-iodonitrophenol in Ugi-Smiles reaction coupled with Heck cyclization



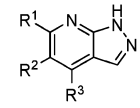
• Adib [5]
• 3CR of 2-aminoheterocycle, ArCHO, and imidazoline-2,4,5-trione



• Akai [10]
• 3CR of 3-TBDMS-benzynes with furan derivatives then Hiyama cross-coupling reaction with aryl iodides

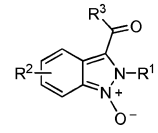


• Alizadeh [16]
• 3CR of *o*-phenylenediamine, dialkyl acetylenedicarboxylates, and $ArSO_2NCO$

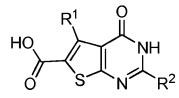


• Almansa [25]
• 3CR of $R^1COCH_2R^2$, R^3CHO, and 3-aminopyrazole

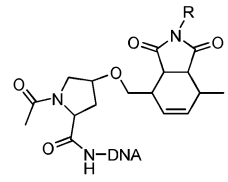
Table 9. Continued



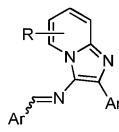
• Bouillon [59]
• tandem condensation of R^1NH_2 2-NO_2-PhR^2SO_2Cl, and $BrCH_2COR^3$



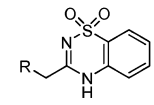
• Bogolubsky [53]
• cyclization of 2-amino -thiophen-3,5-dicarboxylates with RCN then hydrolysis



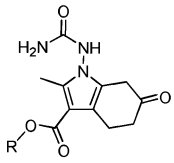
• Buller [67]
• DNA-encoded library via Diels-Alder cycloaddition



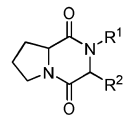
• Adib [7]
• 3CR of 2-aminopyridines, ArCHO, and imidazoline -2,4,5-trione



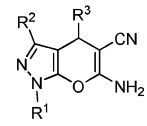
• Kim [211]
• Cu-catalyzed 3CR of alkynes, $ArSO_2N_3$, NH_4Cl then intramolecular *N*-arylation



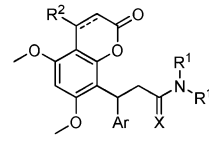
• Karapetyan [209]
• domino reaction via $ZnCl_2$-catalyzed conjugate addition/cyclization sequence of 1,2-diaza-1,3-butadienes and 1,3-bis(silylenol ethers)



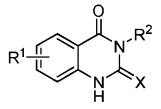
• Jainta [191]
• MW-assisted condensation of unprotected amino acids by a phosphite-promoted one-step coupling reaction



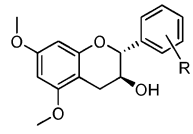
• Lehmann [234]
• 3CR of pyrazolones, malononitrile, and R^3CHO



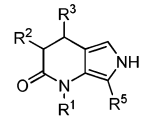
• Li [239]
• multistep sequence via sequential C-H functionalization of phenols

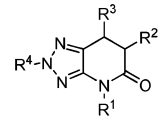


• Li [244]
• MW-assisted reaction of substituted methyl anthranilate, and iso(thio)cyanates in DMSO /H_2O without catalyst or base

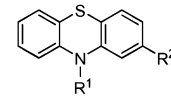


• Liu [251]
• DOS via thiourea/$AuCl_3$ /AgOTf-catalyzed annulations of aryl epoxides

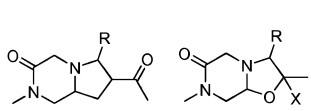




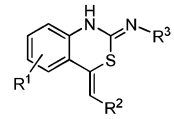
• Gao [158]
• [3+2] cycloaddition of 5-benzenesulfonyl -3,4-dihydro-1*H*-pyridin-2-one derivatives with azides or isocyanides



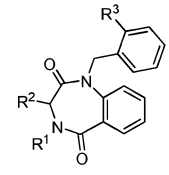
• Dahl [117]
• Pd-catalyzed, MW-assisted 3CR of 2-Br-thiophenol, amine, and 1-Br-2-iodobenzene



