JOURNAL OF combinatorial CHEMISTRY

Volume 9, Number 6 November/December 2007

Reviews

Comprehensive Survey of Chemical Libraries for Drug Discovery and Chemical Biology: 2006

Roland E. Dolle,*,† Bertrand Le Bourdonnec,† Allan J. Goodman,† Guillermo A. Morales,‡ Joseph M. Salvino,§ and Wei Zhang||

Adolor Corporation, 700 Pennsylvania Drive, Exton, Pennsylvania 19341, Semafore Pharmaceuticals Inc., 8496 Georgetown Road, Indianapolis, Indiana 46268, Cephalon, Inc., 383 Phoenixville Pike, Malvern, Pennsylvania 19355, and Fluorous Technologies, Inc., 970 William Pitt Way, Pittsburgh, Pennsylvania 15238

Received July 12, 2007

This is the tenth installment of the comprehensive survey series in combinatorial chemistry.[1] The title of the tenth annual review is updated to reflect the trend in high throughput chemistry towards the synthesis of smaller-numbered arrays (<1000 members) and their application in drug discovery and chemical biology. The format of the series remains unchanged with literature entries assigned to one of thirteen tables: Tables 1–5 (biological activity disclosed); proteases, nonproteolytic enzymes, G-protein-coupled receptors (GPCRs), nonGPCRs, and oncolytics/antiinfectives; and Tables 6–13 (no biological activity disclosed); scaffold derivatization, acyclic-, monocyclic-, bicyclic/spirocyclic-, and polycyclic/macrocyclic synthesis, reagents/scavengers, linkers, and polymer-supported chiral ligands. The 469 entries published in 2006 are captured in the Tables.[2–429]

In addition to the Tables there are 25 vignettes. Selected vignettes on biologically active libraries include: spirocyclic HIV-CCR5 receptor antagonists,[125] urea-based epoxide hydrolase inhibitors,[157] macrocyclic motilin receptor antagonists,[258] HIV protease inhibitors using triazole as a transition-state mimic,[387] 5-HT_{2A} antagonists,[364] the RCM-based dynamic combinatorial chemistry approach to carbonic anhydrase inhibitors,[319] the discovery of Bcl-x_L inhibitors combining fragment-based "SAR by NMR" with parallel synthesis,[303,384] and the design of multiple kinase-directed libraries yielding dual inhibitors of ERK-1 and RasGAP-dependent signaling pathways (stem cell self-renewal and differentiation).[52] The remaining selections describe new biselectrophilic annulation reagents to prepare piperazines and diazacycles,[250] the simultaneous processing of two heterocycles,[196] novel variants on multicomponent condensation reactions,[109,159,398,350,363] DOS and natural product-based libraries[19,200,217,240,262] and libraries/new methodology generated using fluorous technology.[98,185,282,419,420]

Publications appeared in 2006 on new polymer supports,[430–432] solid-phase trapping for compound isolation,[433] pyridyl tags as phase labels,[434] NMR functional libraries,[435] a molecular building kit for spirocycles,[436] target-family privileged substructures,[437] and in silico identification of biologically active heterocyclic scaffolds.[438] Selected high throughput chemistry reviews published in 2006 include topics on fluorous chemistry,[439–445] multicomponent condensations,[447,448]

* Corresponding author. E-mail: rdolle@adolor.com. Tel.: 484-595-1024. Fax: 484-595-1551.
† Adolor Corporation.
‡ Semafore Pharmaceuticals Inc.
§ Cephalon, Inc.
|| Fluorous Technologies, Inc.

10.1021/cc700111e CCC: $37.00
Published on Web 09/19/2007

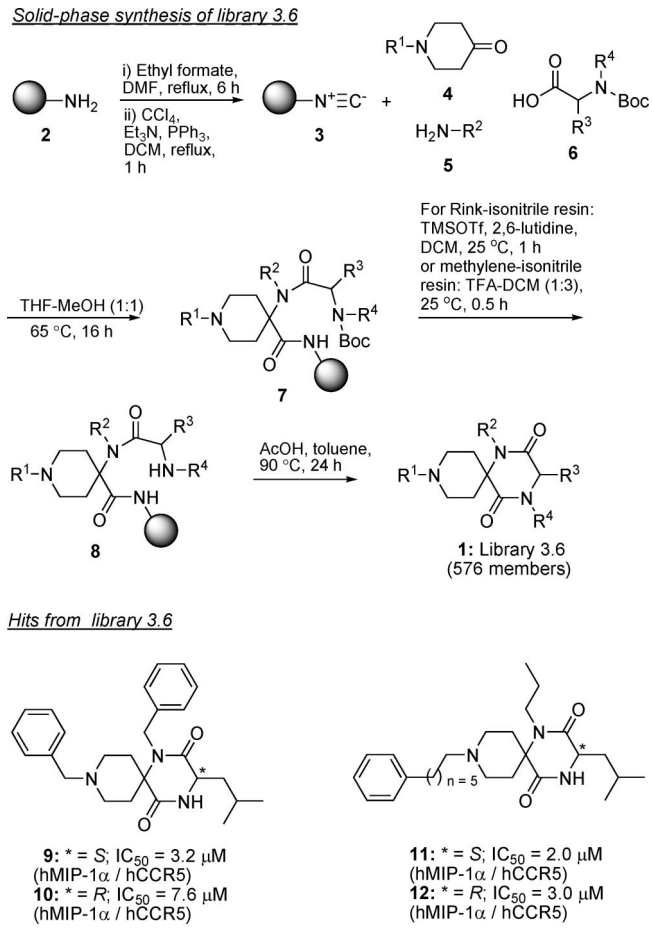


Figure 1. HIV-CCR5 receptor antagonists.[125]

