Review

Comprehensive Survey of Combinatorial Library Synthesis: 2005

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Reviews

Comprehensive Survey of Combinatorial Library Synthesis: 2005

Roland E. Dolle,*,† Bertrand Le Bourdonnec,† Guillermo A. Morales,‡ Kevin J. Moriarty,§ and Joseph M. Salvino⊥

Adolor Corporation, 700 Pennsylvania Drive, Exton, Pennsylvania 19341, Telik Inc., 3165 Porter Drive, Palo Alto, California 94304, Johnson & Johnson, PRDUS, LLC, Springhouse, Pennsylvania 19477, and Cephalon, Inc., 383 Phoenixville Pike, Malvern, Pennsylvania 19355

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Introduction

This is the ninth annual review in an ongoing series of comprehensive reviews in combinatorial chemistry highlighting developments in new methodology and synthesis of small molecule libraries.[1] A total of 434 entries are categorized according to biologically active libraries (Tables 1−5, 110 entries), libraries without disclosed biological activity (Tables 6−10, 256 entries), solid- and solution-phase reagents and scavengers (Table 11, 33 entries), linkers (Table 12, 17 entries), and polymer-supported chiral ligands (Table 13, 18 entries) as published in 2005.[2−377]

The selected publications briefly reviewed herein include contributions from researchers at Merck Frosst on selective caspase-3 inhibitors displaying nanomolar activity in a whole-cell assay,[120,233] and Lindsley (Merck) on iterative heterocyclic libraries derived from 1,2-diketones yielding dual Atk1/2 inhibitors.[210] Pharmacopeia Inc. reported on encoded and optimization libraries of MCH1 receptor antagonist,[116,117] as well as an Ftase inhibitor library.[281] Guba and co-workers (Hofmann-La Roche) created a virtual screening query for NPY5 antagonists based on competitors' reference compounds, which, upon virtual screening of their in-house file collection, led to a proprietary screening hit that was optimized via solution-phase parallel synthesis.[113] A new class of pyrazoline-based progesterone receptor (PR) antagonists was designed, and a library was synthesized on the basis of homology modeling studies with mifepristone.[160] A focused library of $P2X_7$ receptor antagonists was reported by Sanofi Aventis.[237] Selective dopamine D3 ligands were obtained from aminoalkylpiperazines highlighting the utility of "click" chemistry for linker assembly.[29] The former 3-D Pharmaceuticals group published a detailed account of the identification of benzodiazepinones as HDM2-p53 protein−protein antagonists using Thermofluor microcalorimetry assay technology.[110,262] Conceptually novel annulation reagents (SPA*n* reagents) for the single-step conversion of primary amines to heterocycles was a contribution from Adolor.[78] New silyl-based TBDAS[72] and MEM-type[224] linkers were reported as well as "volatilizable" supports by Houghten.[138] Resin-bound 9-BBN was prepared and used in hydroboration reactions.[280] Researchers at BMS studied the addition of organometallic reagents to resin-bound imines for the parallel synthesis of α-branched secondary amines.[345] Also summarized are a series of Ugi-multicomponent condensation reactions (MCR) in tandem with other cyclization chemistry, that is, the intra-

* To whom correspondence should be addressed. Phone: 484-595-1024. Fax: 484-595-1551. E-mail: rdolle@adolor.com.
† Adolor Corporation
‡ Telik, Inc.
§ Johnson & Johnson, PRDUS, LLC
⊥ Cephalon, Inc.

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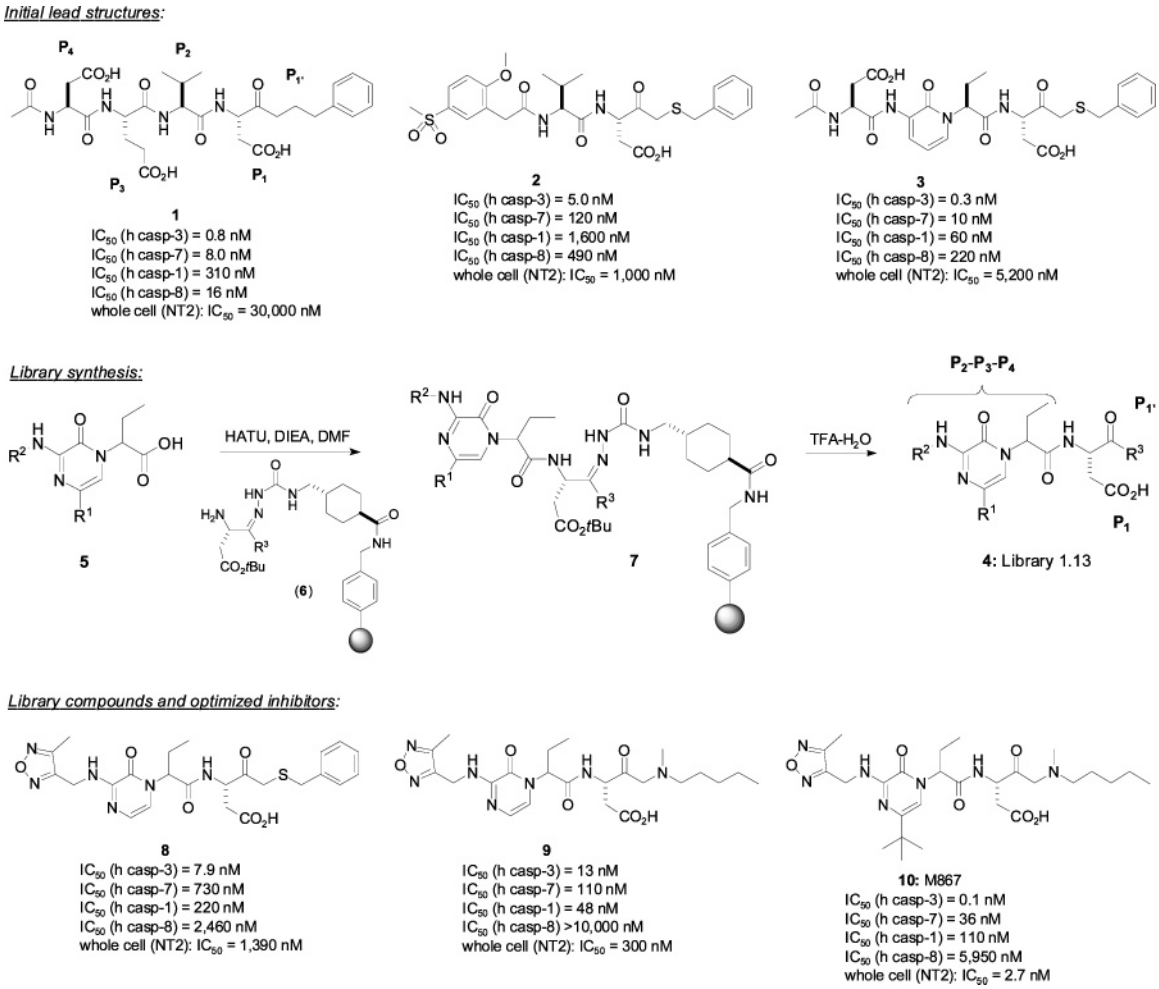


Figure 1. Selective caspase-3 inhibitors.[120]

molecular Diels−Alder reaction,[215] carbonylation/intramolecular amidation,[322] phenol-Ugi−Smiles condensation,[84] based-induced cyclization,[146] and the Staudinger/aza-Wittig reaction,[318] as well as reports using bifunctional reagents in MCRs.[148,151]

In addition to the citations found in Tables 1−13, publications appeared on new tagging methodologies,[378,379] color-facilitated assays for screening[380] and functional group detection,[381] ladder synthesis of "one-bead one-compound" libraries,[382] synthesis on sequentially linked columns,[383] resin distribution tools,[384] ROMPgel beads for use in IRORI Kan format,[385] resin-supported chain transfer agents,[386] TLC-MALDI MS analysis of nonpeptide libraries,[387] and HT purification of single compounds and libraries.[388]

Reviews published in 2005 include topics on compound libraries and chemical genomics,[389] Kenner's safety-catch linkers,[390] 1,3-dipolar additions on solid-phase,[391] sulfide- and selenide-based linkers in phase tag-assisted synthesis,[392] benzoannelated oxygen heterocycles,[393] and convergent approaches to library synthesis.[394]

Caspase-3 Inhibitors. Recent studies toward understanding the molecular mechanisms of apoptosis have highlighted the importance of a group of cysteinyl aspartate specific proteases, the caspases, in the programmed cell death process. To date, 14 mammalian members of caspases have been identified, and these enzymes exist as dormant proenzymes that are processed to the catalytically active mature forms under certain conditions. Caspase-3 (casp-3) has been characterized as the dominant effector caspase involved in the proteolytic cleavage of a variety of protein substrates, including cytoskeletal proteins, kinases, and DNA repair enzymes during apoptosis. The development of potent and selective casp-3 inhibitors has thus emerged as an attractive therapeutic target. Early reversible P_1' aldehyde and ketone casp-3 inhibitors incorporate the preferred tetrapeptide motif DxVD recognized by casp-3/7. These compounds, such as **1**, lack cell potency due to limited cell permeability (Figure 1). Researchers at Merck Frosst previously reported that truncating the tetrapeptide backbone to a dipeptide motif led to the discovery of inhibitors such as **2** with marked improvement in whole-cell potency. The P_2-P_3 motif can also be replaced by a pyridone core, giving compounds such as **3** with good enzymatic activity and selectivity. On the basis of these lead structures, Merck Frosst scientists investigated the replacement of the $P_2-P_3-P_4$ backbone with an aminopyrazinone template.[120] A 23-member library (library 1.13 (**4**)) was first synthesized to optimize the aminopyrazinone R^2 functionality. Carboxylic acid derivatives **5** obtained in seven steps using solution-phase chemistry were coupled to the polystyrene-based resins **6** under classical

peptide coupling conditions. Treating the resultant resin **7** with 90% TFA in water gave the desired library compounds with good purity (>90% by ^{1}HNMR) as a mixture of diastereoisomers. The compounds were screened directly against four human caspases (casp-1, -3, -7, -8), as well as in the cellular assay, that is, camptothecin-induced apoptosis in NT2 cells. The initial rationale for library design was based on molecular modeling studies, which suggested that the aminopyrazinone template in compounds **4** was superimposable with the P_2-P_3 motif of the tetrapeptide inhibitor **1**. In this docking representation, the R^2 group of **4** could potentially interact with amino acid residues (Phe and Asn) of the S_4 pocket. Noncharged heterocycles, such as oxadiazoles at the R^2 position, were chosen on the basis of their potential to form polar interactions with the S_4 pocket of the casp-3 enzyme. From this exercise, the furazan analog **8** showed excellent intrinsic activity ($IC_{50} \sim 8$ nM), with good selectivity and whole-cell activity ($IC_{50} = 1.4$ μM). Optimization at the P_1' position of this lead compound was then investigated. The various aminomethyl ketone derivatives were prepared by classical solution-phase methodology since these compounds could not be obtained by the solid-phase protocol. This study revealed that an *N*-methyl-*N*-alkyl side chain (e.g., **9**) was preferable for obtaining compounds with good whole-cell potency. The whole-cell potency of compound **9** was further improved by introducing a *tert*-butyl moiety at the R^1 position. This led to the discovery of **10** (M867), the most potent and selective reversible casp-3 inhibitor discovered so far. M867 showed subnanomolar binding affinity ($K_i = 0.1$ nM) against human casp-3 and selectivity against other caspases. This compound was highly effective against camptothecin-induced cell death in the NT2 cells ($IC_{50} = 2.7$ nM), in etoposide-induced DNA fragmentation in mice cerebellar granule neurons, and in cycloheximide-induced cell death in white blood cells. M867 was also highly effective in inhibiting casp-3 activity in vivo.

Dual Akt1/Akt2 Allosteric Kinase Inhibitors. Akt, also known as protein kinase B or PKB, is a serine/threonine kinase that plays an important role in the apoptotic signaling pathway. Akt belongs to the ACG kinase family exhibiting a high homology with the PKA and PKC kinases. There are three known human Akt isozymes, namely, Akt1/Aktα, Ak2/Aktβ, and Akt3/Aktγ. The isozymes share a high degree of homology (>80%) and possess an N-terminal Pleckstrin homology (PH) domain. Extracellular stimulation of the Akt pathway involves the overexpression of membrane-bound PtdIns(3, 4, 5)P3 (PIP3) inducing the translocation of Akt to the plasma membrane. It is here where the Akt PH domain serves as a docking site to interact with PIP3 and forms a complex, resulting in a conformational change that allows the phosphorylation−activation of Akt. A high-throughput screening campaign at Merck identified the 2,3-diphenylquinoxaline **11** ($IC_{50} = 2.5$ μM) as an Akt inhibitor with a high selectivity against Akt1 (Figure 2).[210] Assays using mutated Akt isozymes with no PH domain did not exhibit Akt inhibition. In addition, ATP competition assays revealed that this compound was not an ATP-competitive kinase inhibitor. These observations led to the conclusion that compound **11** is an allosteric Akt kinase inhibitor. Lindsley and co-workers developed a microwave-based synthetic strategy for the rapid synthesis of a 2,3-diphenylquinoxaline library (library 2.1a, (**12**)) in which the key step involved the cyclization of benzil amines **16a** with 1,2-diaminobenzenes **17** to form the desired quinoxaline core. Intermediates **16a** were prepared upon the reaction of bromomethyl benzil **15** with 200 commercially available primary and secondary amines, employing polymer-supported DIEA and a fluourous-based thiol scavenger. The benzils were then reacted with 1,2-diaminobenzenes under microwave irradiation reaction conditions to afford the desired 2,3-diphenylquinoxaline library 2.1a. Following screening, compound **19** was identified as a potent Akt1 inhibitor ($IC_{50} = 290$ nM) with high selectivity over Akt2 ($IC_{50} = 2090$ nM) and Akt3, PKA and PKC ($IC_{50} > 50\,000$ nM). Unfortunately, it was found that **19** had a poor solubility profile and was not active in cell-based assays. To find Akt inhibitor candidates with desirable physicochemical properties, three additional heterocyclic compound classes were explored taking advantage of the common benzil amine intermediates. Using benzil amine **16b**, the precursor of **19**, and a set of 24 diverse α-aminocarboxamides **18**, a focused library of 5,6-diphenylpyrazin-2(1*H*)-one regioisomers was made (**13**, library 2.1b). Akt enzyme inhibition assays revealed that each regioisomer had a different inhibition profile and that the nature of the substituent group on position 3 had a major influence in Akt isozyme selectivity. For instance, compound **20** with its methyl group is highly selective against Akt1 ($IC_{50} = 760$ nM), whereas its regioisomer **22** exhibits similar potency against both Akt1 and Akt2 ($IC_{50} \sim 1000$ nM). When an isobutyl substituent is present, compound **21** is inactive against both Akt1 and Akt2, yet its counterpart regioisomer **23** is potent and highly selective against Akt2 ($IC_{50} = 325$ nM). To determine the inhibitory apoptotic effect of targeting a specific Akt isozyme in cells, Merck researchers pretreated A2780 human ovarian tumor cells with either **20** or **23**, followed by incubation with the anticancer agent doxorubicin and observed a 3-fold increase in caspase-3 activity versus doxorubicin alone. In further experiments, when A2780 cells were pretreated with a 1:1 mixture of **20**/**23** a significant 10-fold increase in caspase-3 activity was detected. This observation indicated that dual Akt1/Akt2 kinase inhibition offers a much better apoptotic response, as opposed to targeting exclusively one Akt isozyme. This dual Akt1/Akt2 kinase inhibition approach afforded the same results when the authors used LNCaP prostate cancer cells. With this new insight, the authors focused their efforts on the design of dual Akt1/Akt2 inhibitors. Using the same synthetic methodology and compound **16b** as the starting material, the authors used 50 different aryl-1,2-diamines (**17**) to investigate the substitution effects on the quinoxaline core. Focused library 2.1c (**14**) afforded three tricyclic quinoxaline analogs

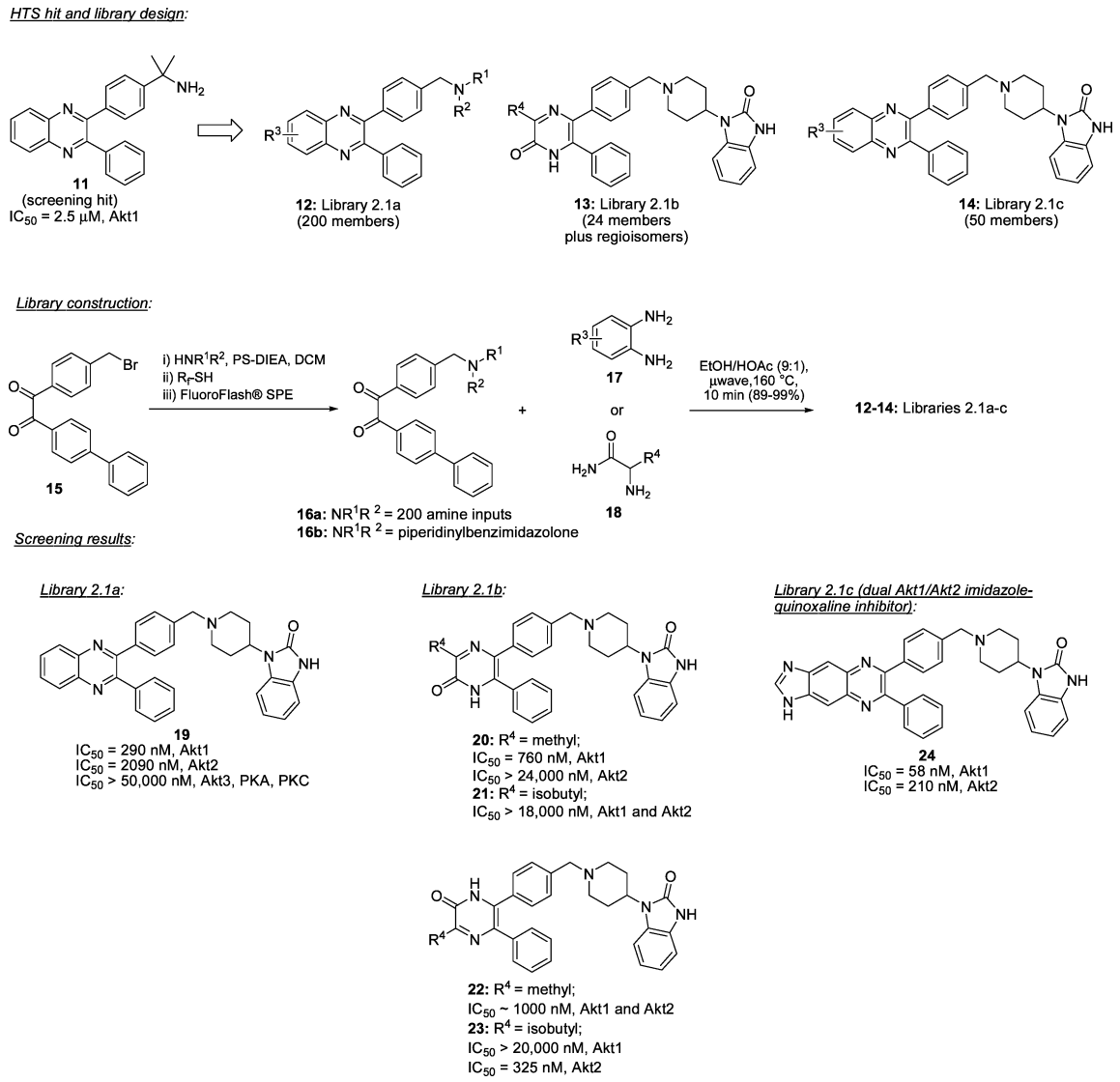


Figure 2. Merck's Atk inhibitors.[210]

with potent dual Akt1/Akt2 inhibition: tetrazoles (regioisomeric mixtures), 1*H*-pyrazole, and imidazole. The tetrazole-containing analogs were not active in the cellular assay, likely due to their zwitterionic nature. The imidazole quinoxaline analog **24** was a potent dual Akt1/Akt2 inhibitor in A2780, LNCaP, HT29, and MCF7 cancer cells. With this encouraging cell-based profile, **24** was further tested in a mouse model (50 mg/kg ip administration, 3 doses, every 90 min). It was efficacious in vivo, inhibiting Akt1 and Akt2 phosphorylation in lungs of mice injected with IGF.

Dopamine D3 Ligands. The dopamine D3 receptor has received much attention because of its potential involvement in the treatment of Parkinson's disease, schizophrenia, and substance abuse. Pharmacological studies implicate D3-mediated neurotransmission in the reinforcing effects of cocaine. In particular, the D3 partial agonist BP 897 (**25**) has been shown to inhibit cocaine-seeking behavior without revealing any intrinsic, primary rewarding effects (Figure 3). On the basis of structure **25**, researchers at the Friedrich Alexander University in Erlangen (Germany) developed a parallel solid-phase synthesis of a BP 897-type arylcarboxamide library (**32**, library 3.2) using the click chemistry derived formyl indolyl methyl triazole (FIMT) resin **29**.[29] A three-dimensional SPOS protocol was established to provide structural variations of the nature of both aromatic moieties and the length of the chain connecting the aryl carboxamide and the basic amino function in the central part of the scaffold. Attachment of the N-protected aminoalkylpiperazines to resin **29** by reductive amination provided the resin **30**. After coupling with activated arylcarboxylic acid derivatives and N-deprotection (using Burgess' methodology, i.e., trimethylsilyl triflate, 2,6-lutidine), a further diversification was conducted using the Buchwald−Hartwig N-arylation methodology. Employing NaO*t*Bu as a base, toluene as a solvent, and $Pd_2(dba)_3$/BINAP as the catalyst, excellent purities were observed for the coupling of the bromoarene derivatives. Unfortunately, the necessity to transfer the reactions from PTFE vessels to glass reactors and vice versa led to low yields for this N-arylation step. The purities of cleaved compounds (average: 85%) were sufficient for the direct submission for biological testing without purification. The compounds were screened for

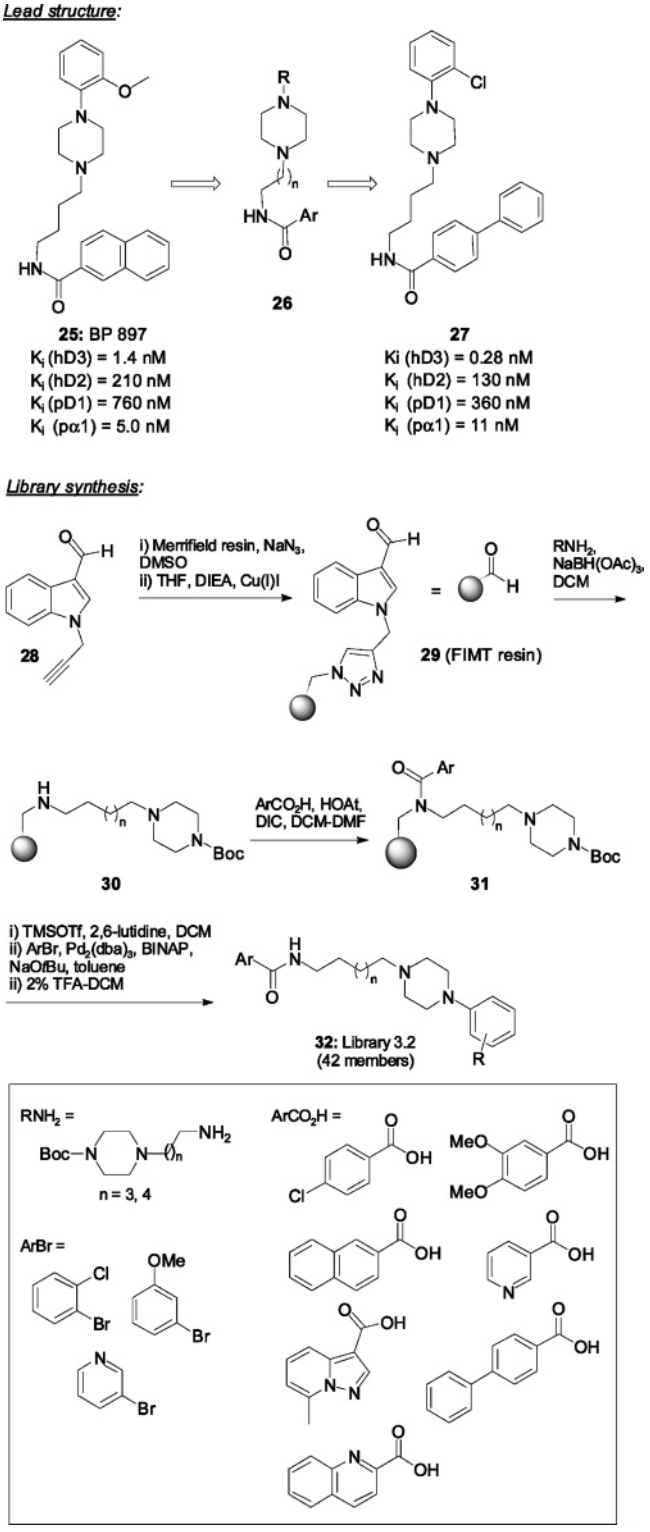


Figure 3. Dopamine D3 ligands.[29]

binding affinities toward the D1, D2, D3, D4, and α1 receptors at concentrations of 100 nM. Selected screening hits were purified by column chromatography. Further binding studies indicated nanomolar D3 receptor affinity for five library members. Combination of the biphenyl moiety with the 2-chloropiperazine substructure and a chain length of four led to the biphenyl carboxamide **27**, which displayed a K_i value of 0.28 nM at the D3 receptor, as compared to a K_i of 1.4 nM for BP 897. Furthermore, compound **27** had only modest affinity toward the D1, D2, and D4 receptors and had the best selectivity D3 versus α1 within the subset of active D3 ligands.