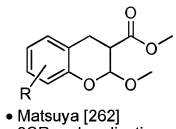
• Garcia-Cuadrado [159]
• DOS utilizing a Petasis 3CR followed by a tandem aza-Cope-Mannich cyclization



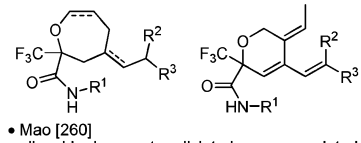
• Ding [132]
• tandem addition-cyclization of 2-alkynylbenzenamines with RNCS catalyzed by AgOTf



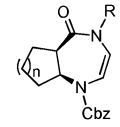
• Salcedo [330]
• Ugi 4CR then Pd-catalyzed domino sequence involving intramolecular *N*-arylation and intermolecular Heck reactions



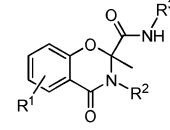
• Matsuya [262]
• 3CR and cyclization of *N*-tosylimines and TMS -substituted propiolate mediated by DABCO



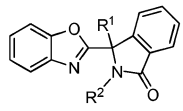
• Mao [260]
• allenyl-hydroxy ester allylated or propargylated then subjected to Rh(I)-catalyzed carbocyclization



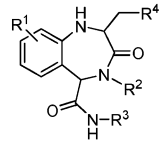
• Balazs [34]
• MW-assisted multistep sequence from cyclic β-amino acids



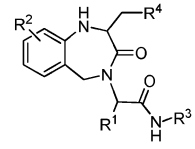
• Banfi [37]
• Ugi/Mitsunobu reaction of α-hydroxybenzoic acids, glycolaldehyde dimer R^2NH_2 and R^3CN



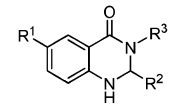
• Salcedo [331]
• Ugi-4CR/postfunctionalization sequence



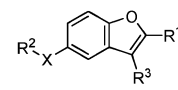
• De Silva [126]
• MW-assisted 4CR of $(2\text{-}NO_2)$ArCHO, cinnamic acids, R^3NC, and R^2NH_2 with Fe/NH_4Cl



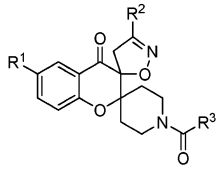
• De Silva [126]
• MW-assisted 4CR of 2-nitrobenzylamines, cinnamic acid, R^1CHO, and R^3NC with Fe/NH_4Cl



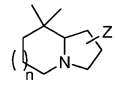
• Chen [88]
• 3CR of isatoic anhydride, ArCHO, NH_4OAc or R^3NH_2 catalyzed by $Ga(OTf)_3$



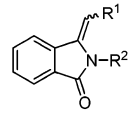
• Cho [95]
• multistep sequence



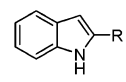
• Carpenter [76]
• multistep sequence from 2-OH-PhCOMe and 4-ketopiperidine



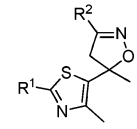
• Coldham [103]
• 3CR of an amino-acid or amino-ester or hydroxyl-amine, an alkene or alkyne dipolarophile and an aldehyde bearing a halide as a leaving group



• Cao [73]
• Pd-catalyzed Sonogashira coupling-carbonylation -hydroamination sequence in phosphonium salt-based ionic liquid

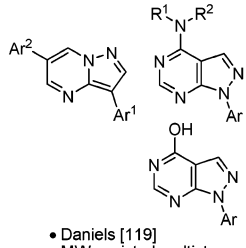


• Miyazaki [273]
• intramolecular cyclization of *o*-amino -arylalkynes via Au(III) polymer supported catalyst

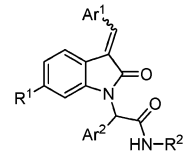


• Milinkevich [270]
• condensation of 3-chloro pentane-2,4-dione with thio -amides and subsequent Wittig olefination, followed by nitrile oxide 1,3-dipolar cycliaddition