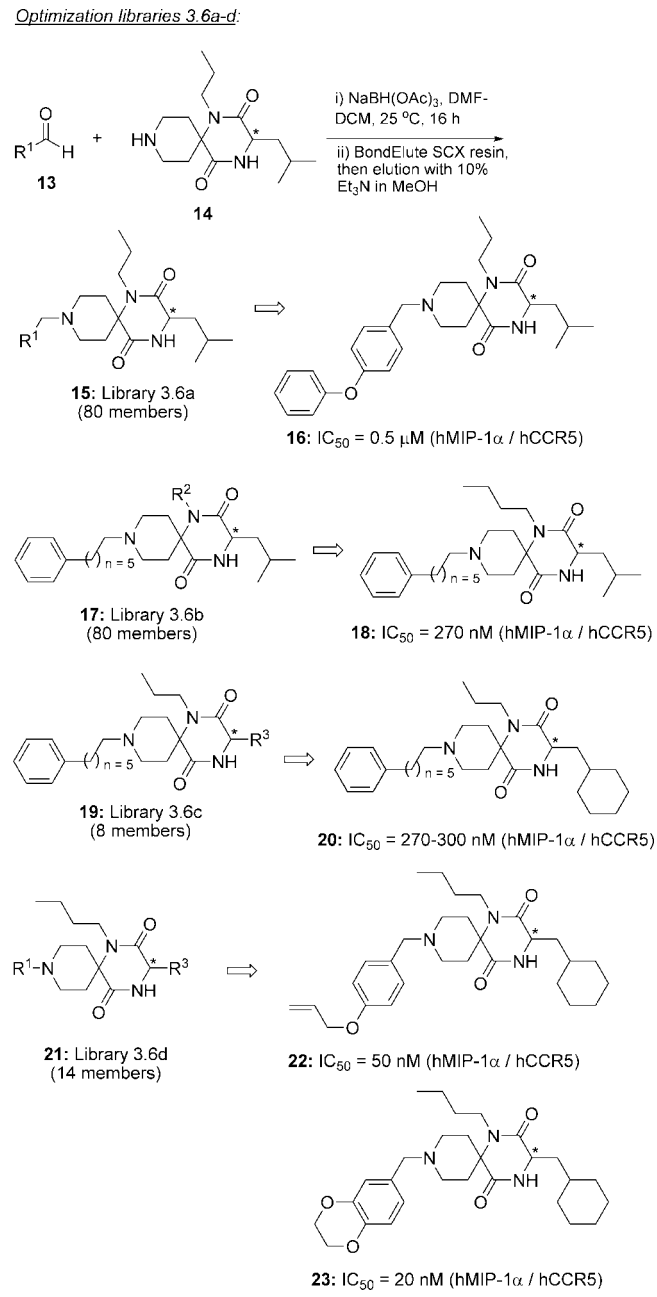


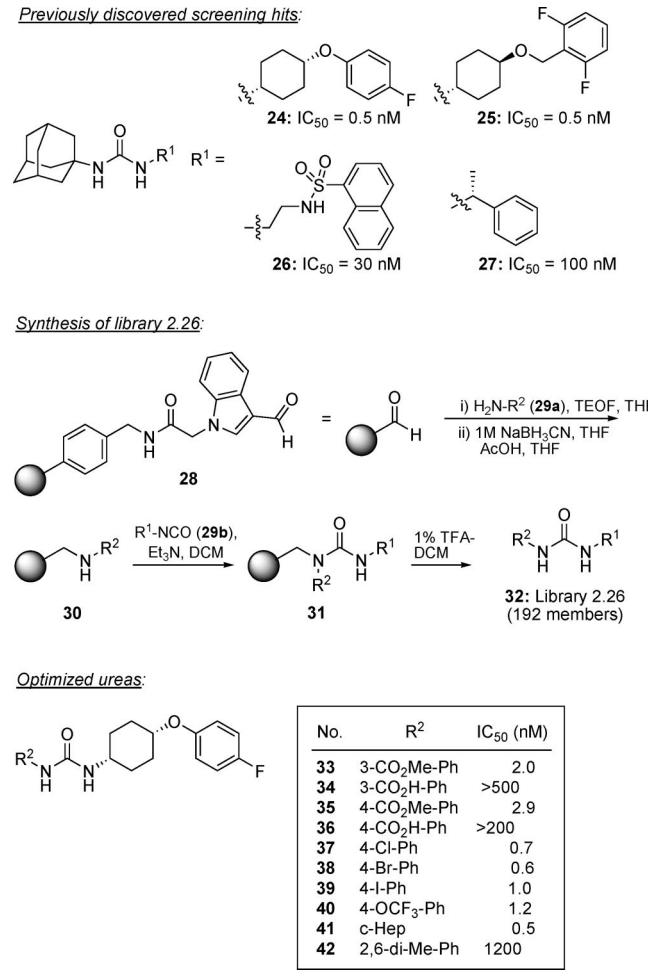
Figure 2. HIV-CCR5 receptor antagonist optimization.[125]

enantioselective synthesis on the solid phase,[449] automated synthesis of heterocycles on the solid phase,[450] fragment-based lead discovery,[451] DNA-encoded chemical libraries,[452,453] dynamic combinatorial chemistry,[454] in situ click chemistry,[455] approaches to preparing discovery libraries,[456] defining the medicinal chemistry diversity space,[457] chemical genomics,[458] DOS,[459] structure-based design and library synthesis,[460] SPOT synthesis,[461] resin-bound reagents and catalysts,[462] and parallel medicinal chemistry.[463]