NPY5 Receptor Antagonists. Neuropeptide Y (NPY) is a 36-amino-acid peptide that activates six receptor subtypes (Y1−Y6). One of the subtypes, NPY5 receptor (NPY5R), regulates appetite in animal feeding models, validating it as a potential target for obesity. To identify novel NPY5R inhibitors, the Lead Generation group at Roche executed a virtual screening campaign using a hybrid topological similarity/3D pharmacophore search approach.[113] A virtual screening query using Accelrys' Catalyst was derived from reference compounds disclosed by Banyu Pharmaceuticals, Amgen, and Roche (**33**, **34**, and **35**, respectively; Figure 4). The query consisted of the common hydrophobic moieties present in **33**−**35**, along with selected topological elements and a molecular shape filter. Virtual screening of Roche's compound collection identified 632 candidates, 31 of which inhibited NPY5R with an $IC_{50} < 10\ \mu M$. Upon hit confirmation, compound **36** ($IC_{50} = 40$ nM) was identified. The compound was active in a mouse feeding model (ip, 10 mg/kg) and a patent search revealed it to be a proprietary structure. To establish an SAR around **36**, the researchers synthesized a 100-member aminothiazole library using previously reported solution-phase methodology. The chemistry involved the condensation of thioureas **37** with *N*,*N*′-dimethylformamide dimethyl acetal **38** under reflux conditions without the use of cosolvents. The resulting intermediates **39** were then reacted with α-bromoketones **40** to afford the desired aminothiazoles **41** (library 3.17). The initial SAR indicated that electron-donating substituents on the 3-position of the phenyl-amine unit favored activity, whereas electron-withdrawing groups on the phenyl ketone unit were particularly preferred at the ortho position (**42**, $IC_{50} = 19$ nM). With this SAR knowledge at hand, a second optimization round was carried out in which a focused 40-member library was made using a much broader range of α-bromo o-substituted aromatic ketones. The CF_3 and CN groups on the 3-position of the phenylamine unit were kept constant. The SAR that emerged from this optimization library indicated that the CN group was favored over the CF_3 group and a preference for the *o*-methyl and -ethyl groups on the aryl ketone as exemplified by compounds **43**, $IC_{50} = 4.2$ nM, and **44**, $IC_{50} = 2.8$ nM. It is also worth noting that when the 2-methylphenyl ketone group was replaced with the isostere analog 2,5-dimethylthiophene group, the corresponding aminothiazole derivative retained high potency against NPY5R (**45**, $IC_{50} = 14$ nM).

Melanin-Concentrating Hormone 1 Receptor (MCH1R) Antagonists. Melanin-concentrating hormone (MCH) is a cyclic 19-amino-acid neuropeptide expressed in the brain of mammals. In vivo studies in mice demonstrated that MCH is responsible for appetite regulation and energy homeostasis, since genetically engineered mice lacking MCH production were hypophagic and leaner, and mice overexpressing MCH were susceptible to obesity and developed insulin resistance. MCH binds and activates two receptors, MCH1R (SLC-1)

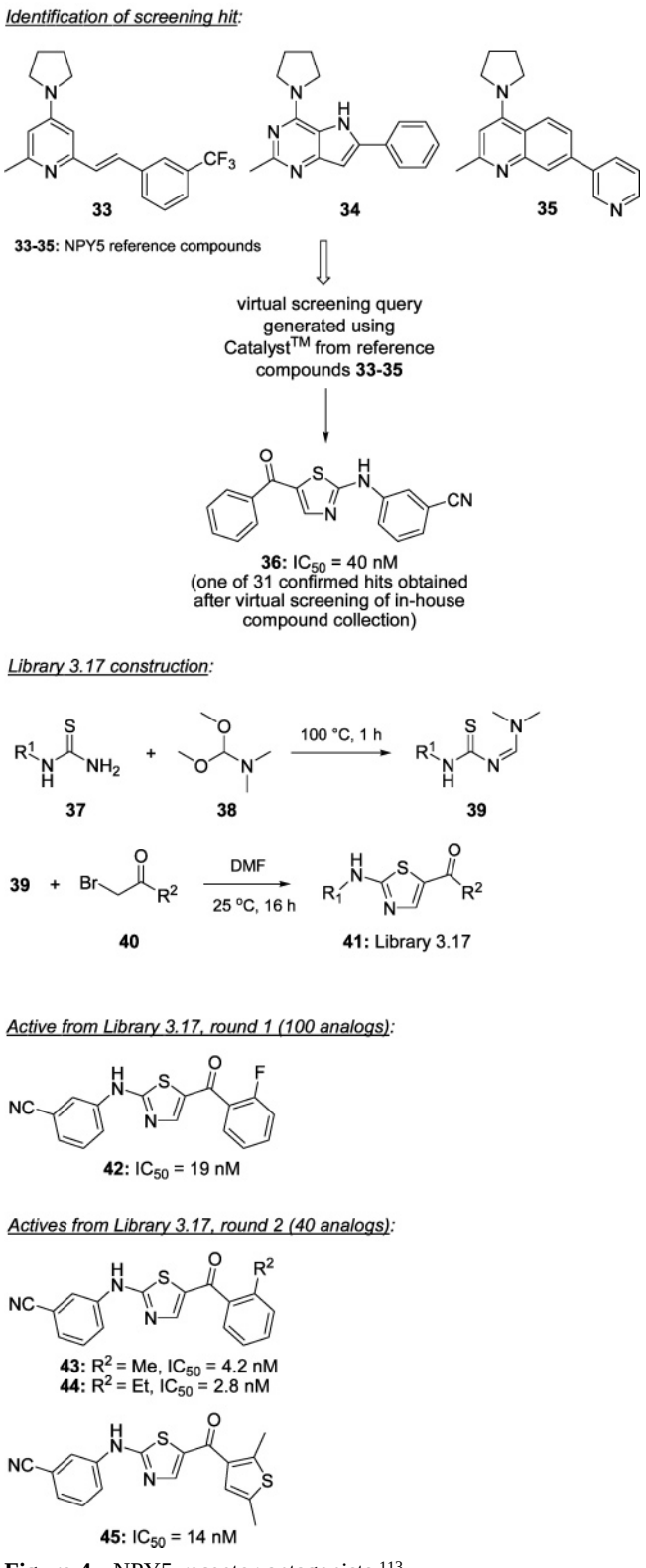


Figure 4. NPY5 receptor antagonists.[113]

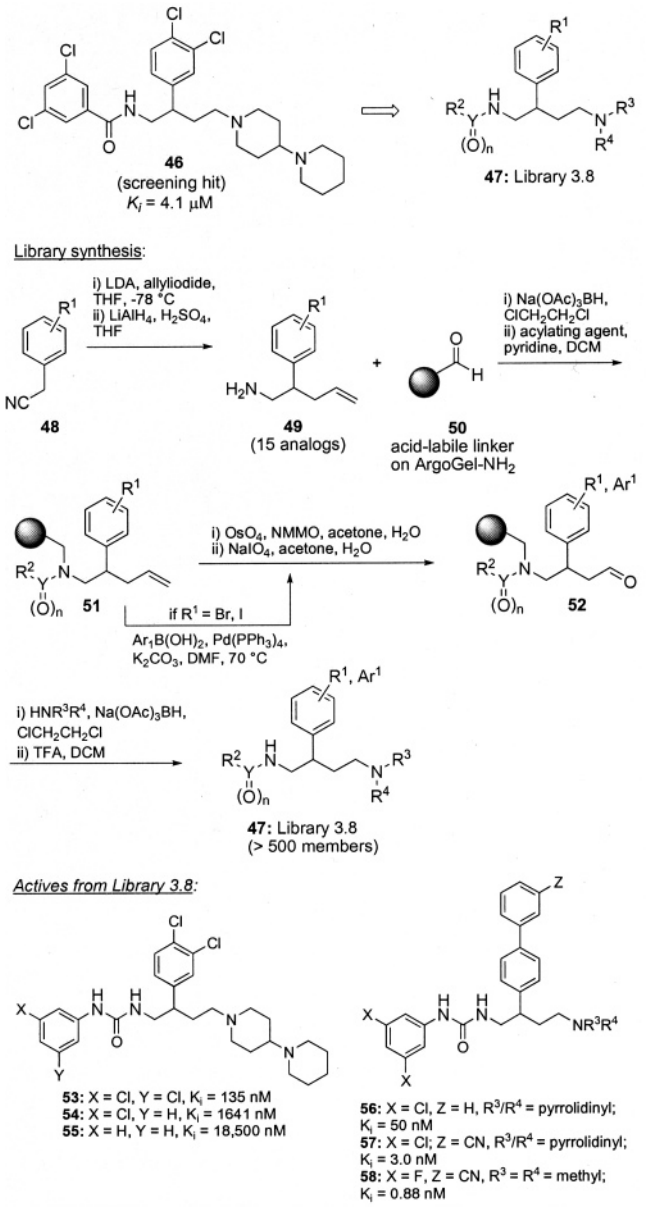


Figure 5. MCH1 receptor antagonists.[116]

and MCH2R (SLT). Although these two receptors are found in humans, only the appetite and metabolism function of MCH1R has been validated in food-intake mice models. To identify nonpeptide MCH1R antagonists, researchers at Pharmacopeia ran a screening campaign using a scintillation proximity assay based on [^{125}I]-MCH binding to membranes expressing human MCH1R as the primary assay.[116] This screening exercise identified several 4-amino-2-(3,4-dichlorophenyl)butylbenzamides with low micromolar potencies (**46**, $K_i = 4.1\ \mu M$). Guo and co-workers developed a solid-phase approach for the rapid synthesis and SAR elucidation around compound **46** via library 3.8 (**47**). The SAR strategy centered on the exploration of three regions of **46**: (a) the central 3,4-dichlorophenyl group, (b) the 3,5-dichlorobenzamide group, and (c) the 4-piperidylpiperidyl group. The construction of **47** began with the alkylation of 15 diverse benzyl nitriles **48** with allyliodide, followed by the reduction of the nitrile group with LAH. The resulting amines **49** were then immobilized on an acid-labile ArgoGel−NH_2-supported aldehyde resin **50** via reductive amination conditions, which upon derivatization with acid chlorides, sulfonyl chlorides, isocyanates, and chloroformates gave resin **51**. At this point, the bromo- or iodophenyl intermediates (derived from bromo- or iodobenzyl nitriles **48**) were further derivatized with aryl boronic acids under Suzuki reaction conditions. The penultimate resin intermediate **52** was generated upon oxidation

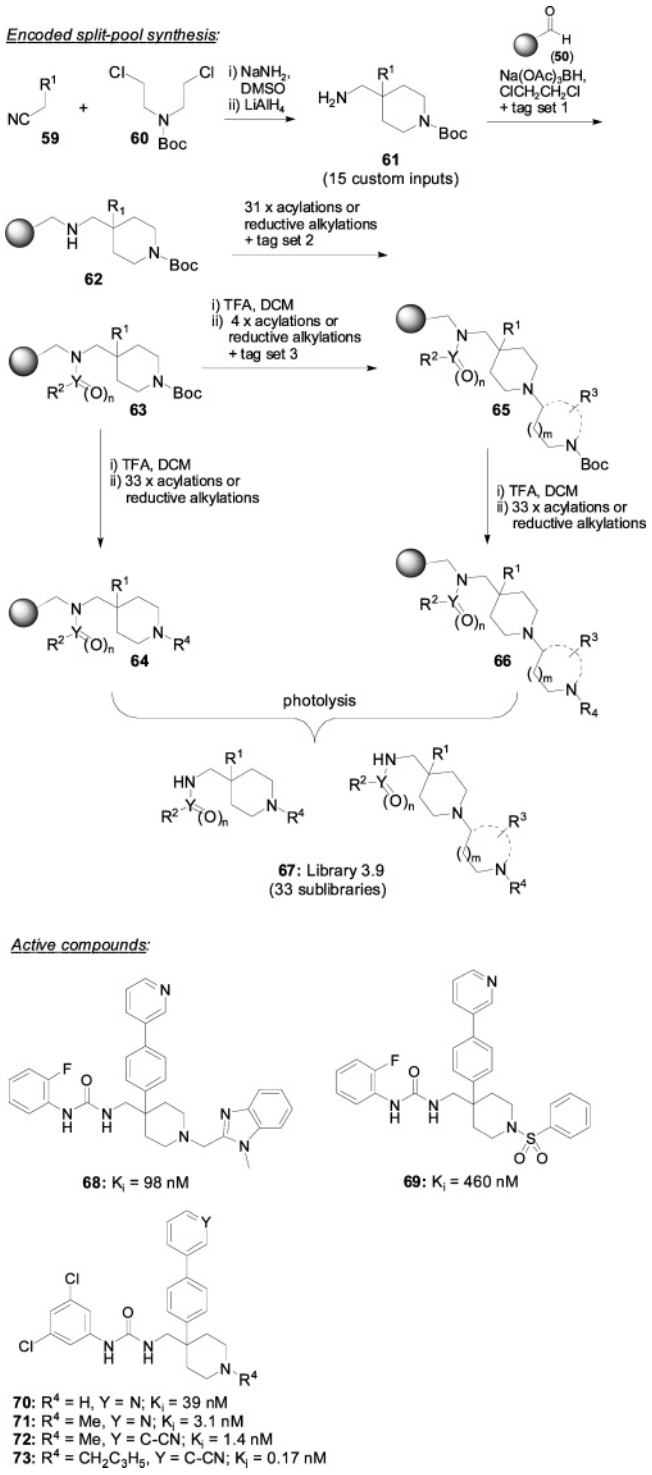


Figure 6. Encoded split−pool library yielding MCH1 receptor antagonists.[117]

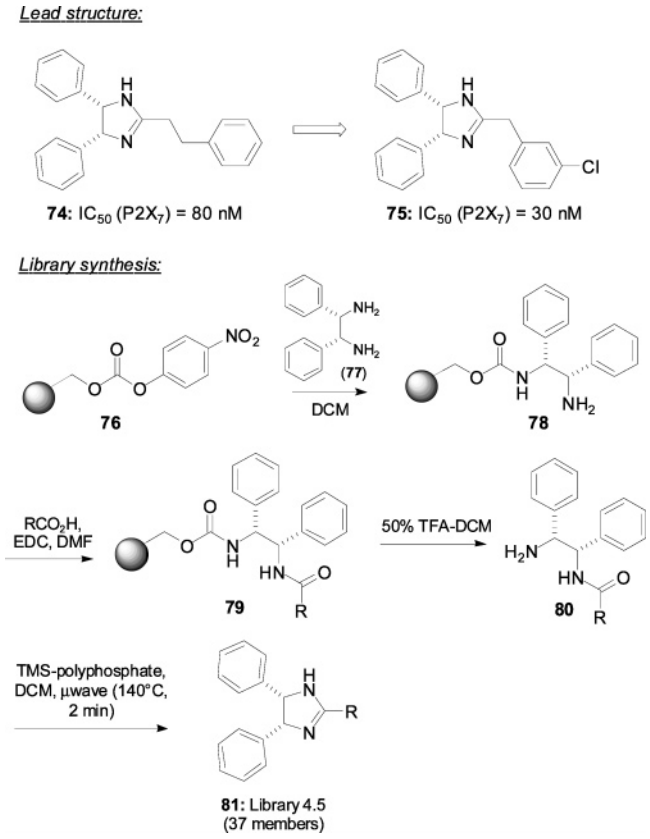


Figure 7. GlaxoSmithKline's $P2X_7$ receptor antagonists.[237]

of the common allyl group (**51** → **52**). Reductive amination of **52** with a selection of amines completed the library 3.8 synthesis (500 members, 5 mg each). The initial SAR revealed that the 3,5-dichlorophenylurea group was the only substitution that increased binding affinity: **53**, K_i = 135 nM; 30-fold increase versus **46**. Sequential removal of the chlorine atoms in **53** was detrimental for activity (**54**, K_i = 1641 nM; **55**, K_i = 18 500 nM). Other diverse dihalogenated phenyl ureas retained submicromolar potency. Biaryl analogs provided an SAR trend with enhanced binding affinity for the receptor. In general, the para-biaryl analogs were more active than the ortho- and meta-linked biaryls. In the biaryl series, it became possible to reduce the size of the 4-piperidylpiperidyl group in **53** without attenuating affinity. For example, the combination of the smaller pyrrolidin-1-yl and unsubstituted 4-phenyl groups resulted in **56** (K_i = 50 nM) with a significant 3-fold increased in affinity when compared to **53**. Substitution at the 3-position of the distal phenyl ring was the most favored substitution site, especially when an electron-withdrawing group such as nitrile was introduced (**57**, K_i = 3.0 nM). This permitted successful exchange of the pyrrolidin-1-yl with *N*,*N*′-dimethylamino: **58**, K_i = 0.88 nM. Since at this point all compounds were isolated and tested as racemic mixtures, the two enantiomers of **56** were resolved and tested individually. The enantiomers of **56** were found to each exhibit a K_i of 3−4 nM. These agents were active in the Ca^{2+} mobilization FLIPR secondary functional assay, in which they antagonized MCH1R with a K_i of 1.0 nM.

Guo and co-workers disclosed another effort toward the discovery and optimization of novel nonpeptide MCH1R antagonists.[117] In this instance, Pharmacopeia's ECLiPS technology was employed.[117] An encoded 19 470-member aryl and biaryl piperidine-based combinatorial library (**67**, library 3.9) was synthesized via a pool-and-split solid-phase strategy using a resin-bound photocleavable linker and haloaromatic alcohols as tags (Figure 6). The required piperidin-4-ylmethanamine scaffolds **61** were constructed by alkylating diverse nitriles **59** with Boc-protected bis-(chloroethyl)amine **60** using sodium amide, followed by reduction

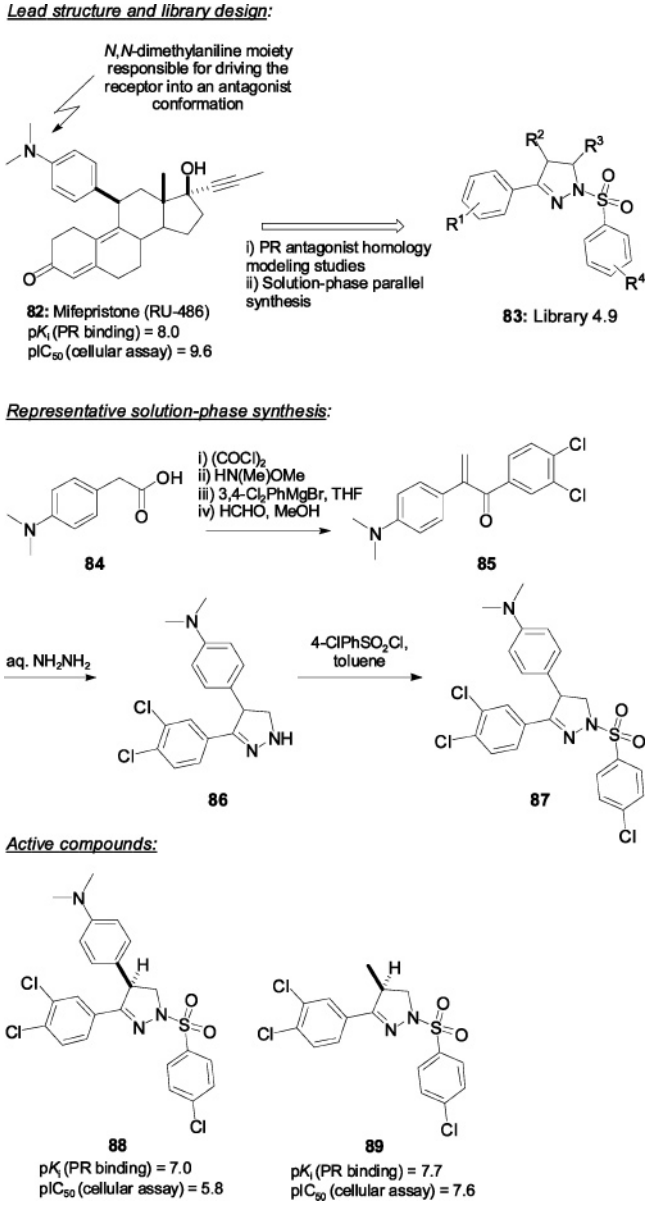


Figure 8. Pyrazoline-based PR antagonists.[160]

with LAH. The resulting 4-(aminomethyl)-Boc-piperidines **61** were immobilized on a resin-bound aldehyde-functionalized photocleavable linker **50** via reductive amination. The resulting resins **62** were encoded with tag set 1. Intermediates **62** were then functionalized using reductive alkylation conditions or a broad range of acylating agents and encoded with tag set 2. Resin intermediate **63** was treated with TFA to remove the Boc protecting group and divided into two portions. Portion 1 was split into 33 reaction vessels and acylated or reductively aminated to give **64**. Portion 2 was split into four reaction vessels and acylated or reductively aminated and then encoded with tag set 3 to give **65**. Resin **65** was combined and split into 33 portions for a final round of acylation or reductive amination furnishing resin **66**. Intermediate resins **64** and **66** were kept separate undergoing photolysis to afford library **67** as 33 separate sublibraries. The physicochemical properties, including cLog P and polar surface area (PSA) of all potential compounds (76 725 based on the total number of inputs), were calculated to determine the most efficient building-block combination to produce the most products with druglike molecular properties (e.g., cLog P $\leq$ 5 and PSA $\leq$ 120 Å^2). On the basis of this analysis, a smaller optimal building-block combination was chosen to produce the 19 470-member library 3.9 in which 95% of the members were predicted to exhibit good oral absorption. Using the same primary assay described previously,[116] a two-phase screening strategy was used: the first phase using compound mixtures to identify active sublibraries ($\sim$10 compounds/well at a concentration of $\sim$10 μM/compound) and the second phase to identify individual active compounds (1 compound/well, $\geq$ 50% inhibition at 10 μM). This process identified 84 hits from 8 sublibraries. Three sublibraries had the greatest number of hits defined by R^4 = benzensulfonyl, phenylpropyl, and 1*N*-methylbenzimidazol-2-ylmethyl. Following a synthon frequency analysis, selected hits were resynthesized, and two potent leads were identified (**68**, K_i = 98 nM; **69**, K_i = 460 nM). A follow-up optimization 130-member library was made using the same solid-phase methodology using Robbins Scientific's FlexChem reaction block system. In this optimization library, the previously identified 3,5-dichlorophenylurea and 3′-cyanobiphenyl-4-yl groups[116] were included, and it was found that the simultaneous combination of these groups led to a dramatic increase in potency. Replacement of the hydrogen with a methyl group (piperidine nitrogen) increased potency by 12-fold (**70**, K_i = 39 nM; **71**, K_i = 3.1 nM; functional antagoinst in Ca^{2+} flux assay, K_b = 0.4 nM). Replacement of the 4-(3-pyridyl)phenyl group with the 3′-cyanobiphenyl-4-yl group increased potency an additional 2-fold (**72**, K_i = 1.4 nM). The alkylation of the piperidine nitrogen with acyclic or cyclic substituents ($\leq$6 carbons, with the exception of the butyl series) was generally well-tolerated, affording products with subnanomolar potency (**73**, K_i = 0.17 nM). Last, consistent with the design and selection of inputs based on druglike properties, compound **71** was orally absorbed in the rat.