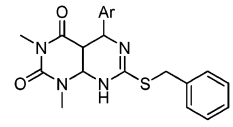
Table 9. Continued



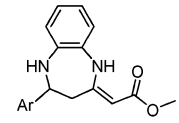
• Daniels [119]
• MW-assisted multistep synthesis



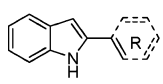
• Dai [118]
• Ugi 4CR of 2-aminophenols, ArCHO, cinnamic acids, RNC then Heck carbocyclization



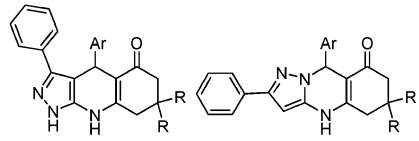
• Dabiri [116]
• 3CR of 6-amino-1,3-dimethyluracil, aldehyde and 2-benzylisothiourea HCl



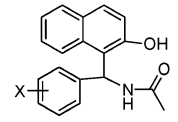
• Murai [278]
• 3CR of ArCHO, 1,2 -phenylenediamine, and β-ketoester



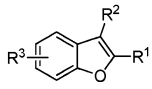
• Kraus [217]
• MW-assisted condensation of 2-aminobenzyl phosphonium salts and RCHO



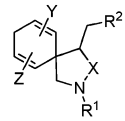
• Chebanov [86]
• 3CR of 5-aminopyrazoles, dimedone, and RCHO



• Shaterian [354]
• 3CR of β-naphthol, aromatic aldehydes and acetamide in the presence of $Fe(HSO_4)_3$



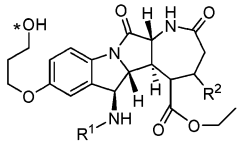
• De Luca [125]
• MW-assisted condensation of (2-bromomethyl)phenols and polymer supported Ph_3P



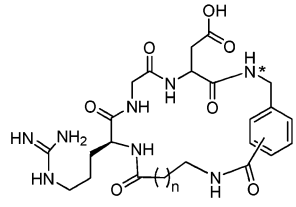
• Ovens [295]
• dearomatizing, thionium ion cyclization of *N*-benzylglyoxamides

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

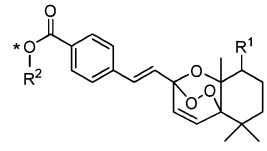
Table 10. Polycyclic and Macrocyclic Synthesis[a]



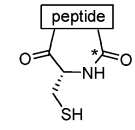
• Brochu [63]
• multistep sequence via intramolecular Michael reaction



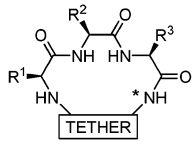
• Kamioka [208]
• multistep sequence from resin-bound *o*-, *m*-, and *p*-iodobenzylamines coupled with RGD sequence and various ω-amino acids then Pd -catalyzed carbonylative macrolactamization



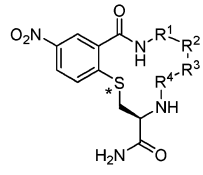
• La-Venia [226]
• photoinduced oxygen capture on immobilized dienone



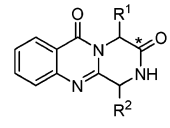
• Li [242b]
• formation of peptide thioesters on volatilizable silica gel support, cleavage and macrocyclization



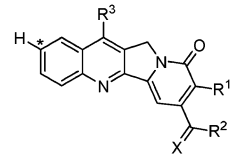
• Marsault [261]
• multistep synthesis via $Ag(OCOCF_3)$-mediated macrocyclization of resin -bound thio peptide



• Grieco [169]
• solid-phase synthesis and MW-assisted tandem combination of S_N2' macrocyclization

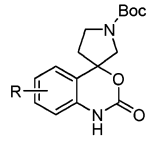


• Tseng [383]
• $Zn(OTf)_2$-mediated double cyclodehydration of linear tripeptides

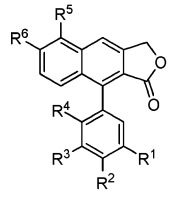


• Tsukamoto [385]
• multiple chemoselective Pd-catalyzed reactions on benzenesulfonate linker