HIV-CCR5 Receptor Antagonists. Chemokines are chemotactic cytokines that play a key role in leukocyte migration, adhesion, and activation and are involved in inflammation and immune cell differentiation. Chemokines are broadly classified in two families based on their cysteine residue structure: CC and CXC. Similarly, their corresponding receptors are also classified in 2 groups: CCR and CXCR, respectively. Chemokine receptors are members of the large family of seven transmembrane domain G-protein-coupled receptors (GPCRs). It has been established that an important step in the HIV infection process is viral binding to the chemokine receptors CCR5 and CXCR4. Consequently, preventing or disrupting the HIV-chemokine receptor binding could lead to potential routes for the treatment of inflammatory, allergic, and infective diseases. Using the priviliged GPCR-binding spirodiketopiperazine structure as a starting point, Habashita and co-workers chose the Ugi multiple component reaction to construct the spiro-diketopiperazine scaffold and combined solid- and solution-phase methodologies for scaffold derivatization and structure–activity relationship (SAR) analysis (Figure 1).[125] The solid-phase approach involved the synthesis and utilization of two types of polymer-bound isonitriles in the Ugi reaction: Rink-isonitrile and methylene-isonitrile resins **2**. Rink amide and aminomethylated resins were *N*-formylated with ethyl formate and then treated with $CCl_4/Et_3N/PPh_3$ to afford the desired isonitrile resins **3**. A 576-member library (**1**: library 3.6) was constructed using 8 × *N*-substituted piperidones **4**, 9 × amines **5**, and 8 × *N*-Boc protected amino acids **6**. The Boc protecting group of the resin-bound Ugi products (**7**) was removed by treatment with either TMSOTf/2,6-lutidine (Rink isonitrile resin) or with TFA/DCM (1:3). The resulting

amide-linked resins (**8**) were heated in the presence of HOAc and toluene to undergo intramolecular transamidation forming the desired diketopiperazine moiety and simultaneously releasing the desired spirodiketopiperazine products (**1**). From the 576-member library, 539 spirodiketopiperazines were isolated with >80% purity (ELSD), and their identities were confirmed by mass spectrometry. Library 3.6 was screened at 30 μM against intracellular calcium mobilization stimulated by MIP-1α in CHO cells. Several compounds exhibited >50% inhibition in hMIP-1R/hCCR5, and the IC_{50} values for four compounds (**9**–**12**) were determined. Compounds **9**–**12** had single-digit micromolar IC_{50} values all displaying selectivity for hCCR5 versus hCCR2, hCCR4, and hCXCR4. These hits indicate that alkylation of the piperidine amine with phenyl-containing alkyl linkers (R^1) is preferred, that alkylation of the spiro-linked amide with benzyl and unbranched lower alkyl groups (R^2) is also favored, that the aliphatic branched isopropyl substituent (R^3) is preferred at the methylene carbon of the diketopiperzine moiety, and that the second amide of the diketopiperazine unit should remain unsubstituted. Compounds **9**–**10** and **11**–**12** are enantiomers of one another showing that chirality at the methylene carbon of the diketopiperzine moeity is not critical for activity. On the basis of the last observation, follow-up compounds were made as enantiomeric mixtures.

To optimize hits **9**–**12**, three libraries were made to explore substitution sites R^1, R^2, and R^3 (Figure 2). For the optimization of R^1, an 80-member solution-phase library (**15**: library 3.6a) was made where the piperidine amine of spiroketopiperazine **14** was reductively alkylated with 80 diversified aldehydes **13** keeping R^2 and R^3 constant (*n*-propyl and isobutyl, respectively) as found in hits **11**–**12**. Hits from library 3.6a indicate that 4-substituted benzyl groups, particularly electron-donating substituents, increase activity against hCCR5 in the sub-micromolar range while maintaining selectivity over hCCR2, hCCR4, and hCXCR4 (**16**: hCCR5 $IC_{50} = 0.5$ μM; hCCR2, hCCR4, hCXCR4 $IC_{50} > 30$ μM). Derivatization of the piperidine amine of **14** to amides, sulfonamides, and ureas showed only modest activity. For the optimization of R^2, an 80-member library (**17**: library 3.6b) was made on solid-phase with 80 diverse amines **5** keeping the same R^1 and R^3 substituents found in **11** and **12**. Screening of this library revealed that *n*-propyl and benzyl groups at the R^2 position increased potency significantly where the former group was selected as the optimal substituent (**18**: hCCR5 $IC_{50} = 270$ nM). For the optimization of R^3 in the diketopiperazine unit, an 8-member library (**19**: library 3.6c) was made via the solid phase with a set of eight commercially available Boc-protected amino acids (**6**) keeping the same R^1 and R^2 substituents found in **11** and **12**. Screening of these compounds indicated that a cyclohexylmethyl group at position R^3 is preferred for high affinity binding towards hCCR5 (**20**: hCCR5 $IC_{50} = 270$–300 nM; hCCR2, hCCR4, hCXCR4 $IC_{50} > 10$ μM). Having determined the best substituents from libraries 3.6a–c, a final 14-member library 3.6d (**21**) was prepared via the solid phase where all three sites were simultaneously combined using 7 × *N*-alkylated piperidin-4-ones **4** (R^1), *n*-butylamine (R^2), and 2 × Boc-protected amino acids **6** (R^3). This library