$P2X_7$ Receptor Antagonists. The P2X family of nucleotide receptors consists of nonspecific, ligand-gated cation channels that participate in a variety of physiological processes. $P2X_7$ is expressed in the periphery on cells of the immune system, such as macrophages and epidermal Langerhans cells. The receptor is also expressed in the CNS on microglia and astrocytes. Due to the presence of the $P2X_7$ receptor on cells of the immune system and the relationship between $P2X_7$-activation and cytokine or glutamate release, this receptor may play an important role in the development and progression of various disease states or conditions, such as chronic inflammation, neurodegeneration, and chronic pain. As a result of a high-throughput screening effort, researchers at Sanofi Aventis identified **74** as potent new $P2X_7$ antagonist lead (Figure 7).[237] Rapid SAR exploration around this 4,5-diarylimidazoline series was conducted using a high-throughput medicinal chemistry approach. Coupling of **77** with the *p*-nitrophenylcarbonate resin **76** afforded the carbamate bound amine **78**, which reacted with a series of carboxylic acids using the standard coupling method to

provide resin **79** in quantitative yield. Attempts to cleave and cyclize in one pot using acids and heat failed to give the desired compounds, affording only the uncyclized amine cleavage products **80**. Treatment of **80** with trimethylsilylpolyphosphate (TMS-PP) in dichloromethane under microwave irradiation afforded the desired imidazoline library 4.5 (**81**). The $P2X_7$ affinity of **81** was assessed using a cellular YO-PRO-1 dye uptake fluorescence assay. Several new potent $P2X_7$ antagonists, exemplified by compound **75**, were identified from this study.

Progesterone Receptor Antagonists. The progesterone receptor (PR) is a member of the intracellular superfamily of ligand-dependent transcription factors. PR agonists play an important role in female reproduction and have been used extensively in female contraception and hormone replacement therapy. PR antagonists, however, have found only limited utility, and their therapeutic potential has not yet been fully elucidated. A selective PR antagonist may be potentially useful for the treatment of various gynecological and obstetric diseases, including hormone-dependent breast and prostate cancers, nonmalignant chronic conditions such as fibroids, and endometriosis. Mifepristone **82**, a clinically available steroidal PR antagonist, demonstrated potent activity at other steroid receptors, such as the glucocorticoid receptor (GR), and this potentially limits its chronic use (Figure 8). Novel PR antagonists that are structurally distinct from the steroid class may have greater potential for selectivity against other steroid receptors (e.g., GR). Researchers at GlaxoSmithKline sought an unexplored, synthetically accessible nonsteroidal mimetic of mifepristone suitable for parallel synthesis of analogs.[160] Docking of mifepristone into a PR antagonist homology model suggested that the *N*,*N*-dimethylaniline moiety was responsible for switching the receptor into an antagonist conformation through displacement of a particular receptor helix (named AF2). From this modeling information, a series of diaryl pyrazolines **83** (library 4.9) with the aim of mimicking the conformational changes induced by mifepristone was designed. Biological data on the pyrazoline sulfonamides synthesized as described in Figure 8 was reported. The compounds were tested for receptor binding as well as functional activity in CV-1 cells. As predicted by homology modeling, these compounds behaved as PR antagonists, inhibiting progesterone-stimulated PR activity in cells. The best compounds in this study, **88** and **89**, exhibited >10-fold steroid receptor selectivity over the androgen and glucocorticoid receptors.

HDM2−p53 Antagonists. p53 is a tumor suppressor transcription factor expressed in response to DNA damage and plays a critical function in cell cycle arrest and apoptosis, ultimately preventing neoplasia. Over 50% of human tumors have mutations in the p53 gene, resulting in a loss of functional p53. The human DM2 protein (HDM2), the human homologue of mouse DM2 (MDM2), is the principal down-regulator of p53. HDM2 contains a p53-binding domain that is used to bind to the N-terminal transactivation domain of p53, translocates p53 from the nucleus to the cytoplasm, and then stimulates degradation through the ubiquitin pathway.

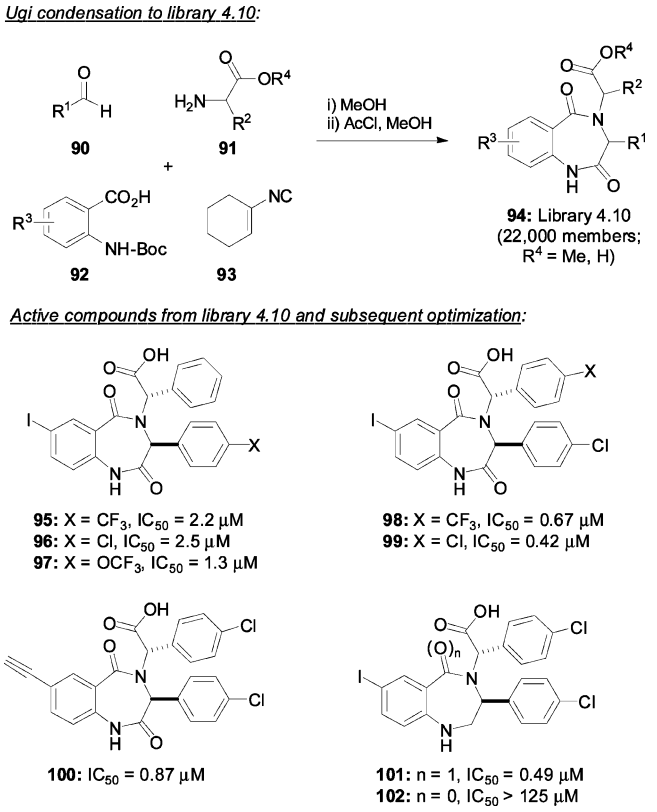


Figure 9. HMD2-p53 protein−protein antagonists.[262,110]

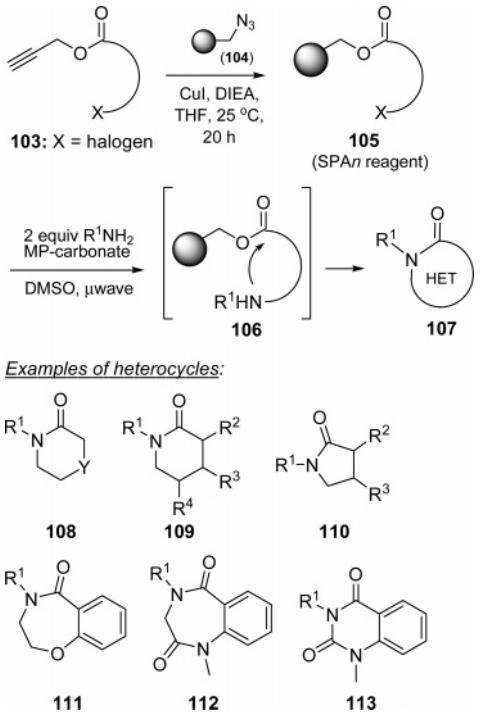


Figure 10. SPA*n* reagents: primary amines to heterocycles.[78]

Disrupting the HDM2-p53 protein−protein interaction offers a viable route for cancer therapy due to the up-regulation of functional p53. Parks and co-workers at Johnson & Johnson reported the synthesis of 1,4-benzodiazepine-2,5-diones as antagonists of the HDM2-p53 complex formation (Figure 9).[262] A 22 000-member 1,4-benzodiazepine-2,5-dione library was designed using the computational package Directed

Diversity and synthesized via the Ugi-4CR (**94**, library 4.10). Commercially available and custom α-amino esters were used as the amino component. A proprietary high-throughput ThermoFluor microcalorimetry screening technology was used to identify hits. Microcalorimetry measures the melting point differentials in protein−compound complexes. By using a series of different compound concentrations, a compound's dissociation constant (K_d) can be calculated. The ThermoFluor screening hits were confirmed in a secondary fluorescence polarization assay. Due to the poor solubility of the 1,4-benzodiazepine-2,5-dione esters in the latter assay, the esters were saponified to their corresponding more soluble carboxylic acids (isolated as diastereomeric mixtures). Initial library screening identified hit **95** with micromolar activity (IC_{50} = 2.2 μM). NMR experiments established that the active diastereomer had the *S*,*S* configuration. Compound **95** was subjected to a systematic optimization process. Overall, a relatively tight SAR was observed. Substitution of the CF_3 group at the para position was tolerated only with Cl and OCF_3 groups (**96**, IC_{50} = 2.5 μM; **97**, IC_{50} = 1.3 μM). An aromatic ring was required at R^2 with phenyl substituted in the para position with spherically symmetrical hydrophobes, such as CF_3 and Cl, yielding a 4−6-fold increase in binding (**98**, IC_{50} = 0.67 μM; **99**, IC_{50} = 0.42 μM). Attempts to lower the molecular weight by removing the iodine atom generally led to a sharp loss of activity. The exception was the replacement of iodo with an ethynyl group, which afforded a submicromolar analog **100**, IC_{50} = 0.87 μM. It was hypothesized that the vector of the ethynyl group (its size notwithstanding) occupies a similar region in space as the iodo atom favoring interactions with the protein target. Attempts to lower the cLog P of **99** into an acceptable range of druglike compounds included the replacement of the 4-Cl-phenyl groups at R^1 and R^2 with a 6-chloropyridin-3-yl group. Unfortunately, these changes negatively impacted potency. Working together in the same research program, Grasberger and co-workers cocrystallized and resolved the HDM2-**99** complex (PDB code: 1T4E) and a HDM2-9-mer peptide (PDB code: 1T4F). Examination of the HDM2-9-mer complex with the reported HDM2-p53 15-mer complex showed the 9-mer peptide occupied the pockets originally taken by HMD2's Phe,[19] Tyr,[23] and Leu[26] side chains. Interestingly, not only was it observed that **99** occupies the same three pockets that the 9-mer does, its pendent groups also adopt an α-helix orientation, conferring **99** an amphipathic binding conformation. This is the first reported example of a benzodiazepindione acting as an α-helix mimetic. The 1T4E crystal structure also shows the presence of three water molecules interacting through hydrogen bonds with **99**'s diazepine ring carbonyl and diazepine ring nitrogen. To determine the importance of these bound water molecules, **99** methyl ester was reduced with $BH_3{\cdot}SMe_2$ in THF and saponified to afford monosubstituted amide **101** (major product) and fully reduced tetrahydrobenzodiazepine **102**. Since removal of one of the ring carbonyls did not affect potency (**101**, IC_{50} = 0.49 μM), and in conjunction with the observation that a ring nitrogen alkylated benzodiazepindione analog was also found to retain potency, it was concluded that the bound waters are not essential for binding. In addition, the total loss of activity exhibited by **102** (IC_{50} > 125 μM) suggests that conversion of both sp^2 carbonyl carbons into sp^3 carbons confers too much structural flexibility to **102** to allow it to find and adopt the required optimal conformation for binding. Last, **99** was found to suppress cell proliferation in JAR choriocarcinoma cells overexpressing both press p53 and HDM2 in a dose-dependent manner.

SPA*n* Reagents for Primary Amine Derivatization. High-throughput derivatization of amines affording libraries of amides, sulfonamides, ureas, and higher-order amines (via reductive amination, alkylation) is extensively used to develop structure−activity relationships for biologically active leads. Derivatization is carried out in solution using either resin-bound coupling reagents and scavenger resins or activated acyl and sulfonyl transfer resins. The derivatives so obtained are acyclic in nature. Dolle and co-workers[78] described a conceptually new family of annulation reagents for the single-step derivatization of primary amines to heterocycles. The goal was to make available "off-the-shelf" reagents for producing heterocycles in a semiautomated format, complementary to acyclic derivatization methods. To this end, the tandem N-alkylation−intramolecular acylation reaction (**105** → **106** → **107**) was initially chosen as the traceless solid-phase annulation manifold. The major obstacle to reduce the idea to practice was loading the requisite reactive haloalkylacyl reagents onto the solid phase. The reagents were unstable in solution and tended to decompose back into their corresponding lactones from which they were derived. Direct acylation of Wang resin with haloalkyl acids was not viable. This problem was solved by loading haloalkyl propargyl esters **103** onto Merrifield-type azide resin **104** using "click" chemistry. The SPA*n* reagents **105** (acronym derived from *s*olution/solid-*p*hase *an*nulation) readily furnished heterocycles **107** from primary amines. The optimized reaction conditions required 2 equiv of amine in the presence of excess MP-carbonate resin in DMSO under microwave irradiation (30 min, 150 °C). Some 16 SPA*n* reagents were prepared, as well as 20-member demonstration libraries of isoindolinones and isoquinolones. Reagents **105** gave rise to heterocycles with unique topologies and electrostatic potential surfaces.

TBDAS: A New Silyl Linker. Tan and co-workers described new *tert*-butyldiarylsilyl (TBDAS) linker **115** (Figure 11).[72] Lithiation of bromostyrene resin **114** was followed by treatment with *t*-butyl-dichlorophenylsilane, yielding the desired linker **115**, which was then treated with *N*-Fmoc-*β*-alaninol **118** and imidazole in DCM. Fmoc quantitation indicated a 38% alcohol loading. Because of the relatively high cost of the *t*-butyl-dichlorophenylsilane, a second more practical route to **115** was developed. The lithiated bromopolystyrene was silylated with *t*-butylchlorophenylsilane (prepared from *t*-BuLi and dichlorophenylsilane) to afford the stable silyl hydride resin **117**. Linker loading levels corresponding to 60−80% yield relative to

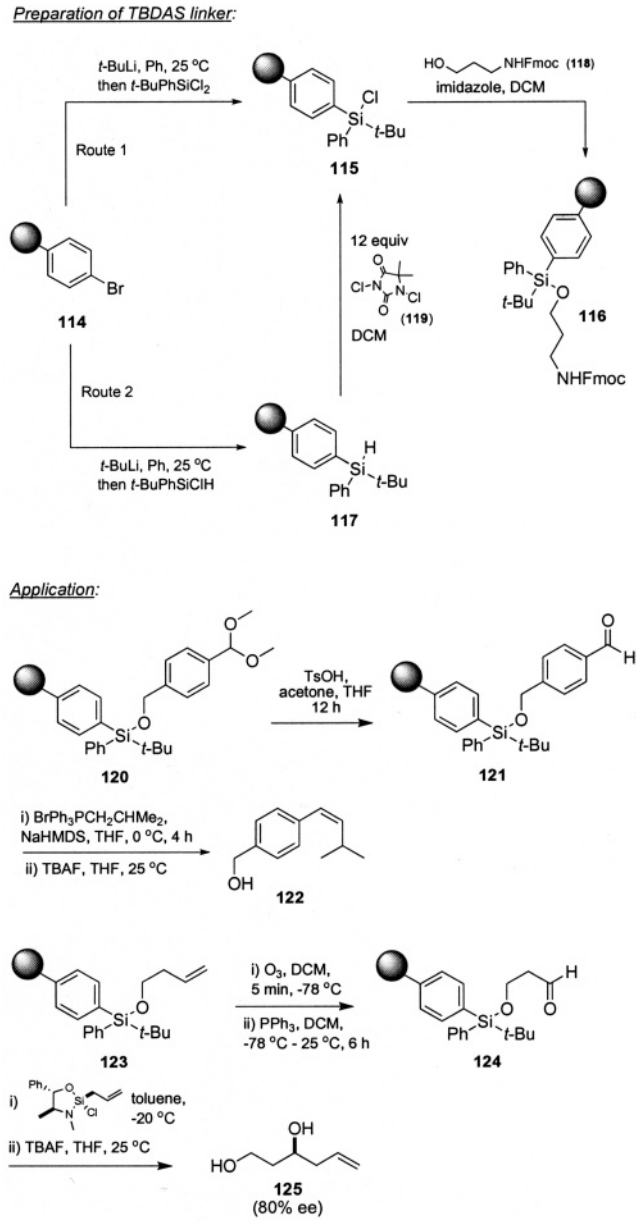


Figure 11. TBDAS: A new silyl linker.[72]

the initial bromine loading levels were achieved (Si elemental analysis). Several methods of activating the silyl hydride resin **117**, including triflic acid, *N*-bromosuccinimide, and trichloroisocyanuric acid were evaluated for alcohol **118** loading. In situ chlorination using 1,3-dichloro-5,5-dimethylhydantoin **119** followed by **118** coupling was the most effective, giving yields of 62−65% (**114** → **117** → **115** → **116**). Loading of the TBDAS linker onto brominated polystyrene SynPhase L-series lanterns was also reported. Tetrabutylammonium fluoride (TBAF) and tris(dimethylamino)-sulfur (trimethylsilyl)difluoride (TAS-F) in THF were found to be rapid and efficient cleavage reagents (100% in <1 h). This is in contrast to HF−pyridine, which proceeds slowly at 25 °C. The TBDAS linker was significantly more stable to protic acids (TsOH and TFA) than the previously reported diisopropylsilyl linkers and also showed good stability to Lewis acids (BF_3·OEt_2 at −78 °C and $AlMe_3$). Moreover, the linker performed well under basic conditions (K_2CO_3−MeOH,

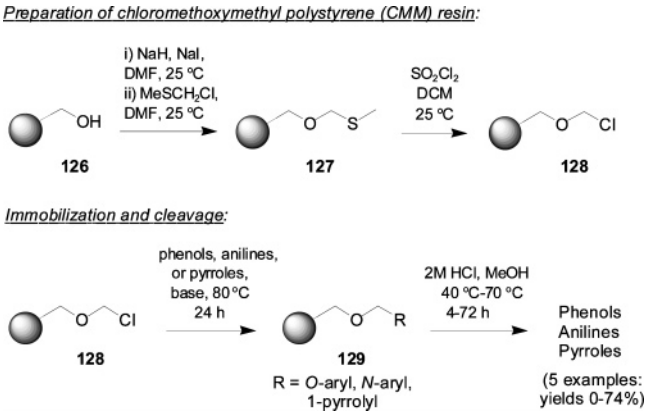


Figure 12. MEM-type linker.[224]

MeLi, KHMDS, and *t*-BuOK) and was stable to extended exposure to aqueous HF in CH_3CN. This enhanced stability to HF potentially permits orthogonal HF-labile protecting group strategies. Resin **115** was found to be compatible with acetal deprotection, ozonolysis, Wittig and Julia coupling, and asymmetric allylation reactions, that is, **120**−**125**.

A MEM-Type Linker. The preparation of a chloromethoxymethyl (CMM)-functionalized resin **128** and its utility as a solid support for the anchoring of phenols and nitrogen heterocycles was described by Álvarez and coworkers.[224] Resin **128** was prepared in a two-step procedure starting with the hydroxymethyl Merrifield resin **126** via first conversion to the methylthiomethyl ether resin **127** using chloromethyl methylsulfide and NaH/NaI. Conversion to **128** proceeded with sulfuryl chloride at room temperature, activating the methylsulfanyl group to nucleophilic displacement by chlorine, yielding the CMM resin. Phenols were attached to the resin using NaOMe in DMF, whereas nitrogen heterocycles were immobilized using NaH in DMF, both requiring heating at 80 °C for 24 h. Cleavage from the CMM resin was carried out using 2 M HCl in MeOH at 25−70 °C over 4−72 h. Under these cleavage conditions, the recovery of phenols was generally poor. Nitrogen heterocycles, however, were recovered in yields of 27−74%.