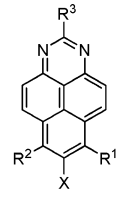
Solution-phase



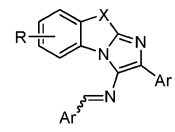
• Nicolaou [284]
• bis-metalation of Boc -protected aniline and addition of *N*-Boc pyrrolidin-3-one



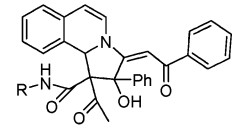
• Eghbali [138]
• 3CR of arylalkynes, 1-Br-2-alkynes and CO catalyzed by AgI



• Aksenov [12]
• 3CR of perimidines or 1,8 -diaminonaphthalene with 1,3,5-triazines and carbonyl compounds or benzonitrile

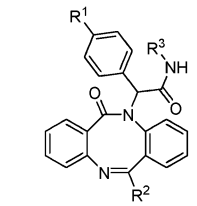


• Adib [6]
• 3CR of 2-aminobenzo -thiazoles or 2-aminobenz -imidazole, ArCHO and imidazoline-2,4,5-tri-one

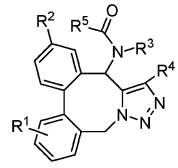


• Alizadeh [23]
• 4CR of amine, diketene, dibenzoylacetylene, and isoquinoline

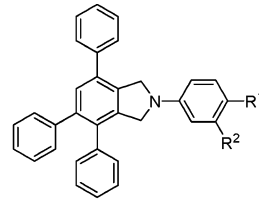
Table 10. Continued



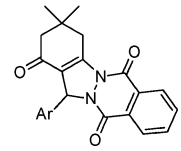
• Corres [109]
• sequential Ugi reaction of ArCHO, 2-acetyl or benzoylanilines, cyclohexyl or benzyl isocyanides, and 2-azidobenzoic acid, followed by a Staudinger/aza-Wittig cyclization with Ph_3P



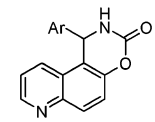
• Mont [274]
• multistep MW -assisted DOS



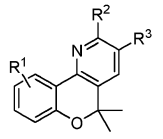
• Bonfield [57]
• 6CR of $ArNH_2$, HCOH and phenylacetylene

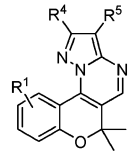


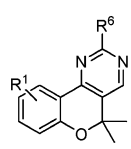
• Sayyafi [336]
• 3CR of phthalhydrazide, dimedone, and aromatic aldehydes

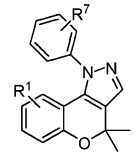


• Shakibaei [351]
• MW-assisted 3CR of 6-quinolinol, ArCHO, and urea

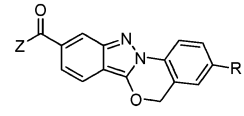




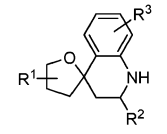




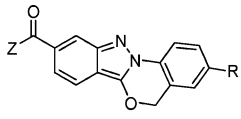
• An [26]
• DOS of benzopyranyl heterocycles from *s-cis*-enones



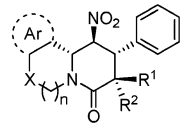
• Butler [68]
• condensation of 2-NO_2PhCHO with 2-aminobenzylalcohol



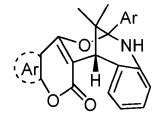
• Barluenga [40]
• one-pot multicatalytic and multicomponent cascade reaction of alkynes, RCHO, $ArNH_2$



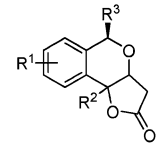
• Butler [68]
• condensation of 2-NO_2PhCHO with 2-aminobenzylalcohol



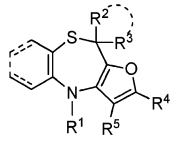
• Jakubec [192]
• nitro-Mannich/lactamization cascade of γ-nitro esters with cyclic imines



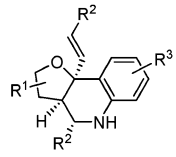
• Lai [225]
• $Yb(OTf)_3$-catalyzed 4CR of various anisidines, ArCHO, isobutyraldehyde, and 4-hydroxycoumarins/dimedone