No.	R^2	IC_{50} (nM)
33	3-CO_2Me-Ph	2.0
34	3-CO_2H-Ph	>500
35	4-CO_2Me-Ph	2.9
36	4-CO_2H-Ph	>200
37	4-Cl-Ph	0.7
38	4-Br-Ph	0.6
39	4-I-Ph	1.0
40	4-OCF_3-Ph	1.2
41	c-Hep	0.5
42	2,6-di-Me-Ph	1200

Figure 3. Optimization of soluble epoxide hydrolase inhibitors.[157]

afforded compounds exhibiting higher potency against hCCR5 ($IC_{50} < 170$ nM) with **22** and **23** possessing IC_{50} values below 100 nM. Compound **23** was the most potent of the entire library possessing an $IC_{50} = 20$ nM. Spirodiketopiperazine **22** was further tested against other GPCRs exhibiting 1000-fold greater affinity towards hCCR5 and modest affinity towards the muscarinic M_3 and sigma receptors ($IC_{50} = 2.07$ μM and 0.183 μM, respectively), and it inhibited the replication of laboratory and primary R5 HIV-1 strains as well as several multidrug-resistant monocyte/macrophage tropic (R5) HIV-1 and was inactive against T cell tropic (X4) HIV-1.

Soluble Epoxide Hydrolase Inhibitors. Epoxide hydrolases (EHs, EC 3.3.2.3) catalyze the hydrolysis of epoxides and arene oxides to produce their corresponding 1,2-diols. In mammals, the soluble epoxide hydrolase (sEH) is involved in the catalysis of arachidonic acid, linoleic acid, and other lipid epoxides. Epoxyeicosatrienoic acids (EETs) are arachidonic acid-based epoxides known to regulate both blood pressure and inflammation making sEH a potential target for the treatment of regulating these conditions.[157] Previous studies by Hammock and co-workers established that adamantyl-based ureas exhibited pico- and nanomolar inhibitory potency against sEH (**24**, **25**: $IC_{50} = 0.5$ nM; **26**: $IC_{50} = 30$ nM, **27**: $IC_{50} = 100$ nM; Figure 3). Leveraging on the

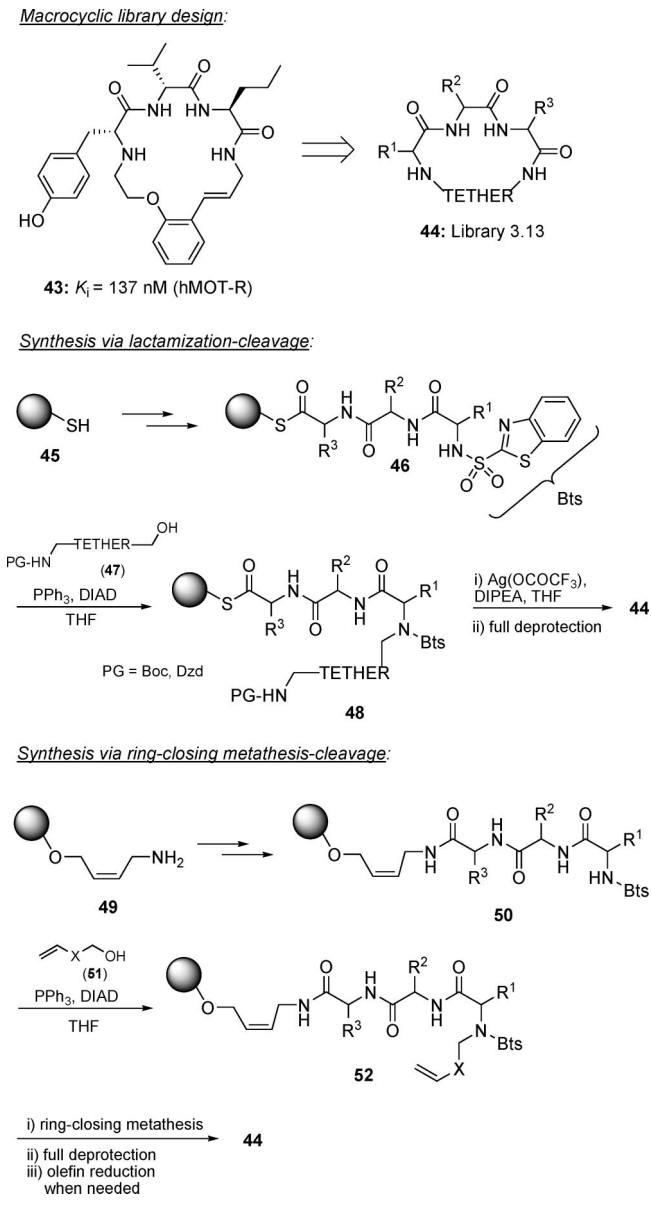


Figure 4. Macrocyclic library of human molitin receptor antagonists.
[258]