Silyl-Based Volatile Linker. Houghten and Yu employed an innovative solid-phase approach utilizing the concept of "volatilizable" solid support synthesis for a series of C- and N-terminal protected peptides and chiral polyamines.[138] The concept relies on the complete removal of the solid support and linker following their decomposition and volatilization during the final cleavage step to yield pure products. Silica gel was chosen as the solid support and functionalized with *p*-chloromethylphenyltrimethoxysilane **131** or 2-(4-triethoxymethylsilanebenzyl)-isoindole-1,3-dione **139** to form the desired chloromethylbenzyl **132** and aminomethylbenzyl **141** (phthalimide protecting group removed) functionalized silica gels. Boc-amino acids were coupled to **132** as their cesium salts. Following removal of the Boc group with 50% TFA−DCM, standard Boc-peptide synthesis chemistry (Boc/TFA/DIC) was applied to generate resin-bound peptides **135**. Treatment of **135** with 10% hydrofluoric acid (pH 4.3) for 1 h at room-temperature resulted in complete decomposition

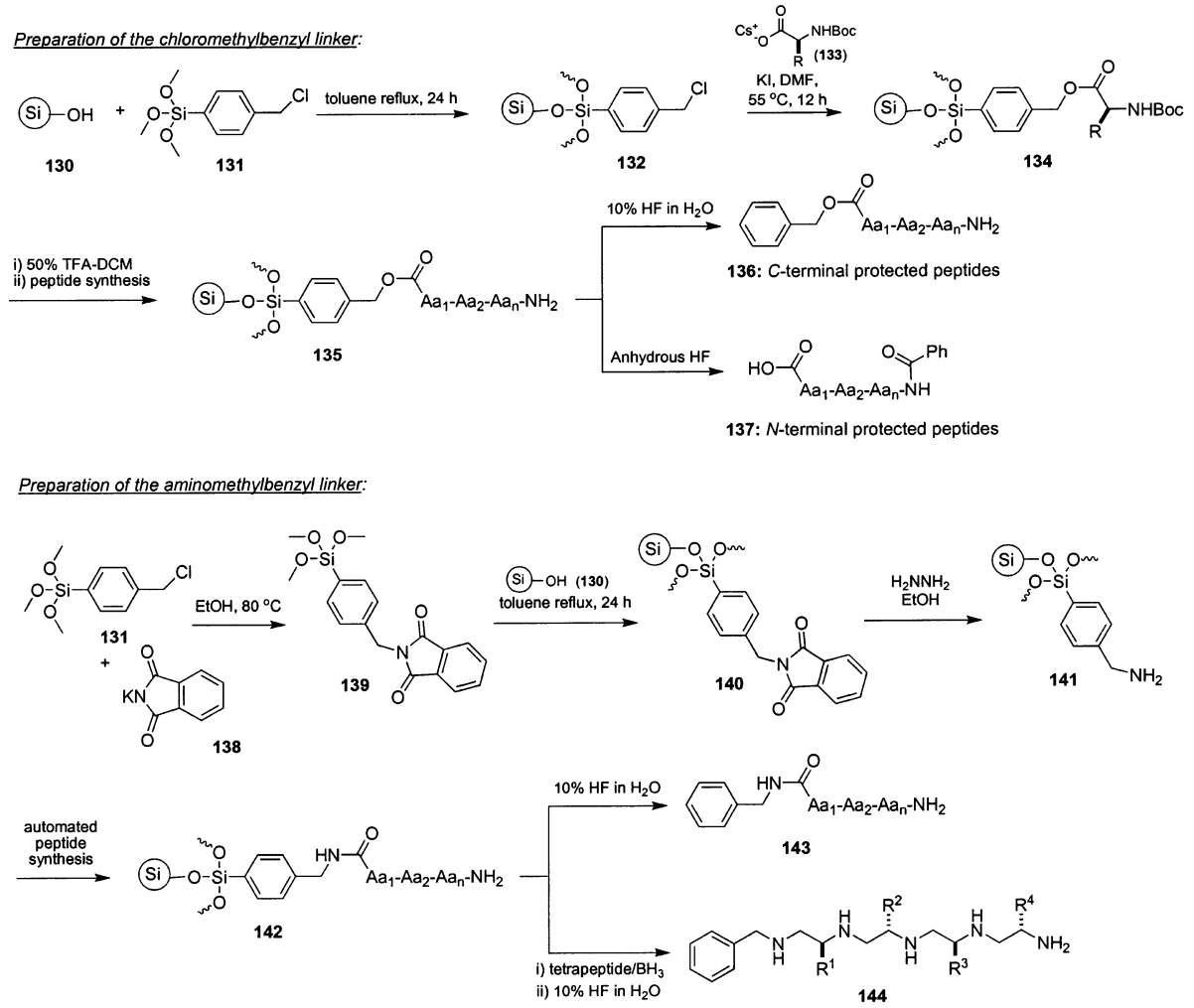


Figure 13. Houghten's silyl-based volatilizable support.[138]

of the silica gel portion of the benzyl ester-linked peptide, yielding the C-terminal benzyl ester-protected peptides **136**, tetrafluorosilane, and water. The solvent, HF, and tetrafluorosilane were removed by either rotary evaporation or lyophilization, and the desired protected peptides were obtained as the sole products remaining in the reaction vessel in excellent yields and purities (>90%). A set of N-terminal modified peptides **137** was similarly obtained in excellent yield and purity (>90%), following N-acylation with phenylacetic acid of **135,** decomposition/volatization of the silica gel with anhydrous HF for 1.5 h at 0 °C, and lyophilization. An automated synthesis of individual compound arrays in a 96-well format using benzylamine-linked silica gel support **141** was demonstrated. Utilizing standard Fmoc peptide chemistry (Fmoc/piperidine/DIC), Fmoc amino acids were coupled to **141** to yield resin-bound peptides **142**, which following volatilization with 10% aqueous hydrofluoric acid and lyophilization yielded C-terminal and side-chain-protected peptides **143** as the sole products in each well in high yields (>85%). Exhaustive reduction of the silica gel-bound Tyr-Tyr-Phe-Pro-benzyl amide was carried out in high yield (81%) using borane to yield the corresponding mono N-benzylated chiral polyamine **144** upon volatilizing cleavage and lyophilization. This methodology could, in principle, be adapted to nonpeptide library synthesis.

Resin-Bound 9-BBN. Polymer-supported 9-borabicyclo-[3.3.1]nonane **147** (9-BBN) was introduced by Ganesan and co-workers for the regioselective reduction of olefins.[280] The reagent referred to as PS-9-BBN is generated in two high-yielding steps. Direct alkylation of deprotonated 1,5-cyclooctadiene **145** (under LICKOR conditions) by high-loading Merrifield chloromethyl polystyrene resin (4.55 mmol/g) yielded the alkylated resin **146**. Hydroboration of **146** afforded the PS-9-BBN (3.24 mmol/g by boron microanaylsis). ^{11}B-NMR showed that the majority of the PS-9BBN exists as a monomeric form, dimerization presumably inhibited by immobilization. Hydroboration reactions are typically performed in THF with 3 equiv of alkene **148** at 40 °C over 24 h. Oxidative release of the resulting immobilized trialkylboranes **149** was carried out with 3 equiv of Bu_4NOH (1 M in MeOH), 5 equiv of aq H_2O_2 (35%) in THF at room temperature for 1 h, then at 50 °C for 3 h. Reaction workup consisted of filtration and concentration, followed by passage through a short plug of silica gel. Yields of the isolated alcohols ranged from 36 to 66%. Alternatively, when **148** is limiting, **147** can be used in 5-fold excess, and

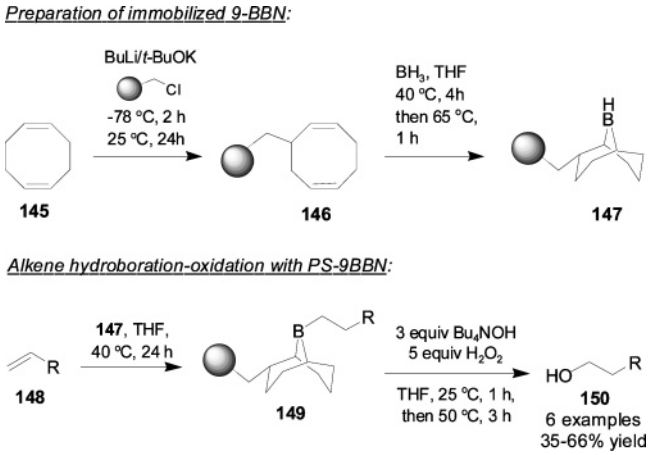


Figure 14. Resin-bound 9-BBN.[280]

higher hydroboration/oxidation conversions are achieved (>85%). Resin **146** is also an effective halogen scavenger.

Addition of Organometallic Reagents to Resin-Bound Imines. Recent work at Bristol-Myers Squibb led to the identification of BMS-196085 (151), a potent β_3 adrenergic receptor agonist having potential as an antiobesity and antidiabetic agent (Figure 15). In an effort to identify additional clinical candidates, exploration around the 1,2-diarylamine portion of the molecule was undertaken.[345] A three-component assembly on solid support was envisioned in which all three modules, resin-bound amine, an aromatic aldehyde, and the organometallic, could be varied in a combinatorial fashion. The nucleophilic addition of organometallic reagents to resin-bound imines was a key step. To this end, primary alcohols **153** and **154** were linked to Merrifield resin through a tetrahydropyranyl (THP) ether linkage and converted to resin-bound intermediates **155** and **156**, respectively. The phenol functionality in the substrates was protected with a 2-(trimethylsilyl)ethoxymethyl (SEM) group, which allowed for its deprotection simultaneously with resin cleavage. The resin-bound amines **155**/**156** were then condensed with aromatic aldehydes in THF at room temperature in the presence of triethylorthoformate as a dehydrating agent to give imines **157**/**158**. Addition of excess organometallic reagents to **157**/**158** in THF at room temperature produced adducts **159**/**160**. Substituted benzyl Grignard reagents were added smoothly (4 h), regardless of the steric or the electronic nature of the substitutents on the benzaldehydes used in the generating imines **157**/**158**. The high intrinsic activity of Grignard reagents precluded their use in those cases in which the imine or the organometallic bore an electrophilic substitutent. Organozinc reagents were successfully used in place of the Grignards when the Ar and R groups contained such sensitive functionality, albeit they required a longer reaction time (20 h). Because of their low reactivity toward many electrophilic groups, the organozinc reagents were effective regardless of the electrophilic character, electronic nature, or the potential for deprotination of the imine substituents. All of the reactions employing an unsubstituted or substituted benzylzinc reagent yielded products with a 1:1 diasteromeric ratio.

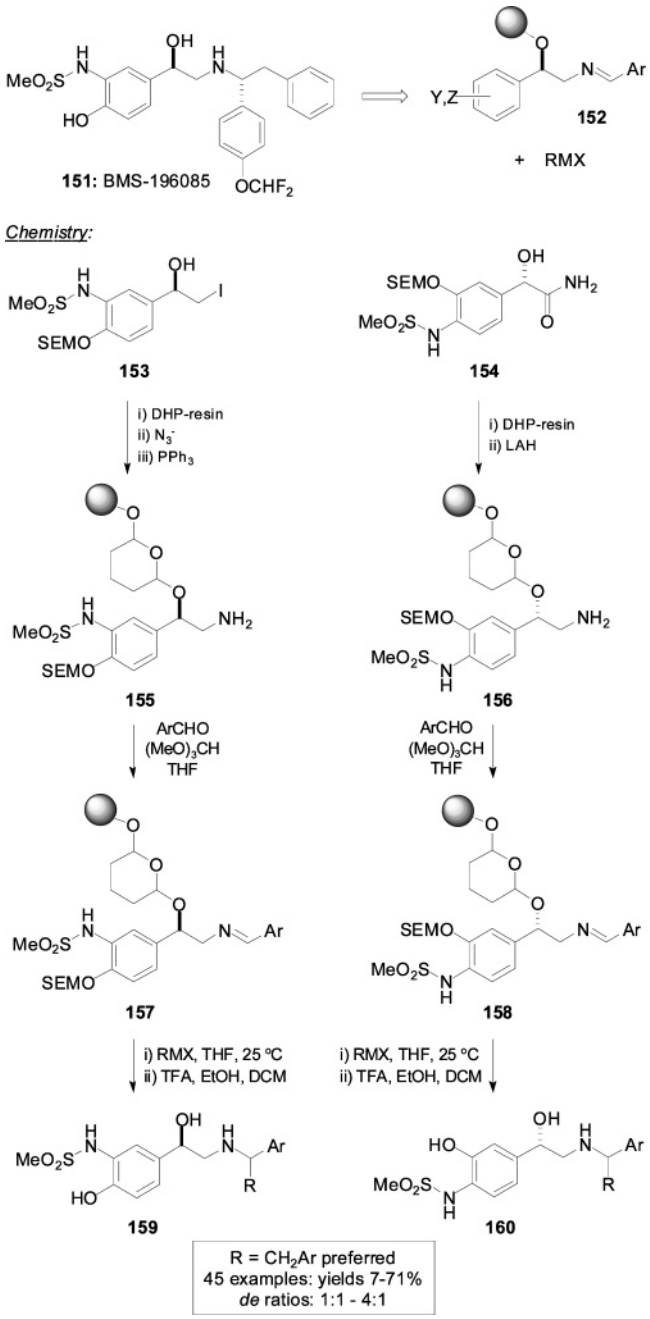


Figure 15. Addition of organometallic reagents to resin-bound imines.[345]

The exception was the methylallylzinc reagent, which gave a 4:1 *S*,*R*-to-*S*,*S* ratio with imine **158**. In contrast, benzyl Grignard reagents did often show a modest stereochemical bias (up to 4:1), depending on the nature of the imine aryl. The scope of the organometallic addition to **157**/**158** was limited to the benzyl anions. The adduct yields obtained from allyl Grignard and allylzinc reagents were low (10−20%), whereas alkyl/aryl Grignard and arylzinc reagents largely failed to react with the immobilized imines. Cleavage of products from the resin and concomitant SEM deprotection was accomplished using a 7:5:5 mixture of TFA−EtOH−DCM. In about one-half of the 45 examples, the crude product purity was >70% (HPLC) after filtration and solvent

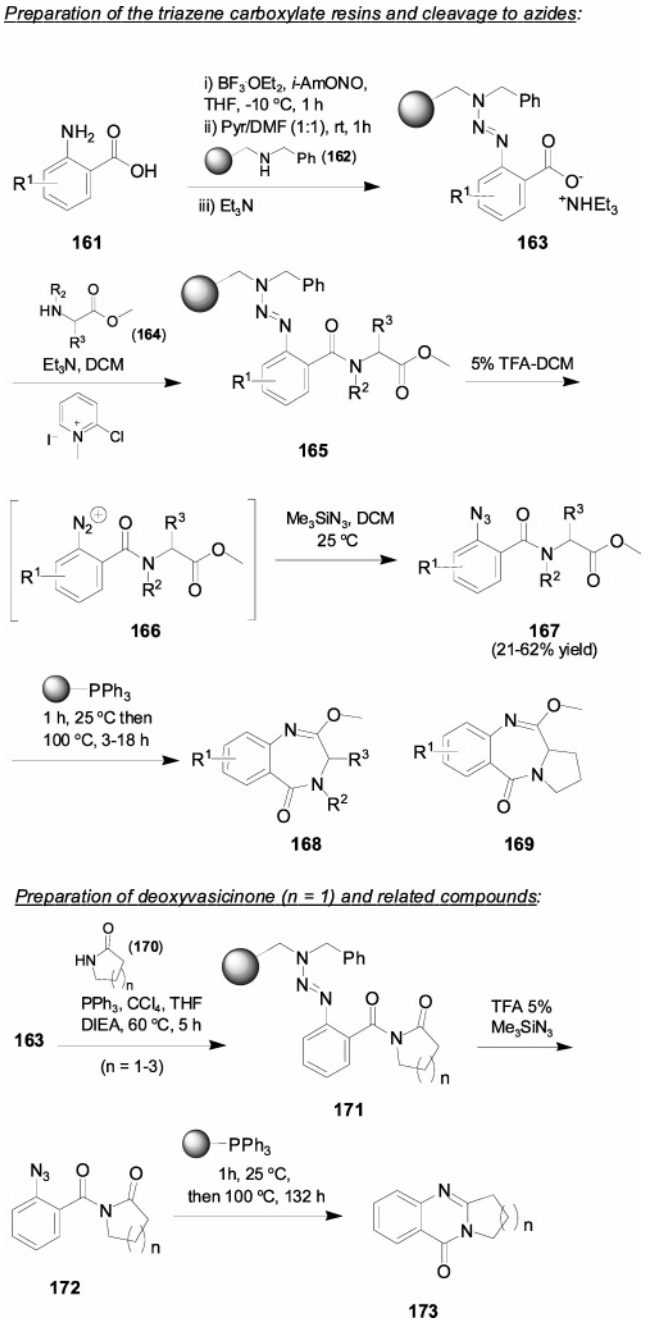


Figure 16. 1,4-Benzodiazepinones using a triazene linker strategy.[104]

evaporation. The major contaminant was the corresponding starting primary amines.

Benzodiazepines via Triazene Linker Strategy. Benzodiazepines were among the first class of small molecules to be prepared on solid phase, and because of their diverse biological activities, they still remain attractive targets for synthesis. A collection of 1,4-benzodiazepin-5-ones **168** were prepared by intramolecular aza-Wittig reactions of *o*-azidobenzoylamides **167** via a postcleavage modification of polymer-bound triazenes **165** (Figure 16).[104] As reported by Gil and Bräse, triazene carboxylate resins **163** were prepared by diazotation of anthranilic acids **161** and subsequent coupling to the benzyl amine resin **162**. Triazene resins **163** were then coupled to the amines **164** using 2-chloro-1-methylpyridinium iodide (Mukayama reagent) as the coupling reagent to give resin **165**. Triazene linker cleavage was achieved using 5% TFA−DCM at 25 °C, generating the corresponding diazonium salts **166**. Salts **166** were immediately reacted with the azide transfer agent, trimethysilyl azide, and the aryl azides **167** obtained were subjected to an aza-Wittig. This was carried out upon reaction of **167** with polymer-supported triphenylphosphine in toluene, first at 25 °C to allow formation of intermediate iminophosphoranes, and then at 100 °C to induce cyclization (3−18 h). Benzodiazepines **168** (**169**) were isolated in 68−99% yield and in 68−94% purity. The methodology was applied to the preparation of deoxyvasicinone **173** ($n = 1$). A modification of the initial coupling procedure was necessary to successfully carry out the synthesis due to the fact that Mukayama reagent is ineffective for coupling of amides to carboxylates (low nucleophilicity of the amides). Since the triazene resins are sensitive to trace amounts of acid, which negates conventional methods of transforming the carboxylate to acid chlorides, the combination of triphenylphosphine and carbon tetrachloride was employed to generate an acid chloride from **163**. This material was in turn reacted in situ with the lactams **170** to obtain amides **171** without the decomposition of the T1 triazene linkage. Carrying out the aforementioned sequence, reactive diazonium salts were converted to azides **172**, followed by the aza-Wittig cyclization to yield deoxyvasicinone and related heterocycles **173** in good overall yields.

Multicomponent Condensations. Yang and Chen described an efficient diversity-oriented approach to benzofurans and indoles by developing a DOS platform to make natural product-like molecules using domino reactions (Figure 17).[215] In this example, the Ugi-4CR and an intramolecular Diels−Alder reaction (IMDA) were integrated into a single synthetic process. The researchers identified a tandem Ugi-4CR-IMDA reaction process followed by oxidative aromatization to generate complex substituted benzofuran and indole scaffolds in a one-pot operation. Intermediate **176** was anticipated to be derived from its precursor **177** via an IMDA reaction. The Ugi-4CR was thus envisioned to generate precursor **177** containing an appropriately oriented conjugated diene and an electron-deficient dienophile. It was assumed that intermediate **176** would undergo an H-shift to form the conjugated aromatic furan or pyrrole **175**, followed by oxidative aromatization to afford the product **174**. In practice, some difficulty was encountered in realizing the IMDA reaction. To achieve a one-pot reaction procedure, upon termination of the Ugi-4CR, the solvent was switched to the higher-boiling xylene, and the reaction was heated to 140 °C in the presence of a positive oxygen pressure for 12 h. Alternatively, DDQ served as a better oxidant, provided substituent groups tolerated the stronger oxidative conditions. Benzofuran and indole heterocycles prepared were isolated in yields ranging from 50 to 80% following chromatography (**178**−**181**). Limitations to the process include the use of unsubstituted pyrroles and

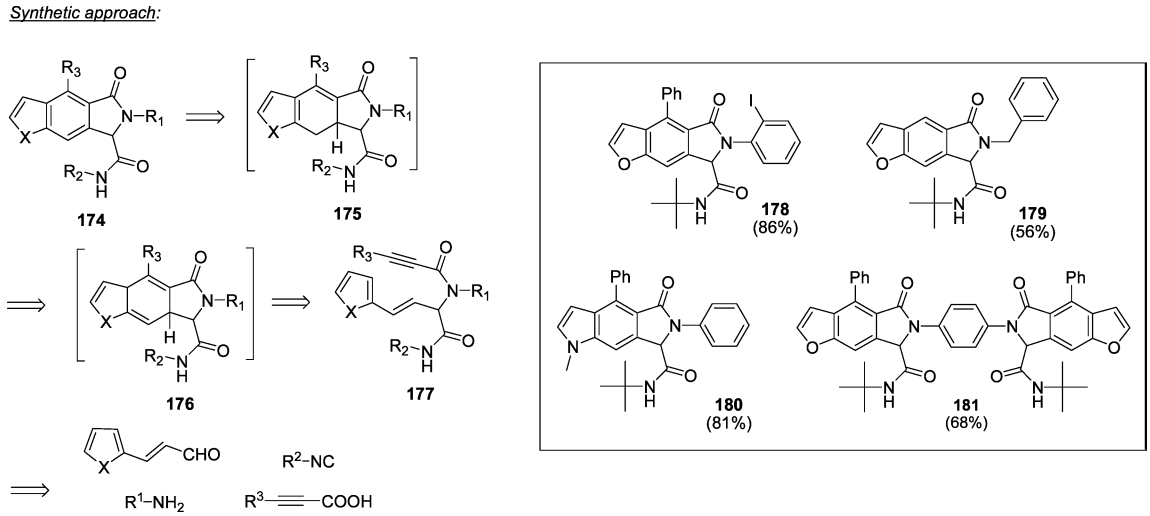


Figure 17. Domino synthesis of benzofurans and indoles.[215]

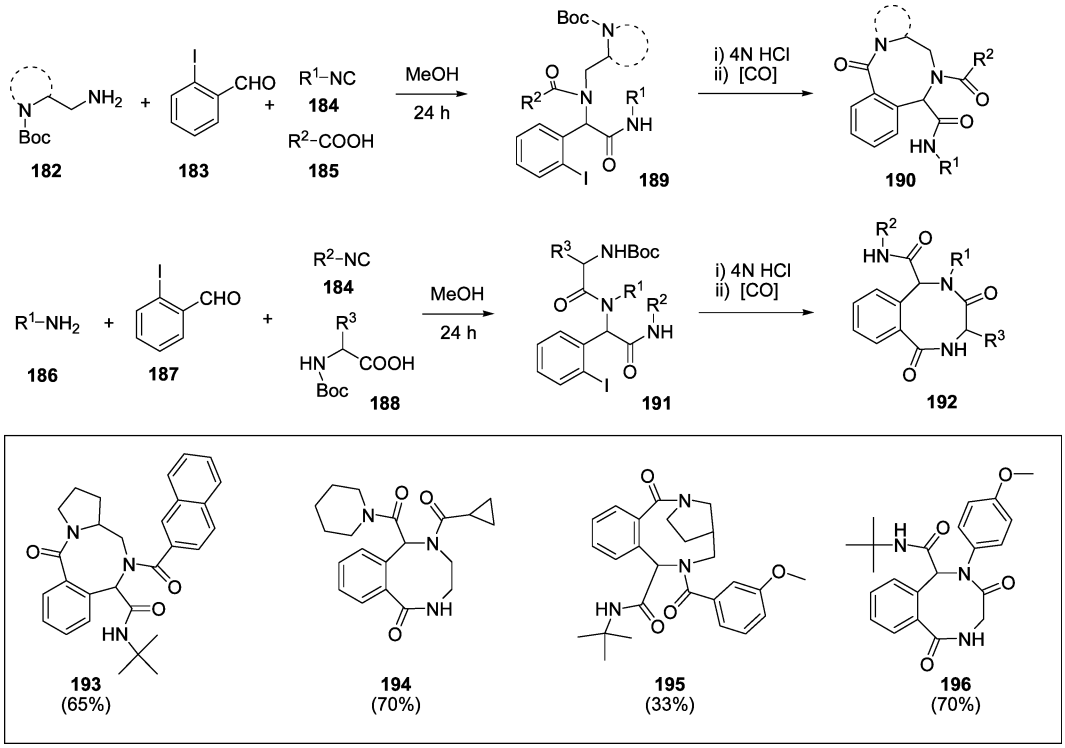


Figure 18. Macrolactams via multicomponent condensation.[322]

benzylamine-derived Ugi products that may decompose during the oxidative aromatization process.