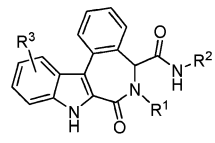
• Li [243]
• DOS via Pd-thiourea -catalyzed alkoxy -carbonylative annulation of 1,2-hydroxymethylaryls

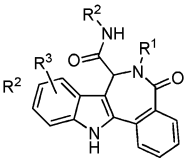


• Ding [131]
• 3CR of thiazoles or benzothiazole carbenes, disubstituted ketenes and activated alkynes

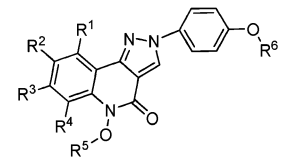


• Barluenga [41]
• one-pot multicomponent cascade reaction of alkynes, ArCHO, RNH_2 catalyzed by Pd-complexes

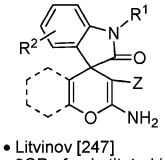




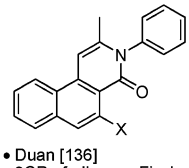
• Beaumont [46]
• 3CR of indole-derived oxo acids, R^1NH_2 and R^2NC



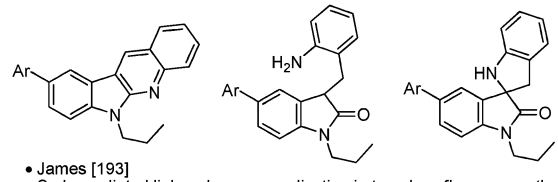
• Christodoulou [98]
• multistep sequence



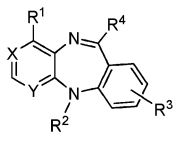
• Litvinov [247]
• 3CR of substituted isatins, cyanoacetic acid derivatives, and carbonyl compounds or phenols



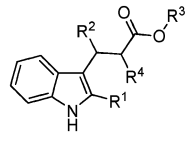
• Duan [136]
• 3CR of alkynes, Fischer carbene complexes, and benzaldehyde hydrazones



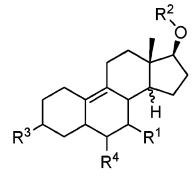
• James [193]
• SmI_2-mediated linker cleavage-cyclization in traceless fluorous synthesis



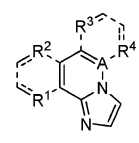
• Shi [356]
• multistep sequence from 2-Cl-nitro -heteroaromatics



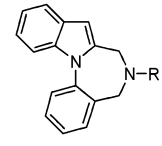
• Renzetti [319]
• $TiCl_4/Et_3N$-promoted 3CR of indoles,aldehydes, and active methylene compounds



• Sunnemann [373]
• multistep DOS

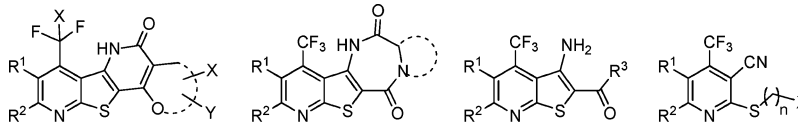


• Parenty [297]
• quaternarization of *N*-hetero -cycle, followed by a cascade reaction involving nucleophilic addition, substitution, rearrangement, and oxidation

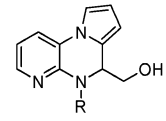


• Ohta [290]
• Cu-catalyzed domino 3CR coupling-indole formation-*N* -arylation under microwave irradiation

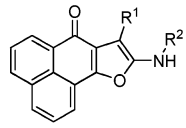
Table 10. Continued



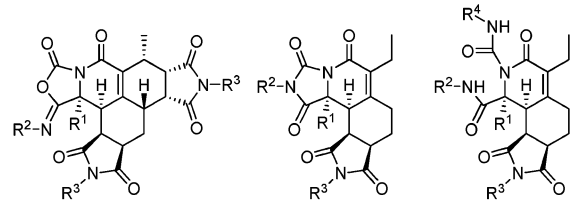
• Rodinovskaya [323]
• DOS from 4-di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones via cascade reactions