recently developed fluorescent sEH substrates by the same research group, a continuous fluorescence assay was used to measure the activity of additional urea-based inhibitors. In order to optimize this compound series and find alternatives to the adamantyl group, the authors used a solid-phase approach to produce a focused 192-member compound library (library 2.26) using commercially available acid-labile formylindole resin **28** and an IRORI AccuTag combinatorial chemistry system. Keeping the amines used in **24**–**27** constant, the authors selected a set of 48 isocyanates based on previously reported SAR analysis of reported inhibitors, namely: (1) simple carbocyclic rings, (2) mono-substituted phenyl rings, (3) *ortho*-disubstituted phenyl rings, and (4) 1- and 2-naphthyl groups. From the original 192-member compound library, 181 compounds were isolated with >90% purity which were assayed against the enzyme. As expected, compounds derived from cyclohexyl-based amines in **24** and **25** afforded analogs with higher affinity than those used in amines **26** and **27**. Interestingly, it was observed that ureas derived from (1*S*, 4*S*)-4-(4-fluorophenoxy)cyclohexanylamine (the amine used in **24**) were the most potent inhibitors of the series. The observed SAR indicates that methyl ester groups exhibited single nanomolar affinities (**33**, **35**: IC_{50} = 2–3 nM) and were at least 100-fold more potent than their corresponding carboxylic acids **34** and **36**. The fact that carboxylic acids are not tolerated as well as the observation that the *meta* position is less tolerable than the *para* position could be rationalized based on the analysis of recently resolved X-ray crystal structure of sEH complexed with a different alkyl urea. In the sEH crystal structure, it is observed that there is a protonated imidazole on His523 which would offer a strong ionic interaction with the carboxylate of the urea preventing the urea from binding optimally at the active site. Another explanation offered is that water solvation of the carboxylate could either cause repulsive interactions with residues in the active site or prevent access of the urea to the active site. The observed SAR also indicated that, in general, *para*-substituted phenyl groups exhibited higher potency (**37**–**41**: IC_{50} = 0.5 – 1.2 nM). The 2-naphthyl group is preferred over the 1-naphthyl group, and phenyl alkyl groups with at least a 2-carbon alkyl spacer (spacer ≥ ethyl) were well tolerated while sterically hindered groups and 2,6-disubstituted phenyl groups were not (**42**: IC_{50} > 1200 nM). These results suggest that sterically less hindered lipophilic groups that effectively replace the adamantyl group are likely to fit in the enzyme's narrow, hydrophobic tunnel.

Human Molitin Receptor Antagonists. Molitin is a 22-amino acid peptide involved in intestinal motility regulation. The human motilin receptor (hMTO-R or GPR38) is a GPCR expressed in the antrum, duodenum, and proximal small intestine whose activation results in the movement of gut content in the gastrointestinal track. Marsault and co-workers screened a proprietary library of about 10 000 macrocycles in a high-throughput fluorescence-based whole cell assay identifying hit **43** (K_i = 137 nM; Figure 4).[258] To study and optimize this macrocycle, the authors prepared library 3.13 (**44**) to study the influence of the substituent and chiral center of each of the three amino acids that comprise the tripeptide portion of **43** as well as the tether unit of the macrocycle. Two solid-phase approaches were used. In one approach, a thiol-functionalized resin **45** was used as the starting point to construct the tripeptide moiety using standard solid-phase peptide synthesis conditions. In the construction of the tripeptide moiety, the third amino acid used was already protected with the betsyl (Bts) protecting group. Sulfonamide **46** was then alkylated with an amino-protected-containing tether alcohol **47** under Fukuyama–Mitsunobu conditions. Deprotection of the amino group of the tether unit underwent silver-assisted lactamization to simultaneously release the central macrocycle. Removal of all remaining protecting groups afforded desired products **44**. The second approach used a ring-closing metathesis reaction to construct the macrocyclic system while simultaneously cleaving the mac-