Vasudevan described an approach toward the synthesis of macrolactams **190**/**192** utilizing an Ugi-4CR, followed by a carbonylation/intramolecular amidation (Figure 18).[322] This chemistry involves the use of a monoprotected diamine **182** or a bifunctional acid **188** component. The scope of the reaction was shown to be fairly general on the basis of representative deprotected products **189**/**191** prior to carbonylation/intramolecular amidation (cyclization). A robust synthetic protocol to achieve cyclization was ultimately realized after significant reaction condition optimization. Carbonylation/intramolecular amidation (**189**/**191** → **190**/**192**) was effected by heating the sterically hindered substrates with a mixture of $Mo[CO]_6/Pd(OAc)_2/n\text{-}Bu_3N$ in diglyme at 160 °C for 1 h in a sealed tube. The reaction sequence afforded eight- and nine-membered lactams with multiple sites of diversity, as represented by **193**−**196**. The final products required minimal postsynthetic handling to scavenge the basic side products from the reaction mixture (Bond Elut SCX ion-exchange resin) to yield pure material.

El Kaïm and co-workers reported a highly flexible multicomponent reaction between electron-deficient phenols, amines, carbonyl compounds, and isocyanides to form *N*-aryl amines in phenol-Ugi-Smiles systems (Figure 19).[84] In this modification of the classic Ugi-4CR, these investigators sought a further acidic partner to trigger both imine activation

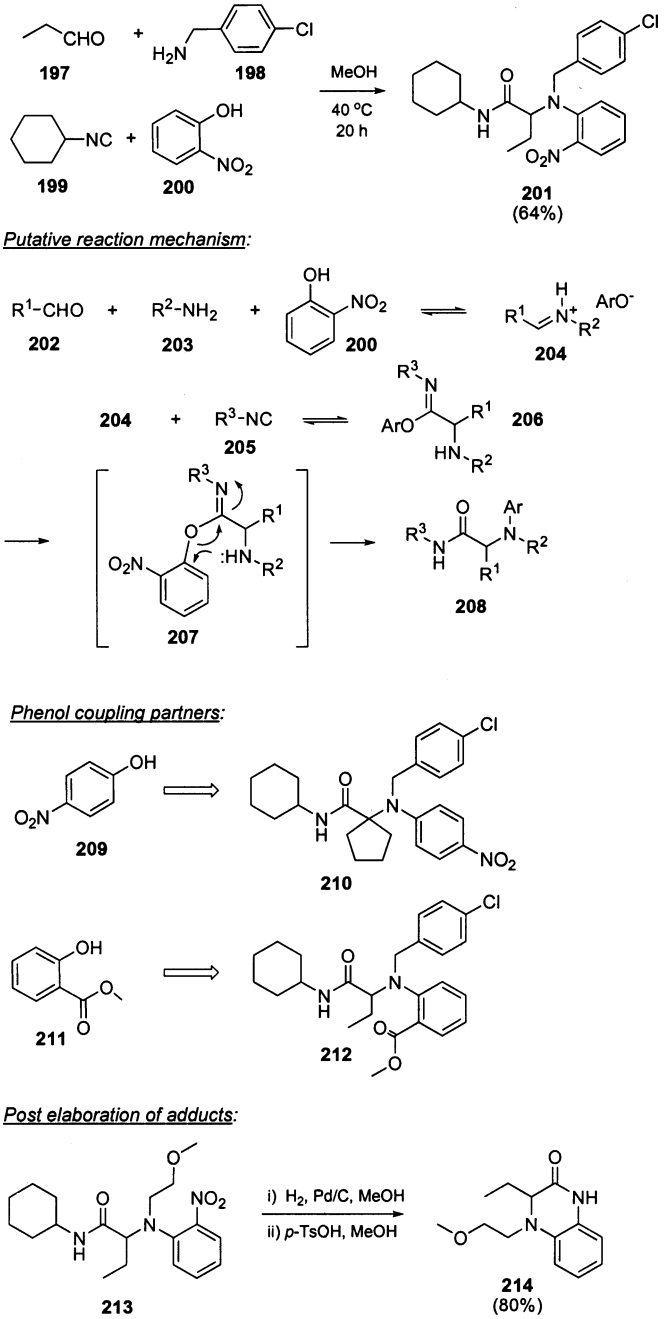


Figure 19. Phenol-Ugi−Smiles condensation.[84]

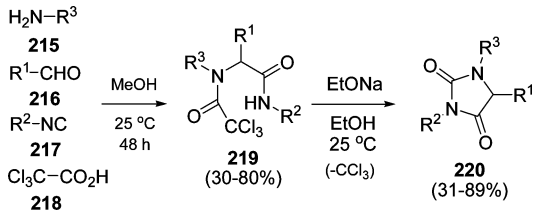


Figure 20. Ugi-4CR as an approach to substituted hydantoins.[146]

and irreversible rearrangement in the key step of the reaction. Thus *o*-nitrophenol **200** meets this requirement and reacts with cyclohexylisocyanide **199**, *p*-chlorobenzylamine **198**, and propionaldehyde **197** at 40 °C in methanol to provide the *N*-aryl amine **201** in 64% yield. The proposed mechanism of this sequence leading to *N*-aryl amines is shown in Figure 19. Presumably, the acidic nitrophenol is able to protonate

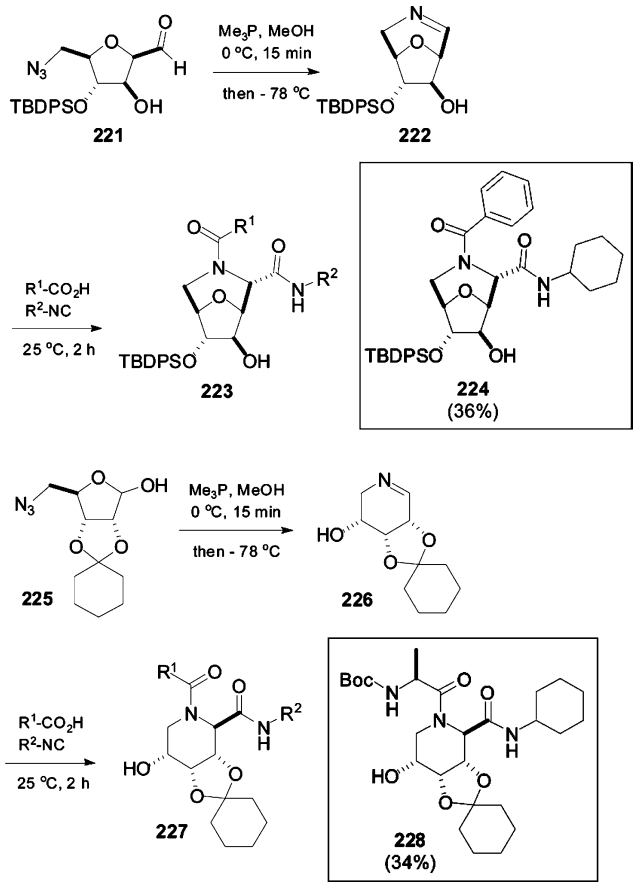


Figure 21. Staudinger/aza-Wittig/Ugi-3CR.[318]

the imine enabling isocyanate addition. The phenoxide is sufficiently nucleophilic to trap the resulting nitrilium intermediate **204** to form imidate **206**. At 40 °C, the latter undergoes a Smiles rearrangement (**206** → **207** → **208**) to provide the more stable *N*-aryl amine **208**, thus providing an irreversible step in the process to drive the equilibria to the desired product in high yield. Aliphatic and aromatic (moderate yields) aldehydes participate in the reaction with various amines and isocyanides. Reaction yields are significantly improved upon the use of a catalytic amount of magnesium perchlorate. Ketones are less reactive than aldehydes and need much longer reaction times to afford the desired products in moderate yields. *p*-Nitrophenol **209**, having an acidity that is comparable to *o*-nitrophenol, undergoes this reaction equally efficiently. Other weak phenolic acids also work in the reaction. For example, methyl salicylate **211** with **197**−**199** in MeOH condensed to provide the *N*-aryl amine **212** at 60 °C (2 days in 74% yield). The presence of the nitro or ester functional group in the final adduct allows further transformation to cyclized products, demonstrated by the conversion of **213** → **214**. This report demonstrates for the first time an example of the Smiles rearrangement intervening in an Ugi-type reaction. These products are of interest in the design of pharmaceutical and agrichemical libraries.

A facile approach to trisubstituted hydantoins was reported by Marcaccini (Figure 20).[146] Primary amines **215**, aldehydes **216**, isocyanides **217**, and trichloroacetic acid **218** were

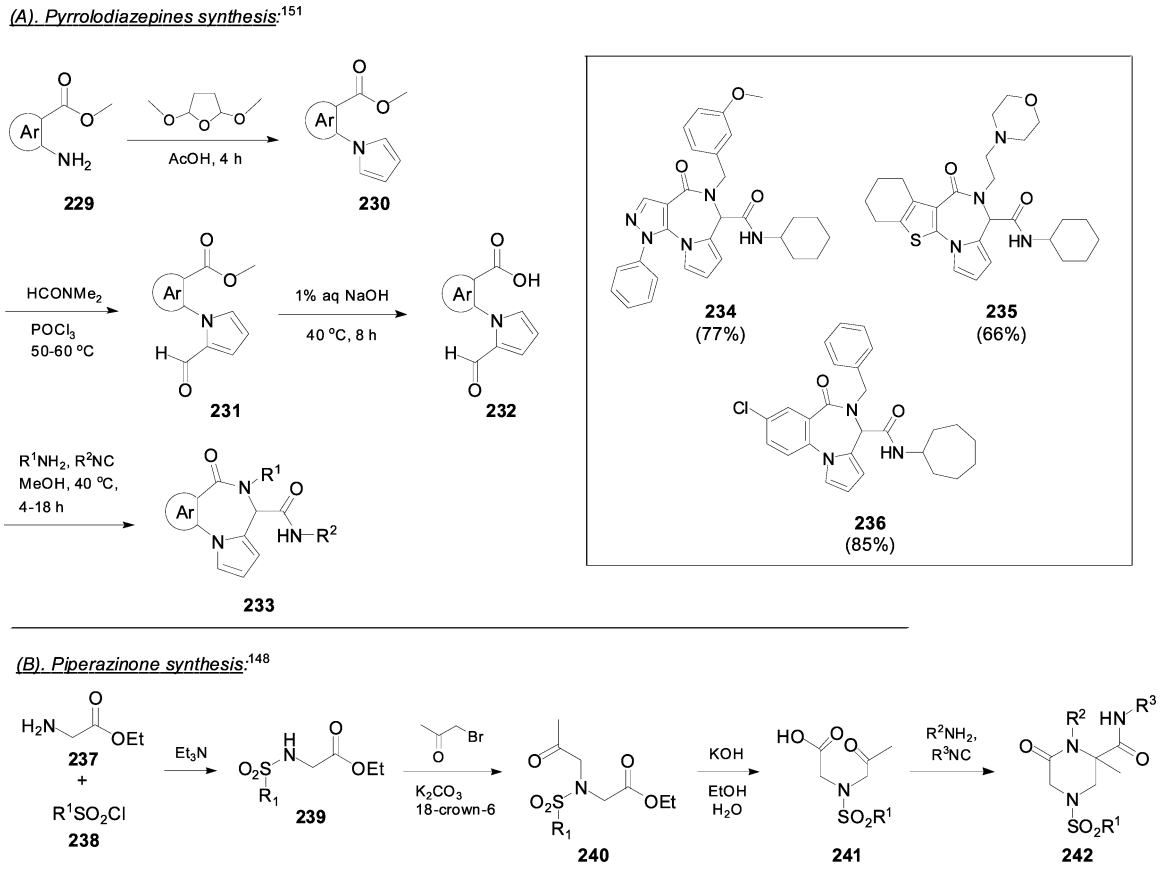


Figure 22. Bifunctional reagents in Ugi-3CR.[148,151]

condensed under conditions in which the Ugi products **219** precipitated from the reaction mixture in pure form. The success of the cyclization of **219** → **220**, was dependent on the rapid addition of sodium ethoxide solution to a suspension of **219** in ethanol. This resulted in the precipitation of hydantoins **220** from the mother liquors in almost pure form. Thus, a facile access to 1,3,5-trisubstituted hydantoins **220** was achieved by combining an Ugi-4CR with a base-induced cyclization. This experimentally simple two-step sequence allows for the creation of a wide variety of substituted hydantoins. Utilization of trichloroacetic acid **218** as the acid component resulted in products with an α-acyl amino group possessing an enhanced electrophilic property to facilitate the ring closure and hydantoin formation.

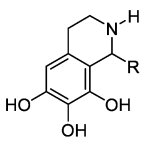
The stepwise combination of the Staudinger/aza-Wittig reactions with an Ugi-3CR was investigated by van Boom and co-workers (Figure 21).[318] Methanolic solutions of azidoaldehydes **221** and **225** were treated with Me_3P for 15 min at 0 °C and then cooled to −78 °C, followed by the addition of a carboxylic acid and an isocyanide. After keeping the reactions at 25 °C for 2 h, the products **223** and **227** were isolated upon standard workup. Employing benzoic acid or *N*-Boc-alanine and cyclohexylisocyanide as Ugi partners, adducts **224** (36%) and **228** (34%), respectively, were obtained as single diastereomers. Two small demonstration libraries were generated, and in each case, complete diastereoselectivity was observed in the isolated products.

Derivatives of pharmaceutically interesting pyrrolo-[1,2-*a*][1,4]benzodiazepines **233**[151] and 4-sulfonyl-2-piperazinones **242**[148] were described by Ivachtchenko and co-workers (Figure 22). In both instances, novel bifunctional oxy-acids, 2-formyl-*H*-pyrroles **232**, and *N*-sulfonyl-*N*-(2-oxopropyl)glycines **241** were generated and used in an Ugi-3CR. Bifunctional reagents **232** were derived from anthranilic esters **229** in a three-step process (Figure 22A). Compounds **232** undergo the desired multicomponent condensation with amines and isocyanides, leading to heterocycles **233**. Satisfactory yields were obtained in an efficient one-pot synthesis, amenable to library assembly. The nature of the heterocyclic core of **232** did not substantially affect the reaction time or yield. Various aliphatic and aromatic primary amines, including anilines and linear branched aliphatic amines, were successfully used without limitation (**234**−**236**). The advantage of this approach for creating diverse compound libraries relies on the ease of construction of the library and the large number of diverse amines. In a similar manner, **241** reacted with primary amines and cycloalkyl isocyanides in methanol to yield the target piperazinones **242**, requiring no purification (Figure 22B).

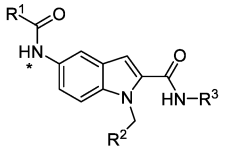
Acknowledgment. R.E.D. is indebted to the continued dedication of K. Rivera, who rendered chemical structure drawing for the tables. Appreciation is also expressed to colleagues B.LeB., G.M., K.M., and J.S., who collectively prepared many of the research summaries highlighted herein and for proofreading the manuscript.

Table 1. Chemical Libraries Targeting Proteases[a]

Metallo-proteases

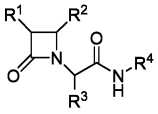


- Library 1.1
- 65 members
- Numa [254]
- Anthrax lethal factor inhibitors

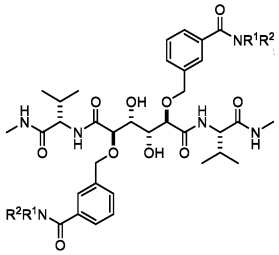


- Library 1.2
- 1332 members
- Brands [34]
- Endothelin-converting enzyme inhibitors

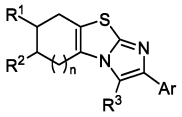
Aspartic acid proteases



- Library 1.3
- 126 members
- Sperka [307]
- HIV-protease inhibitors

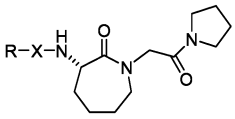


- Library 1.4
- 2x; 7 and 14 members
- Wannberg [339]
- HIV-protease inhibitors

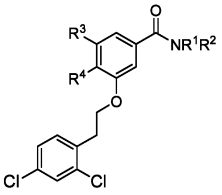


- Library 1.5
- 1043 members
- Pietrancosta [268]
- β-Secretase (BACE-1) inhibitors

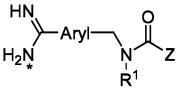
Serine proteases



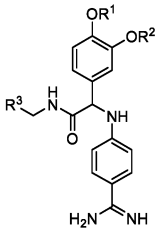
- Library 1.6
- 2x; 79 and 356 members
- Bisacchi [30]
- Factor Xa inhibitors



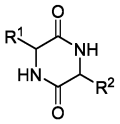
- Library 1.7
- 330 members
- Matter [228]
- Factor Xa inhibitors



- Library 1.8
- >1000 members
- Buckman [39]
- Tissue factor/factor-VIIa (TF/F-VIIa) inhibitors

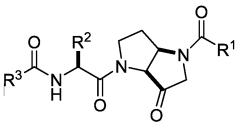


- Library 1.9
- Size not defined
- Zbinden [360]
- TF/F-VIIa inhibitors

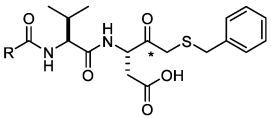


- Library 1.10
- Size not defined
- del Fresno [69]
- Tryptase inhibitors

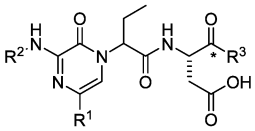
Cysteine proteases



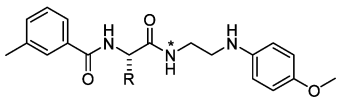
- Library 1.11
- 6 members
- Quibell [276]
- CAC1 inhibitors



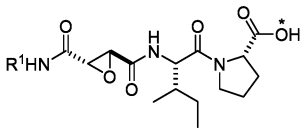
- Library 1.12
- Size not defined
- Mellon [233]
- Caspase-3 inhibitors



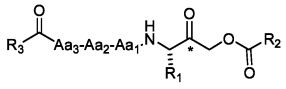
- Library 1.13
- Size not defined
- Han [120]
- Caspase-3 inhibitors



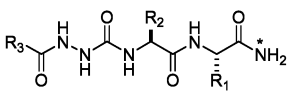
- Library 1.14
- 21 members
- Liu [212]
- Cathepsin S inhibitors



- Library 1.15
- 4 members
- Verhelst [324]
- Cathepsin B inhibitors (cysteine protease probes)



- Library 1.16
- 11 members
- Kato [166]
- Cysteine protease inhibitor probes

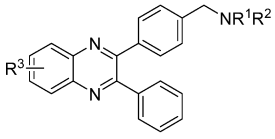


- Library 1.17
- 64,000 members
- Bondebjerg [33]
- Dipeptidyl peptidase I inhibitors

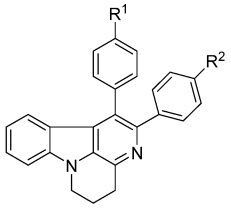
[a] Asterisk is the point of attachment to resin.

Table 2. Chemical Libraries Targeting Nonproteolytic Enzymes[a]

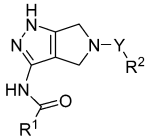
Kinases



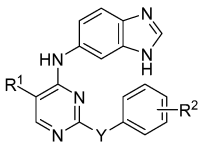
- Library 2.1
- 3x: 200, 24 and 50 members
- Lindsley [210]
- Akt (protein kinase B/PKB) allosteric inhibitors



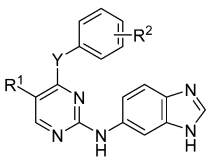
- Library 2.2
- Size not defined
- Lindsley [209]
- Akt kinase inhibitors



- Library 2.3
- ~1000 members
- Fancelli [88]
- Aurora kinase inhibitors

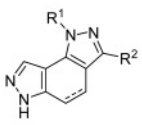


- Library 2.4
- Size not defined
- Verma [325]
- CDK1 inhibitors (library 1)

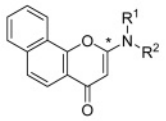


- Library 2.5
- Size not defined
- Verma [325]
- CDK1 inhibitors (library 2)

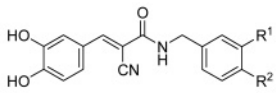
Table 2. (Continued)



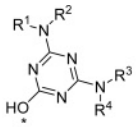
- Library 2.6
- Size not defined
- D'Alessio [63]
- CDK2 inhibitors



- Library 2.7
- ~50 members
- Hardcastle [123]
- DNA-dependent protein kinase inhibitors

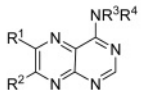


- Library 2.8
- 599 members
- Gu [112]
- JAK2 kinase inhibitor

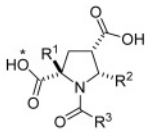


- Library 2.9
- >1000 members
- Baindur [15]
- VEGF-R2 (KDR) tyrosine kinase inhibitors

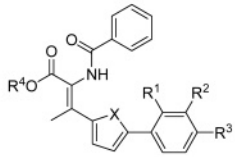
Polymerases



- Library 2.10
- 2x; 8 and 12 members
- Ding [73]
- HCV NS5B RNA-dependent RNA polymerase inhibitors

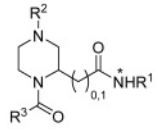


- Library 2.11
- Size not defined
- Burton [41]
- HCV RNA-dependent RNA polymerase inhibitors

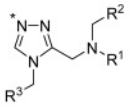


- Library 2.12
- Size not defined
- Pfefferkorn [265]
- HCV NS5B polymerase inhibitors

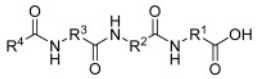
Transferases



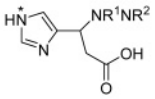
- Library 2.13
- 11,718 members
- Rokosz [281]
- Farnesyltransferase (Ftase) inhibitors



- Library 2.14
- Size not defined
- Saha [289]
- Ftase inhibitors

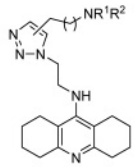


- Library 2.15
- <100 members
- El Oualid [86]
- Geranylgeranyl protein transferase-1 inhibitors

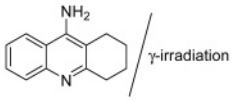


- Library 2.16
- Size not defined
- Saha [288]
- Geranylgeranyl protein transferase-1 inhibitors

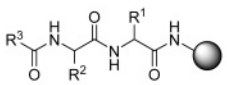
Alphabetical listing



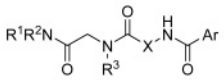
- Library 2.17
- Up to 104 members
- Krasinski [183]
- Acetylcholinesterase inhibitors



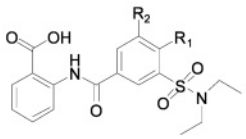
- Library 2.18
- Size not defined
- Kapkova [165]
- Acetylcholinesterase inhibitors



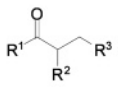
- Library 2.19
- 74,088 members
- Dixon [75]
- Aldose reductase ligands



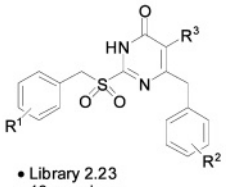
- Library 2.20
- 40,000 members
- Capps [43]
- Aminoimidazole carboxamide ribonucleotide transformylase inhibitors



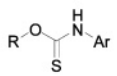
- Library 2.21
- ~20 members
- Nie [250]
- FabH (bacterial β-keto-acyl-ACP synthase) inhibitors



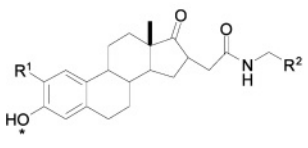
- Library 2.22
- 2464 members
- Brauer [35]
- Glucose-6-phosphate translocase inhibitors



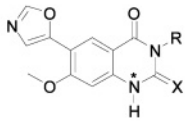
- Library 2.23
- 10 members
- Togninelli [319]
- HIV-1 reverse transcriptase (RT) inhibitors



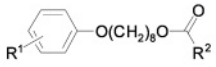
- Library 2.24
- 50 members
- Ranise [278]
- HIV-1 RT inhibitors



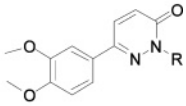
- Library 2.25
- Size not defined
- Lawrence [194]
- 17β-Hydroxysteroid dehydrogenase Type 1 inhibitors



- Library 2.26
- 60 members
- Buckley [38]
- Inosine monophosphate dehydrogenase inhibitors

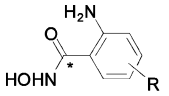


- Library 2.27
- 54 members
- Velu [323]
- Nicotinamide adenine dinucleotide synthase inhibitors

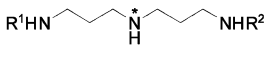


- Library 2.28
- 320 members
- Krier [187]
- Phosphodiesterase 4 inhibitors

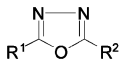
Table 2. (Continued)



- Library 2.29
- Size not defined
- Lee [202]
- Prostaglandin H_2 synthesis peroxidase inhibitors



- Library 2.30
- ~21 members
- Dixon [74]
- Trypanothione reductase inhibitors

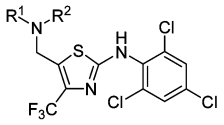


- Library 2.31
- ~52 members
- Khan [175]
- Tyrosinase inhibitors

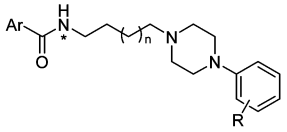
[a] Asterisk is the point of attachment to resin.