• Xiang [417]
• Tandem iminium cyclization and Smiles rearrangement



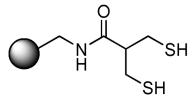
• Teimouri [374]
• 3CR of 3-OH-1*H*-phenalen -1-one, R^1CHO, and R^2NC



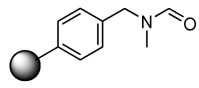
• Werner [405]
• multistep sequence via amino-acid derived cross-conjugated trienes

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

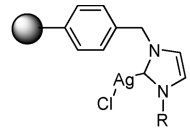
Table 11. Polymer-Supported Reagents, Scavengers, and Linkers



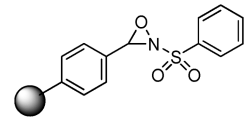
• Wiehn [408]
• dithiane-type linker for immobilizing aldehydes and ketones



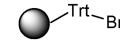
• Encinas [142]
• reaction with oxalylchloride give chlorinating reagent



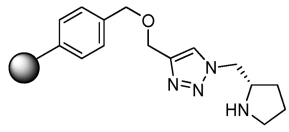
• Li [241]
• catalyst for 3CR of RCHO, alkyne, and RNH_2



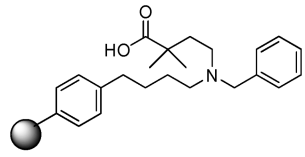
• Gao [157]
• Davis reagent for oxidations



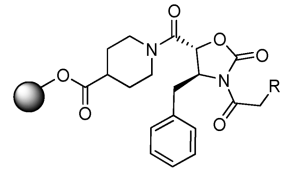
• Crestey [111]
• resin loading of acid and heat sensitive alcohols



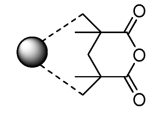
• Miao [268]
• asymmetric Michael addition of cyclohexanone to nitroolefins



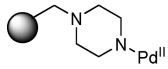
• Davies [124]
• oxidatively-activated safety catch linker



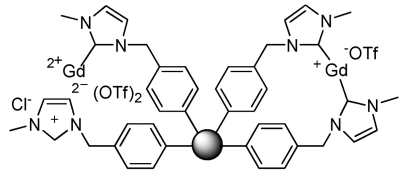
• Green [168]
• polymer-supported Evans' oxazolidin-2-one



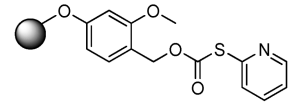
• Sanna [332]
• amine scavenger



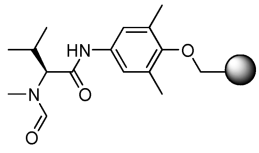
• Wu [413]
• catalyst for phosphine-free Heck reaction of activated and non-activated aryl or heteroaryl substrates with olefins



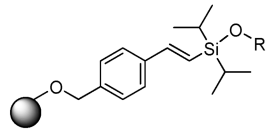
• Yoon [429]
• Lewis acid catalyst for acetylation of alcohols and phenols



• Zhao [438]
• mild immobilization of alcohols and thiols, cleavage with 1% TFA

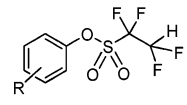


• Malkov [258]
• asymmetric reduction of imines with trichlorosilane

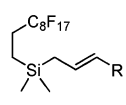


• Pedersen [298]
• regio and stereoselective hydro -silylation of terminal alkynes on solid support using diisopropyl hydrosilanes

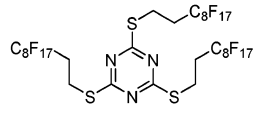
Table 12. Fluorous Catalysts, Reagents, Scavengers, Linkers, and Library Synthesis



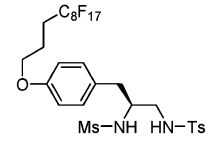
• Rostovtsev [456]
• various synthetic applications of aryl tetraflates



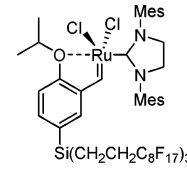
• Boldon [54]
• allylic fluoride synthesis