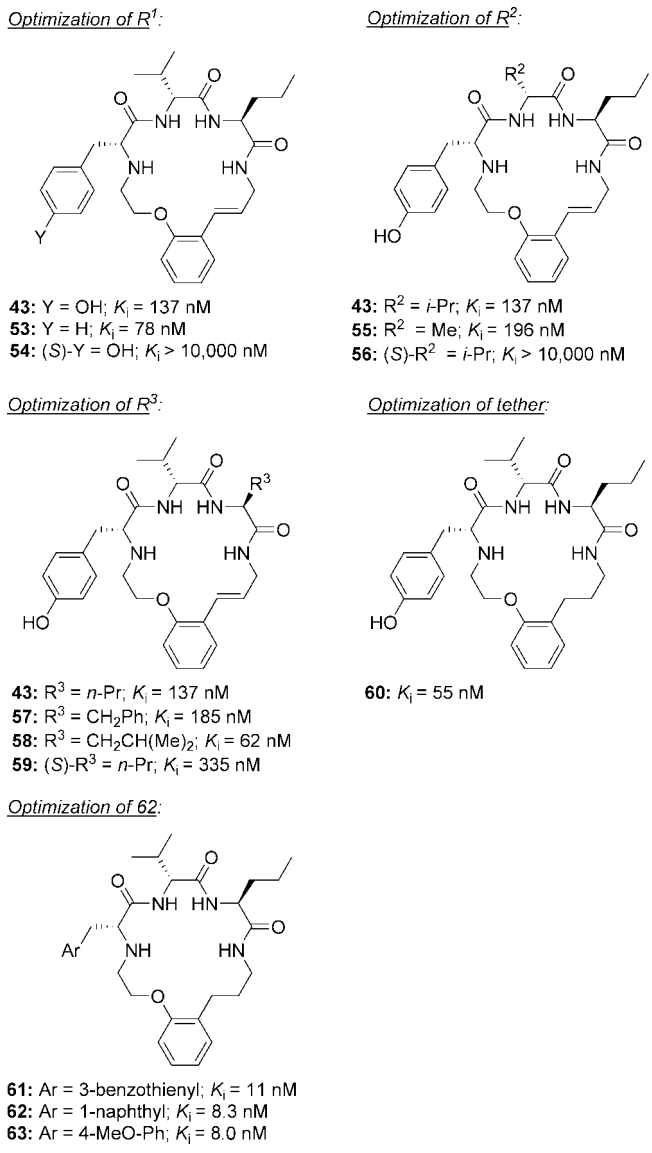


Figure 5. Human molitin receptor antagonist optimization.
258

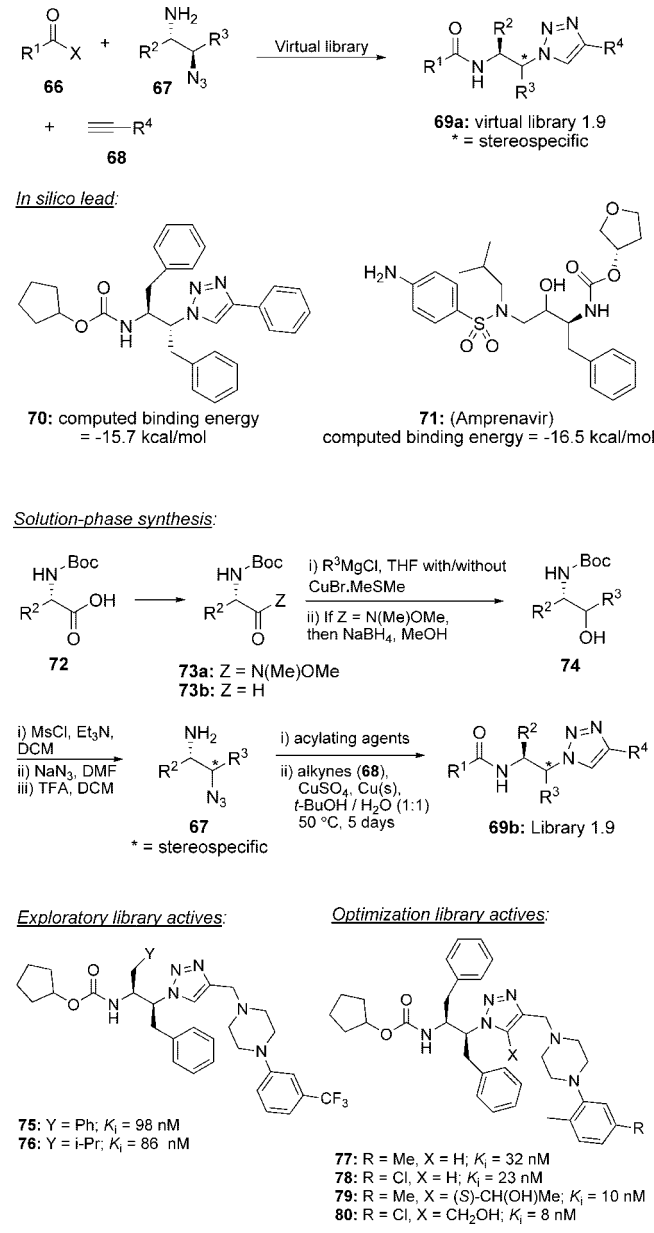


Figure 6. HIV-1 protease inhibitors.
387

rocycle from the solid support. In this approach polymer-supported ether-linked (*Z*)-4-aminobut-2-en-1-ol **49** was used as a handle to synthesize Bts-protected tripeptides **50** in a similar manner used previously to synthesize **46**. Intermediates **50** were alkylated with olefinic tethers **51** under Fukuyama–Mitsunobu conditions, and the resulting dialkene intermediates **52** underwent ring-closing metathesis to furnish macrocyclic products in solution. These compounds were then deprotected and the olefin moiety was reduced when needed to afford **44**. The SAR during the optimization of the first amino acid (R^1) site indicates that D-amino acids with aromatic side chains conferred high potency while aliphatic or ionizable side chains were not tolerated (Figure 5). When D-Tyr in **43** was replaced for D-Phe (**53**), a 2-fold increase in potency was observed ($K_i = 78$ nM). However, changing the chirality of D-Tyr to L-Tyr (**43** → **54**) was detrimental for binding affinity ($K_i > 10\ \mu$M). For the second amino acid (R^2), a high preference for D-Val and D-Ala (**55**: $K_i = 196$ nM) was observed while residues containing polar or ionizable residues were not well tolerated. As observed previously in R^1, changing the chirality of D-Val to L-Val (**43** → **56**) was detrimental for binding affinity. For the third amino acid R^3, however, the nature of the residue chain was more tolerant since ionizable residues only exhibited a 5-fold loss in potency. It was at this position where replacing the L-Nva residue with other residues, namely L-Phe (**57**) and L-Leu (**58**), afforded compounds with similar or higher affinity ($K_i = 185$ and 62 nM, respectively). It is worth noting that changing the chirality from L-Nva to D-Nva was tolerated (**59**: $K_i = 335$ nM) although this resulted in a slight loss in affinity. The observed SAR on the tether indicates that replacing the oxygen atom by a methylene group, replacing the aryl unit of the tether, and replacing the ethylene unit from the other unsaturated segment of the tether with a methylene group resulted in a drastic loss of potency. However, reducing the ethylene unit of the tether to an ethyl

unit (**60**) resulted in a 2.5-fold increase in potency (K_i = 55 nM). The authors then proceeded to optimize **60** by replacing the phenol unit in the D-Tyr amino acid residue with other aromatic groups finding that more lipophilic groups such as 3-benzothienyl **61** and 1-naphthyl **62** (the former being an isostere of the latter) exhibited a 5–6.6-fold increase in potency (**61**, **62**: K_i = 11 and 8.3 nM, respectively). The methyl ether analog of D-Tyr exhibited the highest potency of all the analogs made (**63**: K_i = 8.0 nM). Further replacement of the amide units in the tripeptide moiety with carbamate and hydrazide links and *N*-methylation of the amide units all resulted in loss of potency.