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

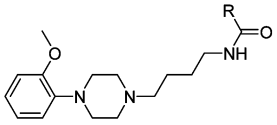
Alphabetical listing



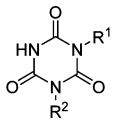
- Library 3.1
- Size not defined
- Zuev [370]
- Corticotropin-releasing factor type-1 antagonists (human)



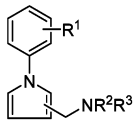
- Library 3.2
- 42 members
- Bettinetti [29]
- Dopamine D3 ligands



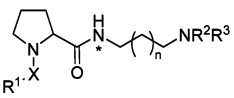
- Library 3.3
- Size not defined
- Heidler [129]
- Dopamine D_3/D_2 ligands



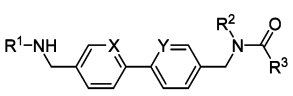
- Library 3.4
- >100 members
- Guo [118]
- Gonadotropin-releasing hormone antagonists



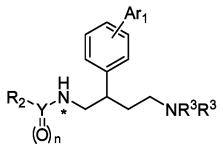
- Library 3.5
- Size not defined
- Paillet-Loilier [257]
- 5-HT_7 ligands



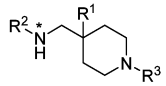
- Library 3.6
- 64 members
- Zajdel [361]
- 5-HT_7 ligands



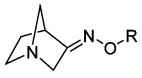
- Library 3.7
- 6625 members
- Corbett [60]
- 5-ht_{5A} antagonists



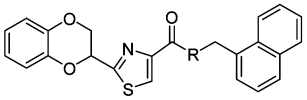
- Library 3.8
- ~500 members
- Guo [116]
- Melanin-concentrating hormone-1 (MCHI) antagonists (human)



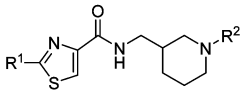
- Library 3.9
- 19,470 members
- Guo [117]
- MCHI (human)



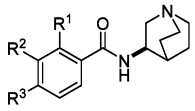
- Library 3.10
- 225 members
- Benting [26]
- Muscarinic acetylcholine (mAChR) agonists



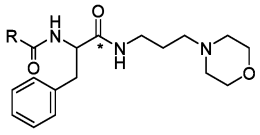
- Library 3.11
- Size not defined
- Sagara [287]
- Muscarinic M3 antagonists



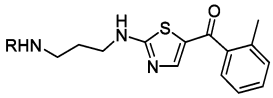
- Library 3.12
- Size not defined
- Sagara [287]
- Muscarinic M3 antagonists



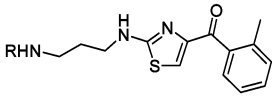
- Library 3.13
- 42 members
- Bodnar [32]
- α7 Nicotinic acetylcholine (nAChR) agonists



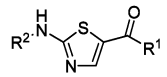
- Library 3.14
- Size not defined
- D'Andrea [66]
- NK_2 antagonists (human)



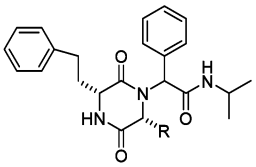
- Library 3.15
- 50 members
- Nettekoven [249]
- NPY5 ligands (mouse; library 1)



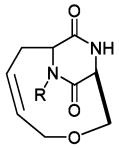
- Library 3.16
- 35 members
- Nettekoven [249]
- NPY5 ligands (mouse; library 2)



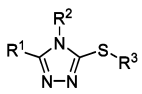
- Library 3.17
- ~140 members
- Guba [113]
- NPY5 antagonists



- Library 3.18
- 48 members
- Wyatt [346]
- Oxytocin antagonists



- Library 3.19
- Size not defined
- Besada [28]
- P2Y agonists

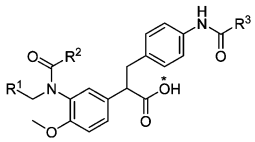


- Library 3.20
- >700 members
- Contour-Galcera [59]
- Somatostatin sst_2/sst_5 agonists

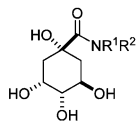
[a] Asterisk is the point of attachment to resin.

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

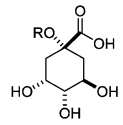
Integrins and selectins



- Library 4.1
- 96 members
- Hoshina [136]
- VLA-4 antagonists

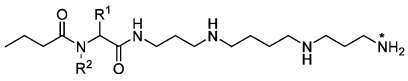


- Library 4.2
- 111 members
- Kaila [162]
- sLex-P-selection blockers

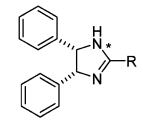


- Library 4.3
- ~400 members
- Kaila [162]
- sLex-P-selection blockers

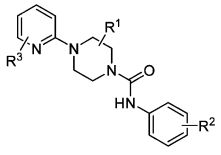
Ion channels



- Library 4.4
- Size not defined
- Jorgensen [161]
- AMPA receptor antagonists

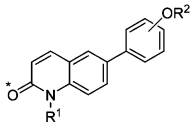


- Library 4.5
- 36 members
- Merriman [237]
- $P2X_7$ receptor antagonists

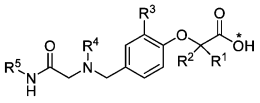


- Library 4.6
- 3 x 48 members
- Swanson [313]
- TRPV1 vanilloid receptor antagonists

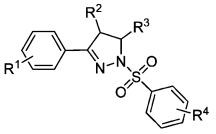
Nuclear hormone receptors



- Library 4.7
- 30 members
- Ruda [285]
- Androgen receptor ligands

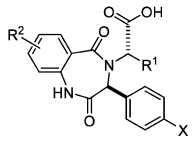


- Library 4.8
- Size not defined
- Weigand [340]
- PPARδ agonists

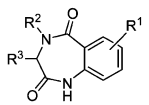


- Library 4.9
- Size not defined
- Jones [160]
- Progesterone receptor (PR) antagonists

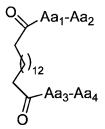
Protein-protein interactions



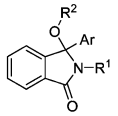
- Library 4.10
- 22,000 members
- Parks [262]
- HDM2-p53 antagonists



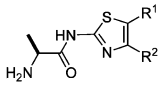
- Library 4.11
- 338,000 members
- Grasberger [110]
- HDM2-p53 antagonists



- Library 4.12
- Size not defined
- Hwang [144]
- HIV-1 protease dimerization inhibitors

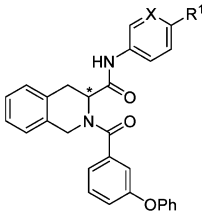


- Library 4.13
- 26 members
- Hardcastle [122]
- MDM2-p53 antagonists

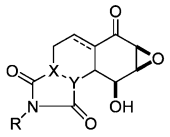


- Library 4.14
- Size not defined
- Park [259]
- X-linked IAP (XIAP) inhibitors (human)

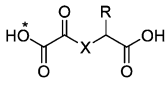
Alphabetical listing



- Library 4.15
- 3x; 550, 240 and 7 members
- Hirth [134]
- CFTR-mediated chloride transport

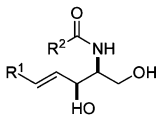


- Library 4.16
- 244 members
- Lei [203]
- Heat shock protein (HSP) induction inhibitor

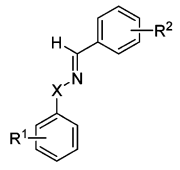


- Library 4.17
- Size not defined
- McDonough [230]
- Hypoxia-inducible factor inhibitors

- Library 4.18
- Size not defined
- Duart [82]
- Inhibition of histamine-induced cutaneous reaction in rats



- Library 4.19
- 80 members
- Park [261]
- Inhibition of IL-4 production in activated T-cells

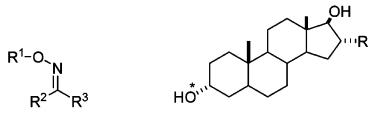


- Library 4.20
- 95 members
- Johnson [159]
- Transthyretin amyloid fibril formation inhibitors

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

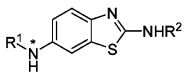
Table 5. Chemical Libraries Yielding Cytotoxic and Antiinfective Agents[a]

Oncolytics

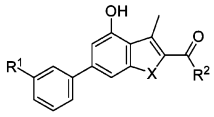


- Library 5.1
- 168 members
- Su [311]
- A549 cell growth inhibitors

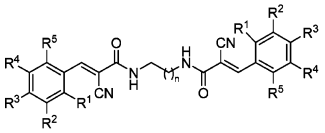
- Library 5.2
- 3 x 122 members
- Maltais [220]
- Antiproliferative and proliferative activities on androgen-sensitive Shionogi cells



- Library 5.3
- ~56 members
- Yoshida [357]
- Antitumor activity against an LLC xenograft model

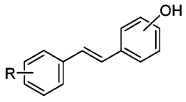


- Library 5.4
- 4 members
- Hayakawa [125]
- Cytotoxic activity; cell line not identified

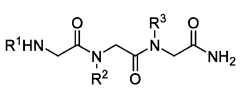


- Library 5.5
- ~60 members
- Hill [132]
- HT29 and G401 cell growth inhibition

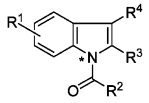
- Library 5.6
- 100 members
- Dothager [80]
- Inducers of apoptotic death in melanoma cell lines



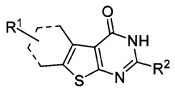
- Library 5.7
- 30 members
- Lion [211]
- MDA MB 468 breast cancer cell line growth inhibitors



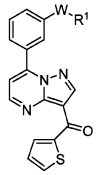
- Library 5.8
- 5120 members
- Masip [226]
- Multidrug resistance reversal agents



- Library 5.9
- 197 members
- Rosenbaum [284]
- MRP-1-mediated multidrug resistance modulators

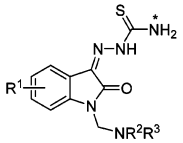


- Library 5.10
- 2x; 47 and 54 members
- Jennings [155]
- p21 chemoselective cytotoxic agents

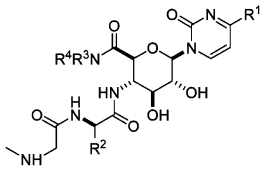


- Library 5.11
- ~30 members
- Gopalsamy [107]
- p21 chemoselective cytotoxic agents

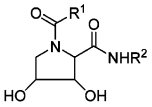
Antiinfectives



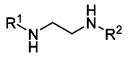
- Library 5.12
- 200 members
- Pirrung [269]
- Anti-poxvirus activity



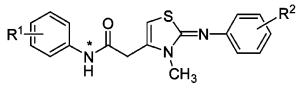
- Library 5.13
- 12 members
- Migawa [240]
- *E. coli* growth inhibitors (gougerotin analogs)



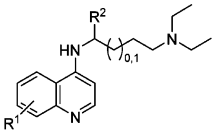
- Library 5.14
- 132 members
- Chapman [50]
- Hepatitus B virus inhibitors



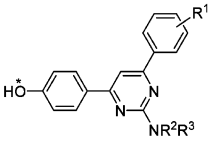
- Library 5.15
- 69 members
- Protopopova [272]
- *M. tuberculosis* growth inhibitors



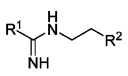
- Library 5.16
- 20 members
- Bae [14]
- *P. grisea* growth inhibitors



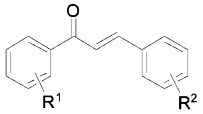
- Library 5.17
- ~34 members
- Madrid [217]
- *P. falciparum* growth inhibitors



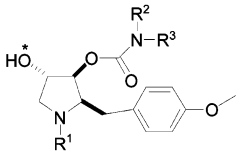
- Library 5.18
- 2x; 20 and 30 members
- Agarwal [3, 4]
- *P. falciparum* (antimalarial) and *M. tuberculosis* (antitubercular) growth inhibitors



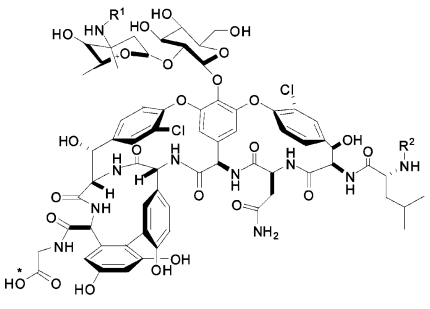
- Library 5.19
- Size not defined
- Meiering [232]
- *T. cruzi* growth inhibitors



- Library 5.20
- 120 members
- Ansari [9]
- *S. aureus* and *B. subtilis* growth inhibitors



- Library 5.21
- 1000 members
- Shi [300]
- *S. aureus* growth inhibitors

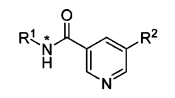


- Library 5.22
- 25 members
- Yao [352]
- Vancomycin-resistant *E. faecalis* growth inhibitors

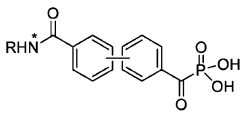
[a] Asterisk is the point of attachment to resin.

Table 6. Scaffold Derivatization[a]

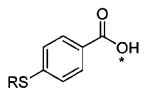
Part A: Solid-phase



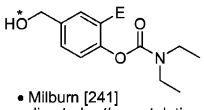
• Fernandez [90]
• Suzuki coupling of resin-bound 5-bromo-nicotinate and $ArB(OH)_2$



• Li [207]
• Suzuki coupling of resin-bound boronic acids and bromobenzoyl phosphonates

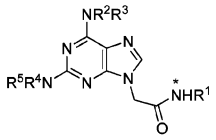


• Gendre [101]
• coupling of resin-bound ArI with thiols with polymer support Ni catalyst

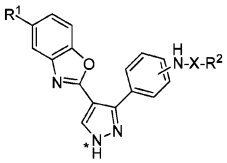


• Milburn [241]
• directed *ortho* metalation of aryl *O*-carbamates on resin using a trityl linker

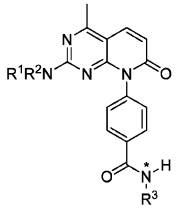
• Vendrell [377]
• acylation of anilines with new coupling reagent, TMUCl Cl



• Austin [11]
• sequential nucleophilic displacement of halogens on resin-bound purine

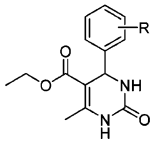


• Berta [27]
• derivatization of resin-bound 2-(3-phenyl-1*H*-pyrazol-4-yl)-1,3-benzoxazole

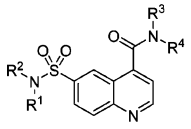


• Angiolini [8]
• oxidation of methylsulfide and amine displacement in resin-bound 4-methyl-2-methylthio-7-oxopyrido-pyrimidinyl benzoic acid

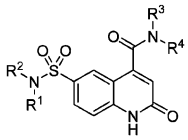
Part B: Solution-phase



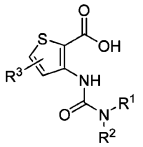
• Wannberg [338]
• assorted microwave-enhanced and metal-catalyzed functionalizations of 4-aryl-dihydropyrimidones



• Ivachtchenko [154]
• amides from corresponding acid

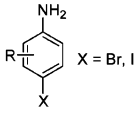


• Ivachtchenko [154]
• amides from corresponding acid



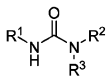
• Le Foulon [197]
• amidation of thiaisatoic anhydrides

• Desai [71]
• formylation of primary and secondary amines using a polymer-supported formate



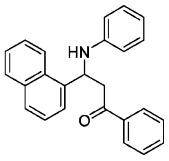
• Chretien [54]
• regioselective halogenation of anilines using resin-bound organotin reagent

• Ho [135]
• hydroxamic acid formation from esters with KCN catalyst

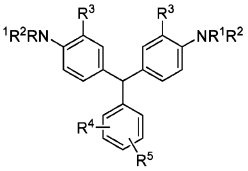


• Gallou [98]
• reaction of amines with isopropenyl carbamates

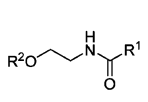
• Sierakowski [303]
• from corresponding chloride and resin-bound fluoride



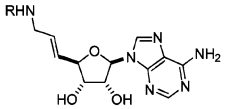
• Lee [199]
• β-aminoketone synthesis using [XP/S-R][X](Yb) resins



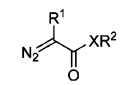
• Guzman-Lucero [119]
• from anilines and ArCHO



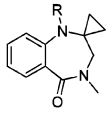
• Zohrabi-Kalantari [368]
• amine acylation via sulfonamide safety-catch linker activated by *O,N,N*-trialkylisoureas



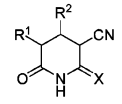
• Heidler [128]
• transfer of activated resin-bound R-groups employing a "red" safety-catch linker



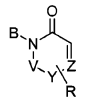
• Schroen [296]
• reaction of esters with resin-bound diazonium salt



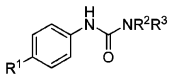
• Lack [193]
• cyclopropanation of benzodiazepinones using optimized Kulinkovich-type reaction protocol



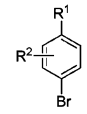
• Martinez-Teipel [225]
• derived from 2-methoxy-6-oxo-tetrahydropyridine-3-carbonitriles



• Coelho [58]
• Pd-catalyzed functionalization of assorted iodoazinones



• Zhang [365]
• fluorous isatoic anhydride (plate-to-plate SPE)

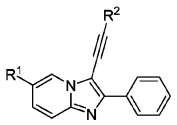


• Kim [176]
• bromination of activated arenes by IBX amide resin and tetraethylammonium bromide

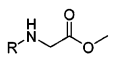
• Nakao [248]
• hydrogenation with nano-Pd catalyst

• Kumar [189]
• oxime cleavage to carbonyl using resin-bound hypervalent organo-iodine

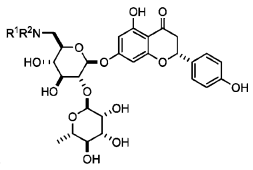
• Harned [124]
• Mitsunobu products obtained via polymer-on-polymer transfer



• El Kazzouli [85]
• functionalization of 3-iodoimidazo[1,2-*a*]-pyridines



• Santagada [376]
• glycine Me ester, RCHO, TEA, MeOH, $NaBH_3CN$, uwave

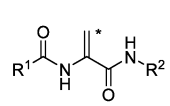


• Hanessian [121]
• standard amine derivatization chemistries

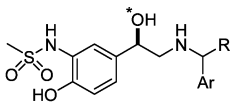
[a] Asterisk is the point of attachment to resin.