• Bernini [443]
• immobilization of phosphine-free perfluoro-tagged palladium nanoparticles on fluorous silica gel

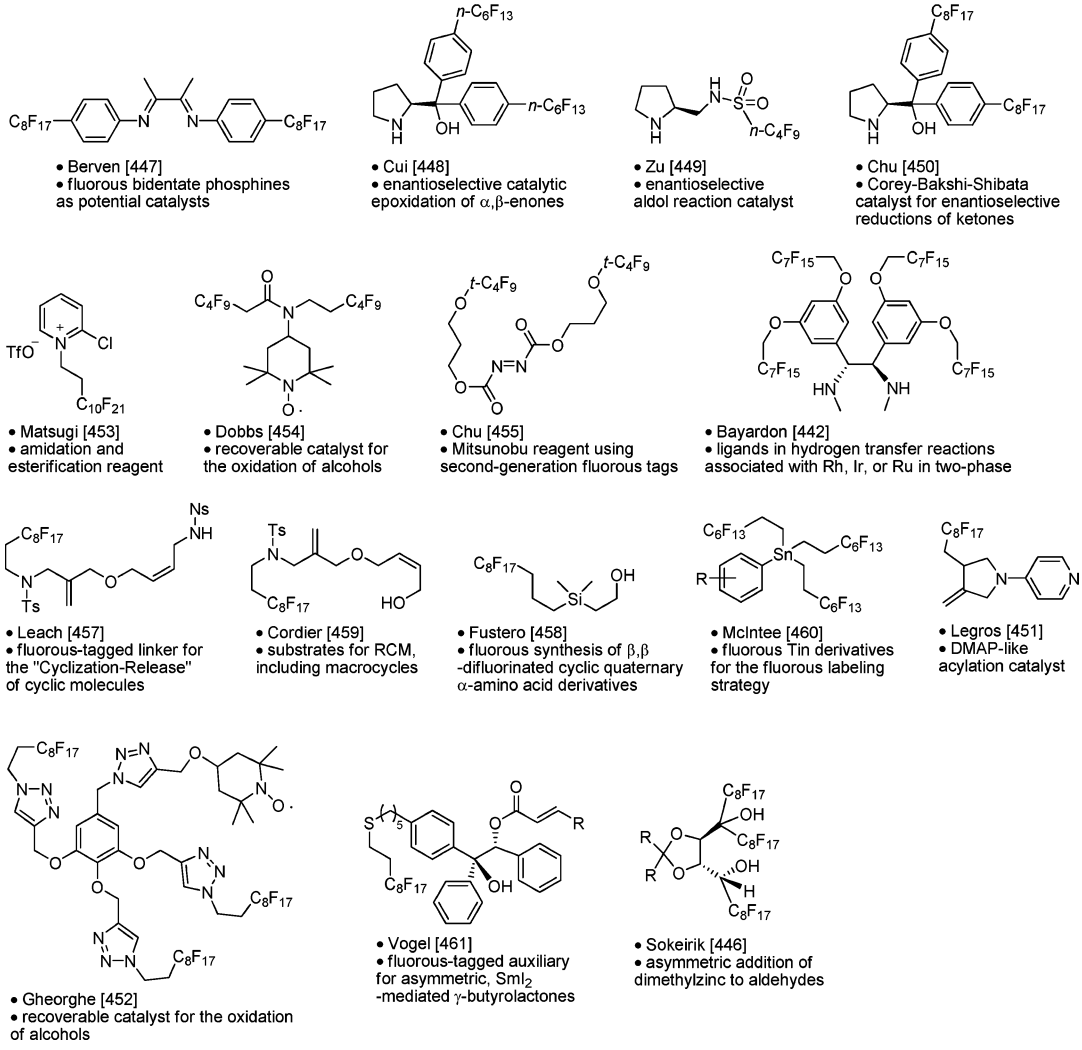


• Miura [444]
• catalytic enantioselective cyclopropanation of allylic alcohols



• Hensle [445]
• Grubbs-Hoveyda-type metathesis catalyst

Table 12. Continued



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