HIV-1 Protease Inhibitors. The human immunodeficiency virus type-1 (HIV-1) is responsible for the development of acquired immunodeficiency syndrome (AIDS) which currently affects millions of people around the world. In order to disrupt the viral cycle, development of HIV reverse transcriptase and HIV protease inhibitors are the focus of intense scientific research. X-ray crystallography data of HIV-1 protease with peptidic inhibitors revealed that this protease exists as a C_2-symmetric dimer where there is a key structural water molecule binding to the NH functions of Ile 50/50′, and hydrogen-bonding interactions between the catalytic aspartic acid residues Asp 25/25′ and the inhibitors. For the identification of novel HIV-1 inhibitors, Whiting and co-workers[387] created a virtual library of triazoles **69a** and conducted an in silico docking screening of the library using AutoDock (Figure 6). The compounds were ranked by binding energies and ease of synthesis, using the known HIV-1 protease inhibitor Amprenavir (**71**) as point of comparison. Compound **70** was selected as a starting point. A copper(I)-catalyzed, click-based, solution-phase route was developed for the library synthesis of 1,2,3-triazoles. The carboxylic acid groups of Boc-protected α-amino acids **72** were converted into aldehydes **73b**, which in turn were reacted with Grignard reagents to afford their corresponding *N*-Boc-protected amino alcohols **74** following borohydride reduction. The alcohols were converted to their mesylates and then treated with sodium azide followed by TFA to produce the necessary amino azide intermediates **67**. Acylation of the amino group followed by the reaction with alkynes **68** in the presence of Cu(I) made in situ in *t*-BuOH–H_2O (1:1) at 50 °C in a sealed tube for 5 days afforded the desired 4-substitued 1,2,3-triazoles **69**. For the initial 759-member library 1.9 (**69b**), 11 enantiomerically pure amino azide intermediates **67** were prepared. The chiral intermediates **67** were acylated with cyclopentyl chloroformate, generating a chiral set of amides where the newly installed R^1 group matched that found in the virtual lead **70**. These chiral amide intermediates were in turn subjected to 1,3-dipolar cycloaddition with 69 diverse alkynes to afford triazole library 1.9. The triazoles so obtained were diluted to 5 μM, transferred to 96-well plates, and assayed against HIV-1 protease where several triazoles exhibited >50% inhibition. It was observed that all the actives possessed an *S,S-syn* amino azide configuration and were derived from propargylpiperazine alkynes. Triazoles **75** and **76** exhibited low nanomolar K_i affinity against HIV-1 protease (K_i = 98 nM and 86 nM, respectively). With this

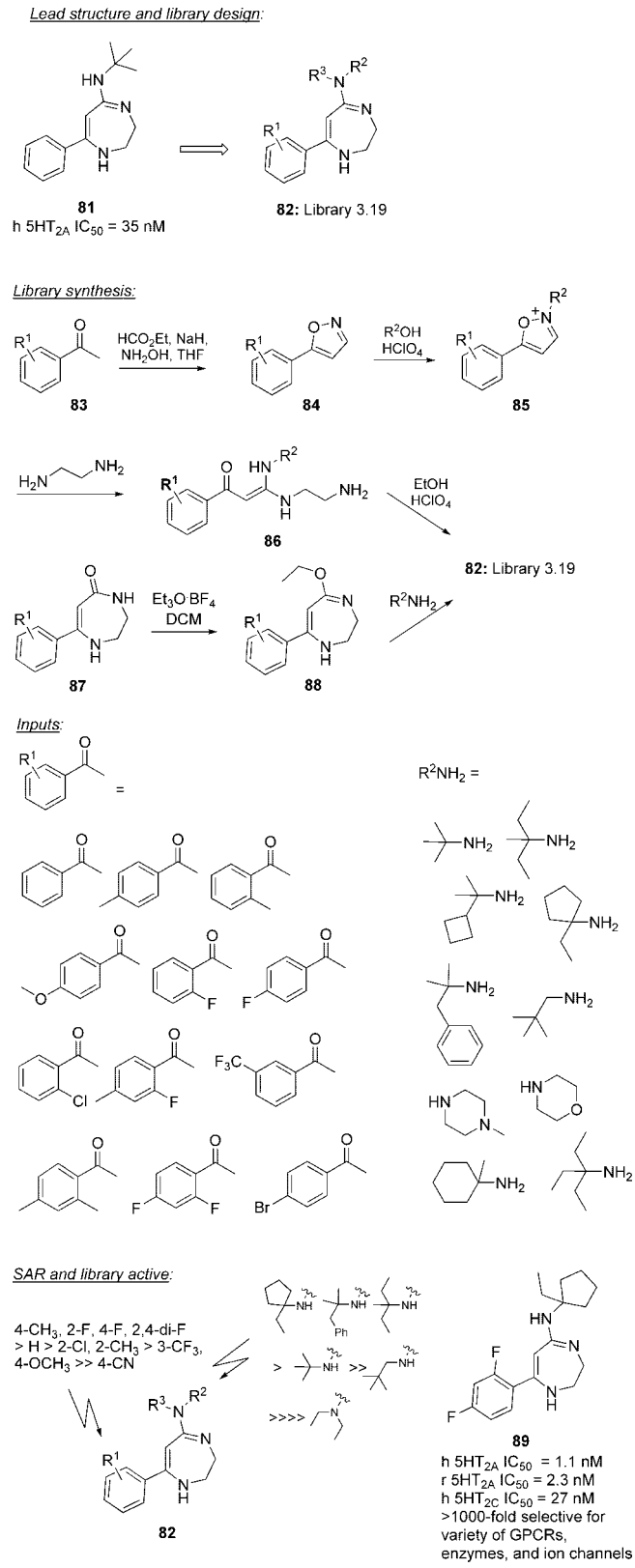


Figure 7. 5-HT_{2A} antagonists.
364

information at hand, two focused libraries were made to optimize both the alkyne and the amino-capping substituents. A set of 36 piperazine- and piperidine-containing alkyne derivatives were used along with template **67** (R^2 = R^3 = Bn). A number a more potent hits were identified. Tetrazoles