Table 7. Acyclic Synthesis[a]

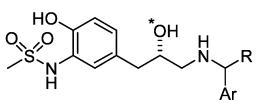
Part A: Solid-phase



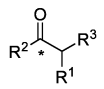
• Ayida [12]
• from selenium linked amino acid resin



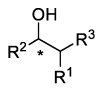
• Wu [345]
• addition of organo metallics to resin-bound imines



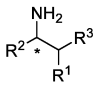
• Wu [345]
• addition of organometallics to resin-bound imines



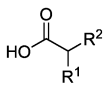
• Lazny [195]
• derived from resin-bound hydrazones



• Lazny [195]
• derived from resin-bound hydrazones

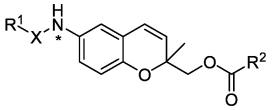


• Lazny [195]
• derived from resin-bound hydrazones

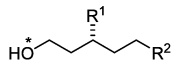


• Lazny [195]
• derived from resin-bound hydrazones

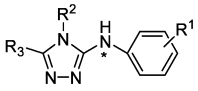
• Lazny [195]
• derived from resin-bound hydrazones



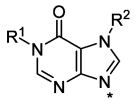
• Hwang [143]
• multistep sequence from a resin-bound 6-amino benzopyran



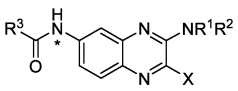
• Spino [308]
• multistep sequence using resin-bound chiral cyclohexanone



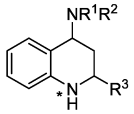
• Zong [369]
• reaction of PEG-bound anilines with RNCS, arylacyl hydrazides then cleavage



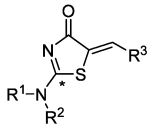
• Fu [95]
• coupling 6-chloropurine to the REM resin oxidation, *N*-alkylation, quaterization and product release



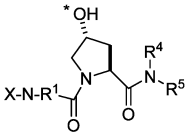
• Jeon [156]
• from resin-bound 6-amino-2,3-dichloro quinoxaline;
X = OMe, NRR



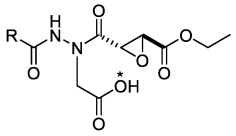
• Bazin [21]
• reaction of resin-bound 4-Cl-quinolinium salt with amine, Grignard addition, borohydride reduction, cleavage



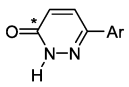
• Pulici [273]
• Knovenagel condensation of RCHO with resin-bound rhodanine then traceless cleavage with amines



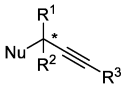
• Simon [304]
• from resin-bound *N*-Fmoc hydroxyproline allyl ester



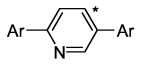
• Kato [167]
• multistep sequence from resin-bound bromo acetate and Fmoc-hydrazine



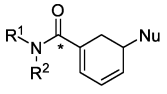
• Salives [290]
• Suzuki coupling of Wang resin-bound chloropyridazine



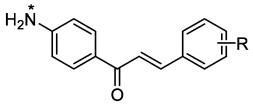
• Gachkova [96]
• Nicholas reaction of resin-bound propargyl ethers



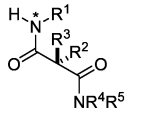
• Pierrat [267]
• from resin-bound 2-chloro-5-bromopyridine on silicon linker



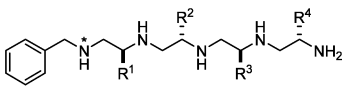
• Graden [109]
• treatment of resin-bound cationic iron cyclohexadienyl complex with carbon, oxygen, nitrogen, and phosphorus nucleophiles, followed by cleavage with amines and decomplexation



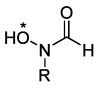
• Yi [355]
• Claisen-Schmidt condensation reaction between resin-bound *p*-aminoacetophenone and aromatic aldehydes



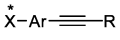
• Voegtle [327]
• coupling of diacid chloride to amine-containing resin then second amide-bond formation



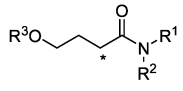
• Houghten [138]
• prepared via peptide synthesis then borane reduction on a "volatilizable" support



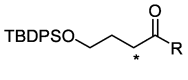
• Price [271]
• alkylation of *N*-formyl Wang-*O*-hydroxylamine resin



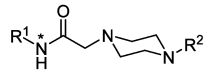
• Tulla-Puche [320]
• Sonogashira coupling by resin-to-resin transfer



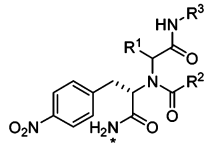
• McKerlie [231]
• ring-opening of resin-bound 2-phenoxy-α-butyro lactone, *O*-derivatization then SmI_2-mediated cleavage



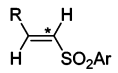
• McKerlie [231]
• ring-opening of resin-bound 2-phenoxy-α-butyro lactone, *O*-derivatization then SmI_2-mediated cleavage



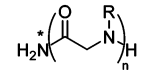
• Minkwitz [242]
• from resin-bound chloroacetamide and piperazine



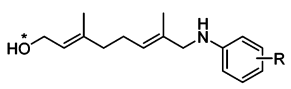
• Lin [208]
• 4-CC on planar cellulose support and photochemical cleavage



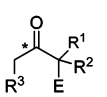
• Sheng [299]
• derived from resin-bound selenomethyl aryl sulfones



• Gorske [108]
• from resin-bound bromo acetamide and amines in microwave



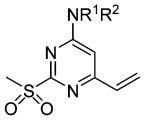
• Subramamian [312]
• from resin-bound geranyl aldehyde and anilines



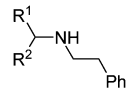
• Margathe [374]
• ring opening of resin-bound methyleneaziridines with Grignard reagents, alkylation then hydrolysis

Table 7. (Continued)

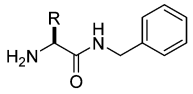
Part B: Solution-phase



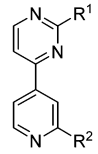
• Radi [277]
• from 2-methylthio-6-(2-hydroxyethyl)-pyrimidinone



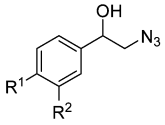
• Guisado [114]
• Fukuyama-Mitsunobu procedure



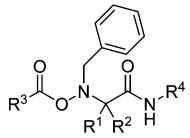
• Basso [18]
• Ugi condensation using a chiral auxiliary



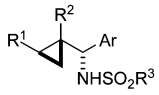
• Stanetty [309]
• Negishi-type cross coupling then subsequent nucleophilic substitutions



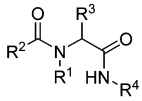
• Brenelli [36]
• displacement of halomethyl ketones with azides resin then borohydride reduction



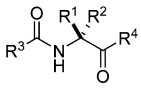
• Basso [17]
• 4-CC via nitrones as imine surrogates



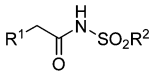
• Wipf [344]
• one library of a "libraries of libraries" derived from a cascade reaction of alkynes, Cp_2Zr and phosphinoyl imines



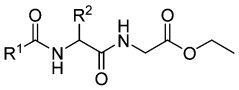
• Portal [270]
• 3-CC using an analytical construct



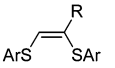
• Garcia [100]
• evaluation of multiple approaches to synthesis of α,α-disubstituted-α-acylamino ketones



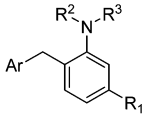
• Cho [53]
• copper-catalyzed hydrative amide synthesis with terminal alkyne, sulfonyl azide, and water



• Pick [266]
• 4-CC with ammonia as coupling partner

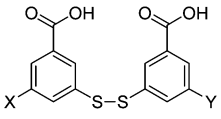


• Ananikov [7]
• Pd-catalized S-S bond addition to terminal alkynes

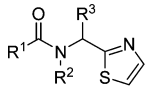


• Rosamillia [283]
• 3-CC between ArCHO, enone and amine

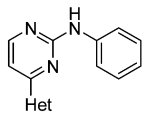
• Theodorou [317]
• alkylation of lithiated tritylamine then TFA cleavage



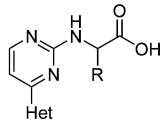
• Leclaire [198]
• dynamic combinatorial library based on exchange of disulfide and thioester linkages



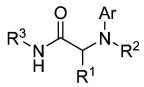
• Kazmaier [171]
• 3-CC then acid-catalyzed cyclization



• Bursavich [40]
• from 2-chloro-4-heteroaryl pyrimidine



• Bursavich [40]
• from 2-chloro-4-heteroaryl pyrimidine

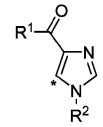


• El Kaim [84]
• phenol Ugi-Smiles reaction

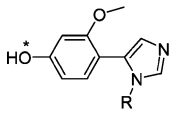
[a] Asterisk is the point of attachment to resin.

Table 8. Monocyclic Synthesis[a]

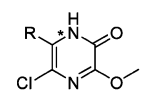
Part A: Solid-phase



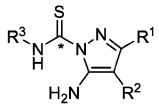
• De Luca [68]
• resin-bound 3-*N*-methylen-*N*-methylamino isocyano-acrylate and primary amines



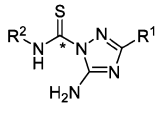
• Samanta [291]
• resin-bound imines and $4\text{-}CH_3C_6H_4SO_2CH_2NC$



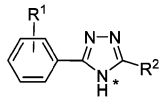
• Kaval [168]
• cyclization of resin-bound α-aminonitriles with oxalyl chloride, treatment with MeOH then cleavage



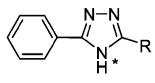
• Hwang [140]
• cyclization of resin-bound dithiocarbazole with electrophiles



• Hwang [140]
• cyclization of resin-bound dithiocarbazole with electrophiles

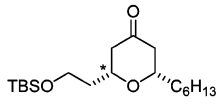


• Samanta [292]
• cycloaddition between DEAD or 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione and resin-bound munchnones

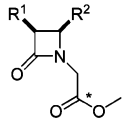


• Wang [330]
• dipolar cycloadditions between DEAD and resin-bound munchnones

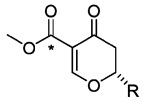
• Molteni [243]
• 1,3-dipolar cycloadditions of MeOPEG-bound azides



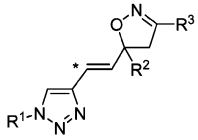
• Liu [213]
• multistep sequence and oxidative cyclo release



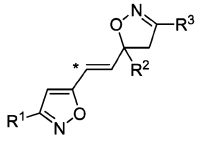
• Delpiccolo [70]
• Staudinger reaction of resin-bound glycine imines



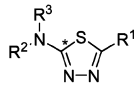
• Wang [329]
• hetero-Diels Alder reaction of aldehydes with (PEG)-bound Danishefsky's diene derived from PEG-bound acetoacetate then cleavage



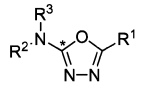
• Xu [349]
• alpha-alkylation of resin-bound selenenylmethyl triazoles with allyl bromides, 1,3-dipolar cycloaddition, elimination



• Xu [349]
• alpha alkylation of resin-bound selenenylmethyl isoxazoles,with allyl bromides 1,3-dipolar cycloaddition elimination

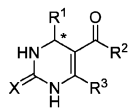


• Hwang [142]
• cyclization of resin-bound acyldithio-carbazates

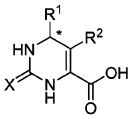


• Hwang [142]
• cyclization of resin-bound acyldithio-carbazates

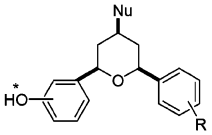
Table 8. (Continued)



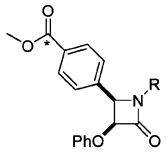
• Li [206]
• condensation of urea or thiourea, RCHO and resin-bound benzenesulfinate then cyclodehydration with β-diketones



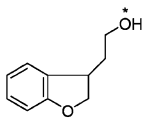
• Li [206]
• condensation of urea or thiourea, RCHO and resin-bound benzenesulfonate then cyclodehydration with α-keto acids



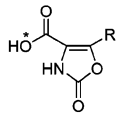
• Kumar [190]
• Barbier allylation-Prins reaction of PEG-bound aldehydes



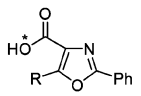
• Shou [302]
• Staudinger reaction via PEG-bound imines



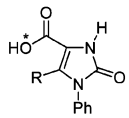
• Chevet [52]
• radical cyclization using hypophosphite salts



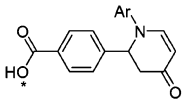
• Yamashita [350]
• ring formation by N-H insertion reaction of resin-bound α-diazo-β-ketoesters



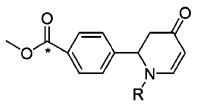
• Yamashita [350]
• ring formation by N-H insertion reaction of resin-bound α-diazo-β-ketoesters



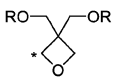
• Yamashita [350]
• ring formation by N-H insertion reaction of resin-bound α-diazo-β-ketoesters



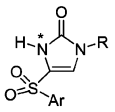
• Guo [115]
• aza-Diels-Alder reaction of Danishefsky's diene and PEG-bound imines



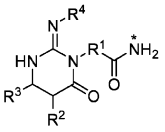
• Shou [302]
• aza-Diels-Alder reaction of Danishefsky's diene and PEG-bound imines



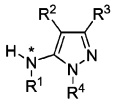
• Behrendt [23]
• diol attached to PS-SO_2Cl then intracyclative cleavage



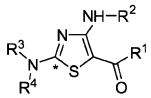
• Patek [263]
• 3-step sequence from resin-bound ureas, glyoxal and sulfinic acids



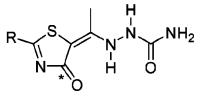
• Wang [333]
• intramolecular cyclization of resin-bound dipeptide thioureas with an aryl isothiocyanate promoted with DIC under microwave



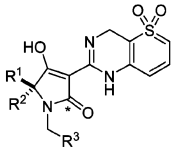
• Dodd [77]
• condensation of resin-bound β-ketoamides with hydrazines, cyclization, cleavage



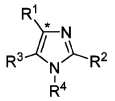
• Lee [201]
• traceless multistep synthesis



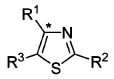
• Attanasi [10]
• thioamides and resin-bound 1,2-diaza-1,3-butadiene



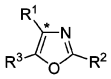
• Fitch [92]
• from α-amino acids or esters, reductive amination then one-pot amide bond formation/Dieckmann cyclization



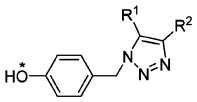
• Li [205]
• multistep sequence using resin-bound sodium benzenesulfinate as traceless linker



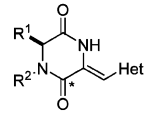
• Li [205]
• multistep sequence using resin-bound sodium benzenesulfinate as traceless linker



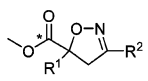
• Li [205]
• multistep sequence using resin-bound sodium benzenesulfinate as traceless linker



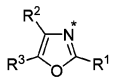
• Attanasi [10]
• thioamides and resin-bound 1,2-diaza-1,3-butadiene



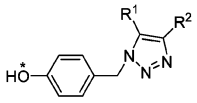
• Couladouros [61]
• multistep sequence using resin-bound phosphinyl glycine (Schmidt's phosphonate)



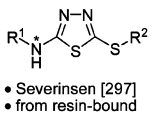
• Tao [315]
• 3-CC of PEG-supported acrylates, RCHO and NH_2OH



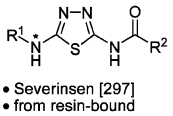
• Pulici [274]
• traceless solid phase synthesis via Robinson-Gabriel reaction of solid supported α-acylamino ketones



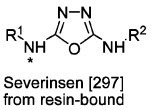
• Wang [331]
• cyclo addition of resin-bound aryl azide and alkyne



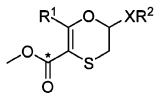
• Severinsen [297]
• from resin-bound thiosemicarbazide



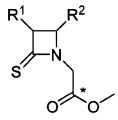
• Severinsen [297]
• from resin-bound thiosemicarbazide



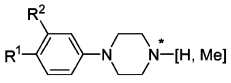
• Severinsen [297]
• from resin-bound thiosemicarbazide



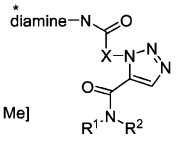
• Menichetti [235]
• hetero Diels-Alder reactions of resin-bound α,α-dioxothiones



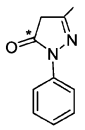
• Mendez [234]
• Staudinger reaction using resin-bound imines then Lawesson's reagent



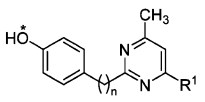
• Rudbeck [286]
• from resin-bound carbamate-linked bis(chloroethyl)amine and anilines then LAH-cleavage



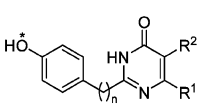
• Coats [57]
• immobilization of azide on REM resin, regioselective 1,3-dipolar cycloation with TMS acetylenes then aq. HF



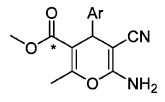
• Shimomura [301]
• from resin-bound acetate, β-keto ester formation at -78°C, $PhNHNH_2$ then interacyclative cleavage



• Cesar [48]
• condensation of resin-bound 4-hydroxy-benzamidines and 2-(4-hydroxyphenyl)-acetamidines with 1,3-dielectrophiles



• Cesar [48]
• condensation of resin-bound 4-hydroxy-benzamidines and 2-(4-hydroxyphenyl)-acetamidines with 1,3-dielectrophiles

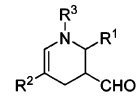


• Yi [354]
• condensation of ionic liquid bound acetoacetate with arylidenemalononitriles then cleavage

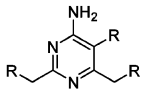
• Dolle [78]
• annulation reagents yielding heterocyclic lactams from primary amines

Table 8. (Continued)

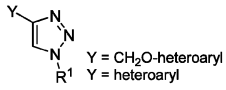
Part B: Solution-phase



• Carranco [44]
• derived from a multicomponent reaction

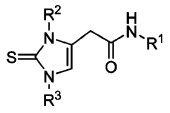


• Baxendale [19]
• trimerization of nitriles with KO*t*Bu and microwave

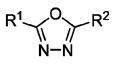


• Kaval [169]
• 1,3-dipolar cycloaddition reaction

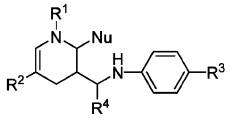
• Teduka [316]
• 3-hydroxyethyl ethers and resin-bound hypervalent iodine reagent



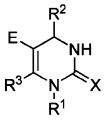
• Bae [13]
• condensation of amines with α–chloroacetoacetanilide, reaction with R^3NCS



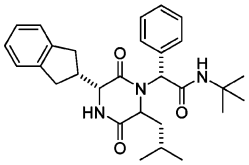
• Wang [336]
• from carboxylic acids and hydrazides with PS-PPh_3/CCl_3CN



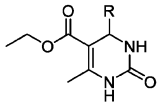
• Carranco [44]
• derived from a multicomponent reaction



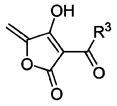
• Dallinger [65]
• Biginelli synthesis and derivatization



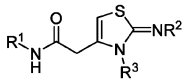
• Sollis [305]
• Ugi condensation



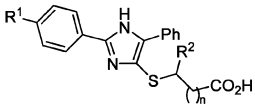
• Wang [337]
• resin-bound ionic-liquid-catalyzed Biginelli reaction



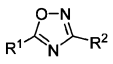
• Schobert [295]
• ring closing tandem addition-Wittig alkenation reaction of the respective protected or immobilized glycerates then PCCO and acylation



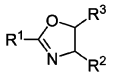
• Bae [13]
• condensation of amines with α-chloroacetoacetanilide reaction with R^3NCS



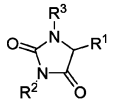
• Le Bas [196]
• 3-CC of ArCHO, oxythio acetamide and bromoalkyl acid



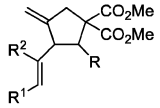
• Wang [335]
• condensation of carboxylic acids and amidoximes



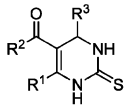
• Crosignani [62]
• coupling of carboxylic acids with amino alcohols then cyclodehydration



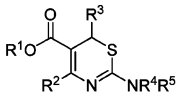
• Ignacio [146]
• 4-CC then base-induced condensation



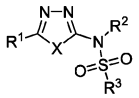
• Nakai [245]
• cycloisomerization reaction using PEG-supported Pd(dba)(triarylphosphine)2



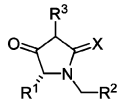
• Jiang [158]
• 3-CC of β-keto esters, RCHO, thioureas using Yb-resin catalyst



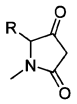
• Strohmeier [310]
• condensation of enones and thioureas



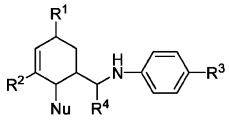
• Baxendale [20]
• 3-CC of acylhydrazine, isocyanate, and RSO_2Cl



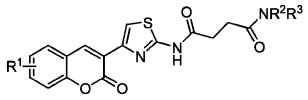
• Lu [216]
• classical hydantoin synthesis using fluorous tagging



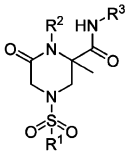
• Schobert [294]
• *N*-methyl amino acid t-butyl esters and resin-bound (triphenylphosphoranylidene) ketene then acid-catalyzed enol ether cleavage



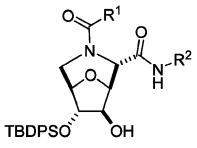
• Carranco [44]
• derived from a multicomponent reaction



• Zhuravel [367]
• reaction of 3-(ω-bromacetyl)coumarins with 3-amino(thioxo)methylcarbamoyl-propanoic acid and derivatization



• Ilyin [148]
• 3-CC of keto acid, amine and isocyanate

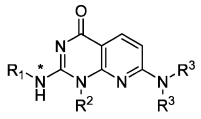


• Timmer [318]
• Staudinger/aza-Wittig, Ugi

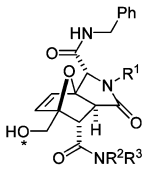
[a] Asterisk is the point of attachment to resin.

Table 9. Bicyclic and Spirocyclic Synthesis[a]

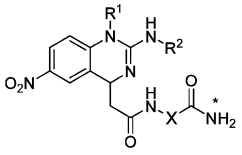
Part A: Solid-phase



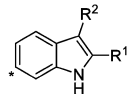
• Schell [293]
• from resin-bound *N*-2,6-dichloronicotinoyl-1*H*-benzotriazole-1-carboximidamides



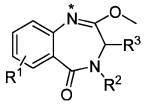
• Oikawa [256]
• tandem Ugi/Diels-Alder reaction



• Wang [334]
• multistep sequence from resin-bound 3-amino-3-(2-fluoro-5-nitrophenyl) propionic acid

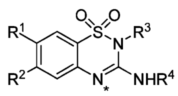


• Mun [244]
• Fisher indole synthesis using "traceless" silicon linked hydrazines

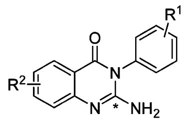


• Gil [104]
• multistep sequence employing T1 triazene linker

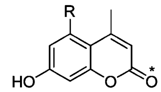
Table 9. (Continued)



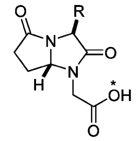
• Blackburn [31]
• reaction of *o*-azidobenzene sulfamides with resin-bound TPP then RNC



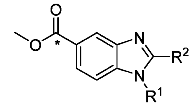
• Kundu [191]
• traceless synthesis via resin-bound thioureas



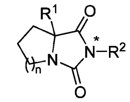
• Hirai [133]
• from resin-bound acetoacetate and phenols



• Nielsen [251]
• cyclization of amide nitrogen moieties with cyclic *N*-acyliminium intermediates

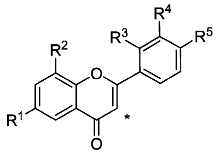


• Chang [49]
• from PEG-bound 3-nitro-4-fluorobenzoic acid

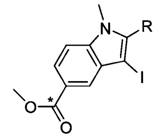


• Alsina [5]
• multistep sequence from resin-bound amino acid ester

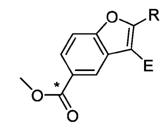
• Zhu [366]
• multistep sequence from hydroxyproline immobilized onto REM resin



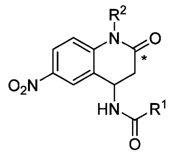
• Huang [145]
• cyclative loading of hydroxy chalcones onto selenium bromide resin then oxidative elimination



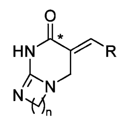
• Yao [353]
• iodocyclization of resin-bound alkynyl anilines



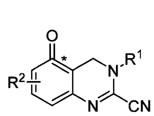
• Yao [353]
• electrophile-mediated cyclization of resin-bound alkynyl anisoles



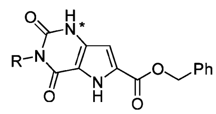
• Wang [332]
• multistep sequence from resin-bound N-alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid



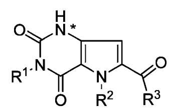
• Pathak [264]
• multistep sequence from resin-bound Baylis-Hillman derivatives



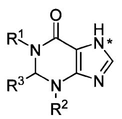
• Jeon [157]
• multistep sequence from resin-bound 2-nitrobenzoic acid



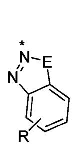
• Rombouts [282]
• multistep sequence from aminopyrroles bound to resin by a cysteamine linker



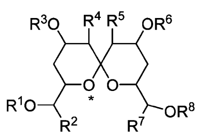
• Fridkin [94]
• multistep sequence from cysteamine linker-bound amino pyrroles



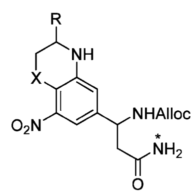
• He [127]
• cyclocondensation of resin-bound amino-imidazole with isocyanates then alkylation



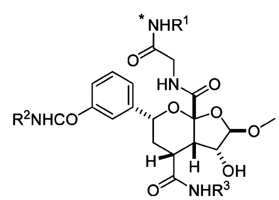
• Kreis [186]
• from resin-bound *ortho* bromo or iodo triazenes and functionalization cleavage



• Barun [16]
• multistep sequence via resin-bound aldehyde

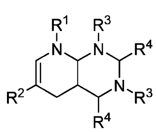


• Dixon [76]
• intramolecular capture of benzyne intermediate as derived from resin-bound *N*-alloc-3-amino-3-(2,4-difluoro-5-nitro phenyl)propionate

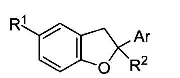


• Messer [238]
• multistep sequence from a ribose derivative

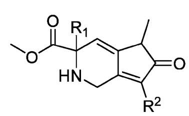
Part B: Solution-phase



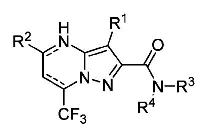
• Carranco [44]
• derived from a multicomponent reaction



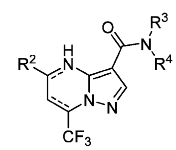
• Kuethe [188]
• one-pot synthesis from *o*-nitrotoluenes and aromatic aldehydes



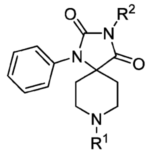
• Manku [221]
• fluorous mixture synthesis via Rh-catalyzed [2+2+1] cycloaddition of alkynyl allenes



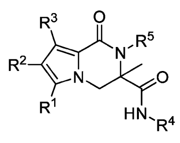
• Dalinger [64]
• condensation of amino pyrazole carboxylic acids with β-diketones, acid chloride formation, then amide generation



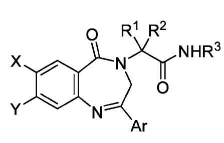
• Dalinger [64]
• condensation of amino pyrazole carboxylic acids with β-diketones, acid chloride formation, then amide generation



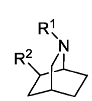
• Nieto [253]
• two-step synthesis from *N*-substituted piperidinones



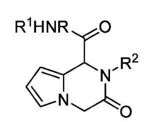
• Ilyn [149]
• 3-CC Ugi condensation



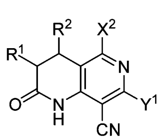
• Marcaccini [223]
• 4-CC Ugi condensation



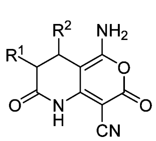
• Levi [204]
• multistep sequence to ibogaine analogs



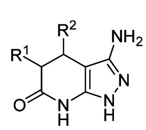
• Ilyn [150]
• Ugi condensation using (2-formylpyrrol-1-yl)acetic acid as a bifunctional coupling component



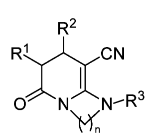
• Martinez-Teipel [225]
• derived from 2-methoxy-6-oxo-tetrahydro-pyridine-3-carbonitriles



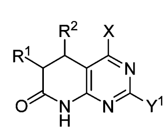
• Martinez-Teipel [225]
• derived from 2-methoxy-6-oxo-tetrahydro-pyridine-3-carbonitriles



• Martinez-Teipel [225]
• derived from 2-methoxy-6-oxo-tetrahydro-pyridine-3-carbonitriles

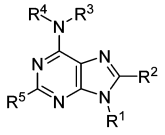


• Martinez-Teipel [225]
• derived from 2-methoxy-6-oxo-tetrahydro-pyridine-3-carbonitriles

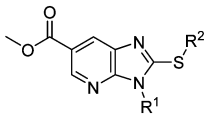


• Martinez-Teipel [225]
• derived from 2-methoxy-6-oxo-tetrahydro-pyridine-3-carbonitriles

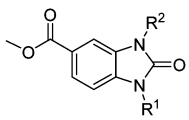
Table 9. (Continued)



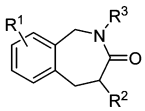
• Yang [351]
• sequential cyclization of 4,5-diaminopyrimidines with either RCOOH or its derivative then Cl displacement with amines



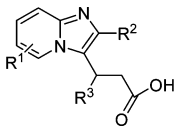
• Vickerstaffe [326]
• classical synthesis from methyl 4-F-3-NO_2 benzoate



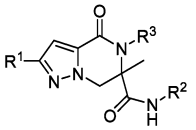
• Vickerstaffe [326]
• classical synthesis from methyl 4-F-3-NO_2 benzoate



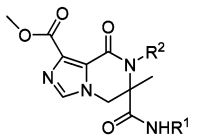
• Carreras [45]
• multistep sequence derived from salicyclic aldehydes, α-bromo acetates and primary amines



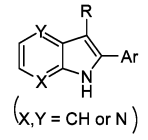
• Gerencser [102]
• 3-component Michael-type reaction of 2-amino-pyridines, 2-bromo-acetophenones and Meldrum's acid



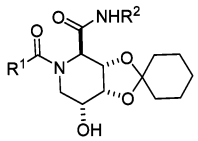
• Ilyn [152]
• 3-CC with pyrrole carboxylates, R^2NC and R^3NH_2



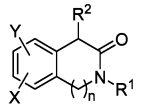
• Ilyn [147]
• 4-CC reaction



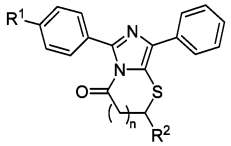
• Cacchi [42]
• aminopalladation-reductive elimination of 2-alkynyl-3-trifluoroacetamido aryls



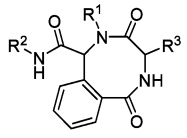
• Timmer [318]
• tandem Staudinger/aza-Wittig/Ugi multicomponent reaction



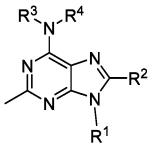
• McAllister [229]
• novel fluorous-phase Pummerer cyclative-capture strategy (R^F = fluorous alkyl)



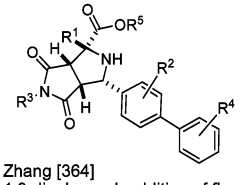
• Le Bas [196]
• 4-CC route to sulfanylimidezoles then intramolecular acylation of imidazole nitrogen



• Vasudevan [322]
• 4-CC the acid-induced intramolecular amidation



• Liu [214]
• multistep sequence from 6-benzothio substituted pyrimidine-4,5-diamines

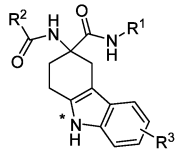


• Zhang [364]
• 1,3-dipolar cycloaddition of fluorous protected hydroxybenzaldehydes then Pd-catalyzed Suzuki coupling reaction with boronic acids

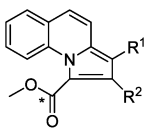
[a] Asterisk is the point of attachment to resin.

Table 10. Polycyclic and Macrocyclic Synthesis[a]

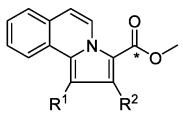
Part A: Solid-phase



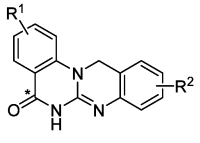
• Koppitz [181]
• Fisher indole cyclization of resin-bound ketal with aryl hydrazines



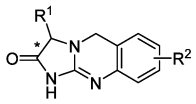
• Yue [359]
• PEG-supported isoquinolinium salt and alkynes



• Yue [359]
• PEG-supported isoquinolinium salt, active alkenes and TPCD as oxidant



• Grover [111]
• base catalyzed intramolecular trans-amidation of resin-bound 2-aminoquinazoline derivatives



• Grover [111]
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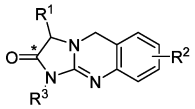
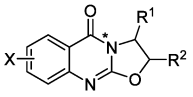
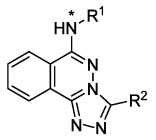


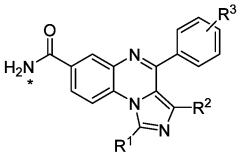
• Kesarwani [173]
• derived from amino acids, 2-nitrobenz-aldehydes and isothiocyanates



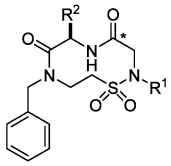
• Jeon [157]
• multistep sequence from resin-bound 2-nitrobenzoic acid



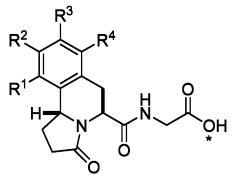
• Hwang [141]
• from resin-bound chlorophthalazines and acylhydrazines



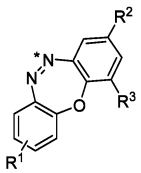
• Kundu [192]
• modified solid-phase Pictet-Spengler reaction of an aromatic amines linked to *N*-1 of imidazole and an aldehyde



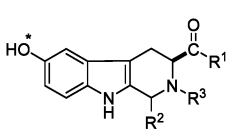
• Wels [342]
• multistep synthesis from resin-bound N-alkylglycines Fmoc $N(Bn)CH_2CH_2SO_2Cl$



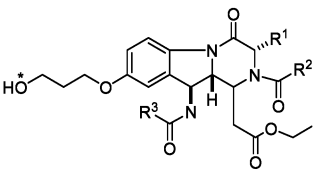
• Nielsen [252]
• intramolecular *N*-acyliminium Pictet-Spengler reaction of phenylalanine derivatives



• Knepper [179]
• Nicolaou-Ullmann reaction of resin-bound T1-linker aryl bromides and phenols then intramolecular aza coupling

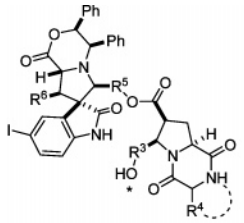


• Danieli [67]
• Pictet-Spengler condensation of RCHO and resin-bound 5-hydroxytryptophan

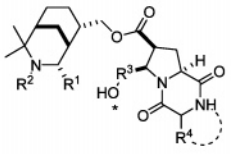


• Gan [99]
• multistep sequence derived from an enantioenriched aminoindoline scaffold

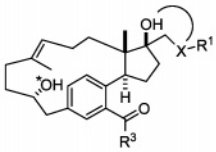
Table 10. (Continued)



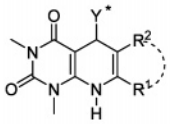
• Chen [51]
• convergent diversity-oriented synthesis



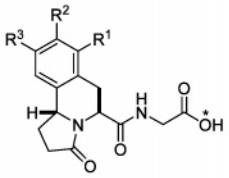
• Chen [51]
• diversity-oriented synthesis



• Kumar [372]
• diversity-oriented synthesis derived from dehydroisoandrosterone

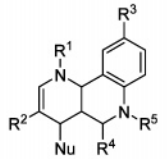


• Agarwal [2]
• from resin-bound aldehyde, 6-amino-1,3-dimethyl uracil and active methylenes

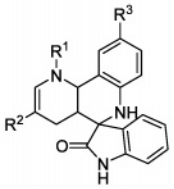


• Nielsen [375]
• oxidative cleavage of resin-bound arylalanines then intramolecular *N*-acyliminum Pictet-Spengler reaction

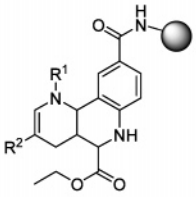
Part B: Solution-phase



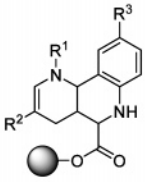
• Carranco [44]
• derived from a multicomponent reaction



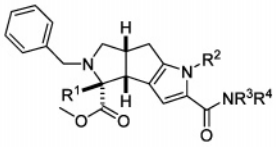
• Carranco [44]
• derived from a multicomponent reaction



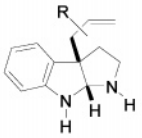
• Carranco [44]
• derived from a multicomponent reaction



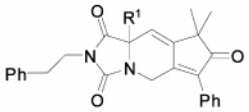
• Carranco [44]
• derived from a multicomponent reaction



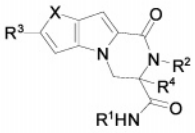
• Brummond [37]
• Pauson Khand/Stetter/Paal-Knorr reaction sequence



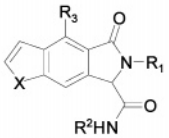
• Kawasaki [170]
• domino reaction sequence starting from hexahydro pyrrolo[2,3-b]indoles



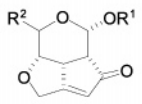
• Manku [222]
• multistep sequence using fluorous tags



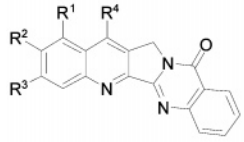
• Ilyn [147]
• 4-CC reaction



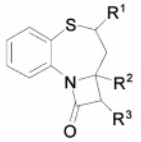
• Lu [215]
• Tandem 4-CC intramolecular Diels-Alder



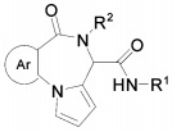
• Hotha [137]
• Ferrier and Pauson-Khand reaction



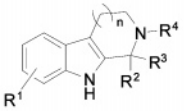
• Tangirala [314]
• from cascade radical annulations of isonitriles and quinazolones



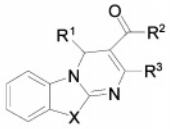
• Xu [348]
• Staudinger cycloaddition of 2,3-dihydro-1,5-benzo-thiazepines and acid chlorides



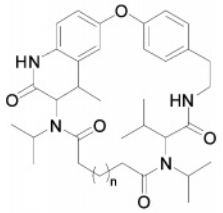
• Ilyn [151]
• 3-CC using bifunctional reagents



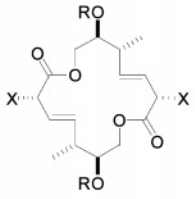
• Fokas [93]
• multiple libraries based on Pictet-Spengler reaction



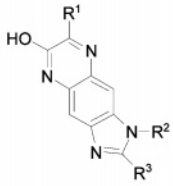
• Shaabani [298]
• 3-CC of RCHO, β-ketoester, 2-amino benzimidazole or 2-aminobenzothiazole



• Wessjohann [343]
• Ugi condensation using unsymmetrical diisonitrile, diacid, amine



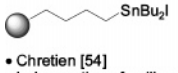
• Beeler [22]
• these and related macrodiolides prepared via cyclodimerization of hydroxy esters



• Zhang [363]
• multistep sequence from 1,5-difluoro-2,4-dinitrobenzene

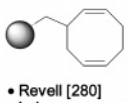
[a] Asterisk is the point of attachment to resin.

Table 11. Polymer-Supported Reagents and Scavengers



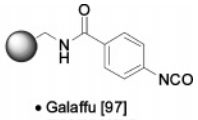
• Chretien [54]
• halogenation of anilines

• Lee [199]
• immobilized YbOTf as catalyst for Mannich-type reactions



• Revell [280]
• halogen scavenger

• Chung [55]
• triflating reagent



• Galaffu [97]
• macroporous polystyrene isocyanates prepared from diisocyanate

Table 11. (Continued)

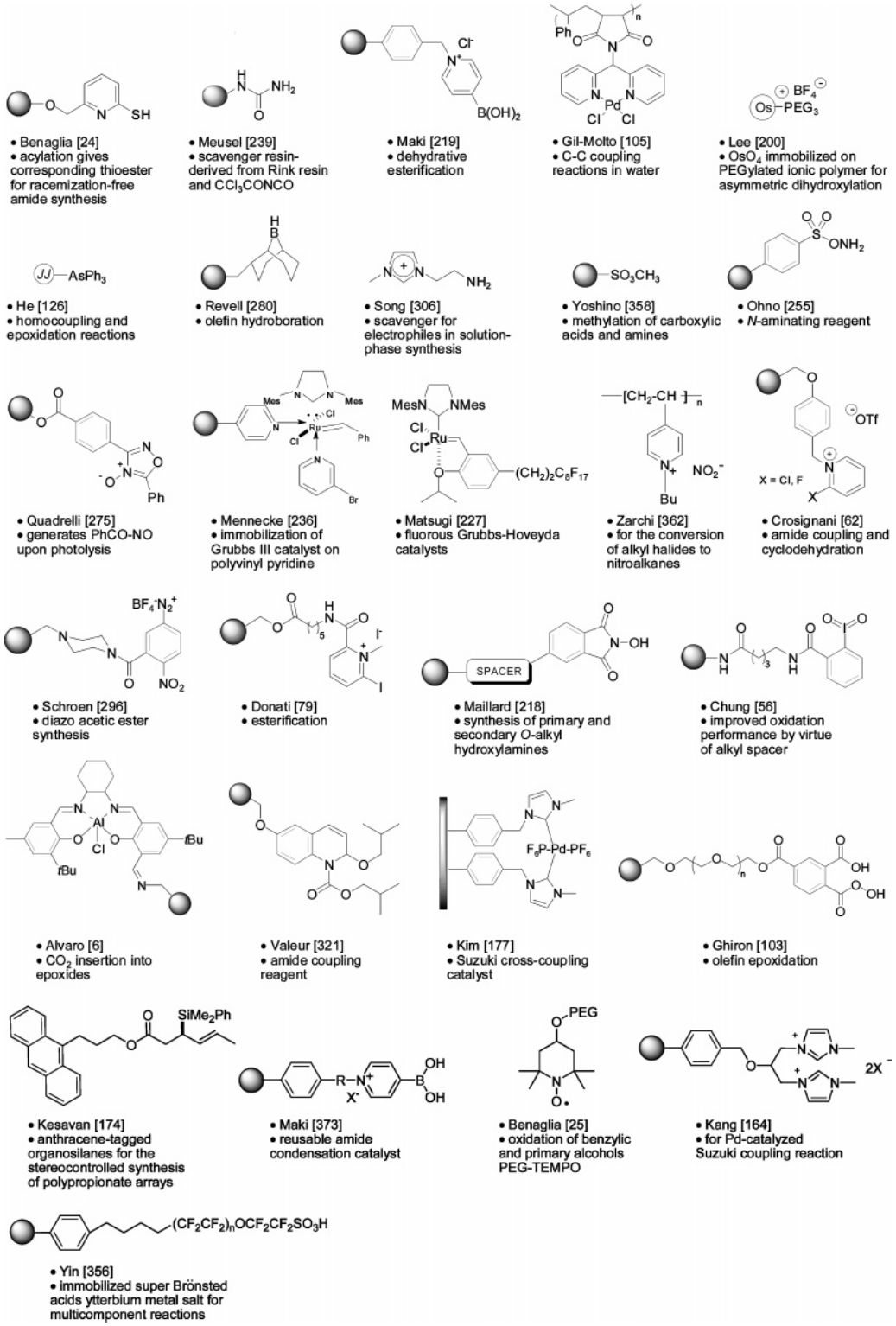


Table 12. Polymer-Supported Linkers

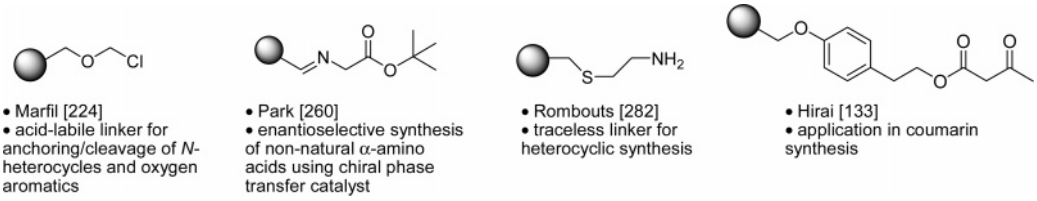
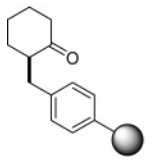
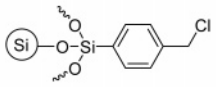


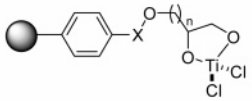
Table 12. (Continued)



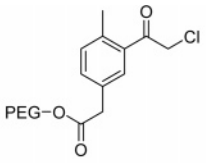
- Spino [308]
- for synthesis of chiral α-carbonyls



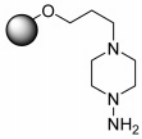
- Houghten [138]
- volatilizable support



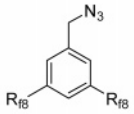
- Dyer [83]
- catalyst for Diels-Alder reaction



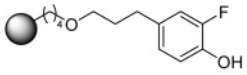
- Du [81]
- photo cleavable linker phenacyl esters



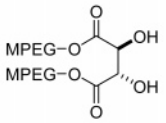
- Lazny [195]
- alkylation of RCHO and RCOR



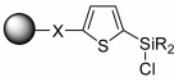
- Kaleta [163]
- fluorous "click" tag



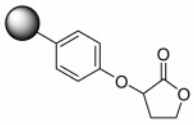
- Hourdin [139]
- fluorinated linker for gel-phase ^{19}F NMR monitoring



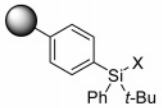
- Reed [279]
- MPEG tartrate ligand for Sharpless epoxidation



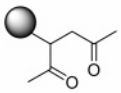
- Fauvel [89]
- functionalizable organosilane resin



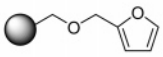
- McKerlie [231]
- SmI_2 cleavable linker



- DiBlasi [72]
- linking alcohols to resin

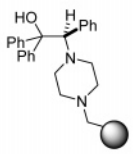


- Paladino [258]
- protecting group for primary amines (pyrrole ring formation)

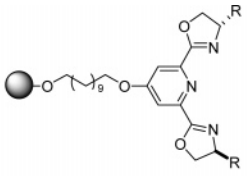


- Keller [172]
- thermally cleavable linker via Diels-Alder retro-Diels-Alder of intermediate oxabicyclo [2.2.1]norbornenes

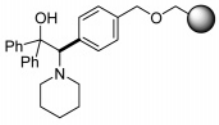
Table 13. Polymer-Supported Chiral Ligands



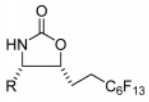
- Castellnou [47]
- enantioselective ethylation of aldehydes



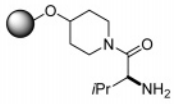
- Weissberg [341]
- heterogeneously catalyzed asymmetric additon of alkynes to imines



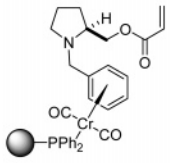
- Castellnou [46]
- asymmetric addition of phenyl zinc reagents to aldehydes



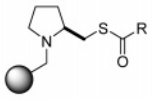
- Hein [130]
- fluorous chiral auxiliary



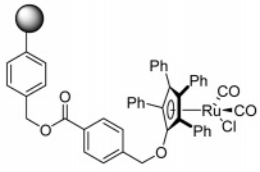
- Kreidler [184, 185]
- for asymmetric Michael reactions



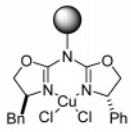
- Xie [347]
- chiral auxiliary for cycloaddition reactions



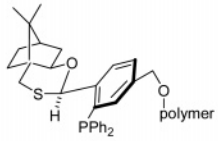
- Eriksen [87]
- enantioselective addition of Et_2Zn to RCHO



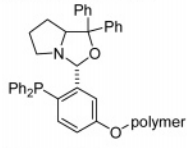
- Kim [178]
- racemization catalyst for dynamic kinetic resolution



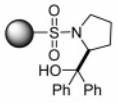
- Gissibl [106]
- asymmetric benzoylations of diols



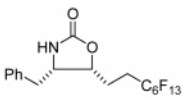
- Nakano [247]
- Pd-catalyzed asymmetric allylations



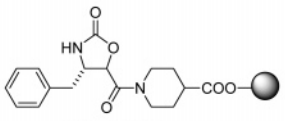
- Nakano [246]
- Pd-catalyzed allylic alkylations and Diels-Alder reaction



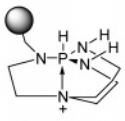
- Wang [328]
- enantioselective reduction of β-keto nitriles



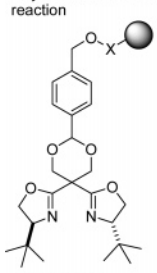
- Hein [131]
- fluorous chiral auxiliary application to 1,3-dipolar cycloaddition reactions



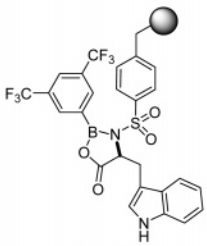
- Kotake [182]
- Evans-type chiral auxiliary



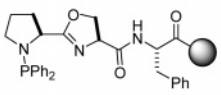
- Fetterly [91]
- reusable hetrogeneous catalyst for aza- and thia-Michael and Strecker reactions



- Knight [180]
- Cu-catalyzed enantioselective cyclopropanations



- Itsuno [153]
- asymmetric Mukaiyama aldol reaction catalyst



- Benito [371]
- asymmetric allylic substitution

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