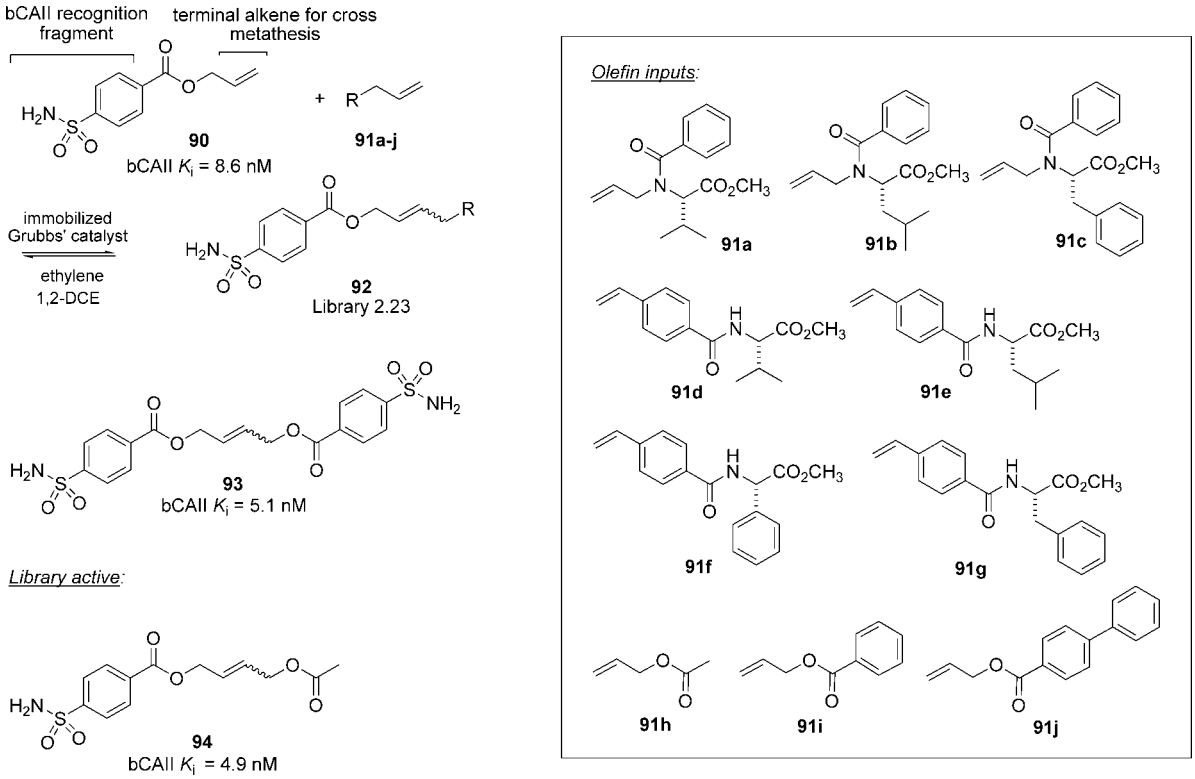


Figure 8. Carbonic anhydrase II inhibitors by dynamic combinatorial chemistry.[310]

77 and **78** exhibited K_i values of <35 nM. The SAR derived from the optimization libraries indicated that 4-phenylpiperazines were more potent inhibitors than those where the 4-phenyl group was replaced with a heterocyclic unit (e.g., 4-pyridyl) or a cyclic alkyl unit (e.g., cyclohexyl). Replacement of the piperazine group for the piperidine group was also detrimental for activity. In a final round of optimization, R^2, R^3, and R^4 substituents in **78** were held constant and 23 additional analogs were generated to explore the influence of different acylating agents and other substituents on the amino unit (R^1). It was found that branched and cyclic carbamates retained potency against HIV-1 while amide and urea derivatives showed a dramatic loss in potency. None of the active carbamates exhibited equal or greater potency than the cyclopentyl group. Replacing the 1,2,3-triazole unit with an amide resulted in loss of potency. Docking of **78** in AutoDock indicated that this triazole analog can adopt a conformation where both the carbonyl oxygen of the carbamate and *N*-3 of the triazole group may interact with the structural water molecule in the active site via hydrogen-bond formation. Interestingly, in this computational model, **78** is not expected to have a direct interaction with the catalytic aspartic acid residues Asp 25/25′ as observed with other HIV-1 protease inhibitors. The above computational model was validated when the (*S,S*)-1,5-triazole analog of **77** was synthesized; this regioisomer was inactive against HIV-1 (IC_{50} > 25 μM). Confirming that the 1,4-disubstitued triazole linkage was crucial for binding in the catalytic site of HIV-1, small polar substituents (X = –(*S*)-CH(OH)CH_3 and –CH_2OH) at position 5 of the triazole group were introduced. This modification led to even more potent compounds (**79**, **80**: K_i = 10 nM and 8 nM, respectively). The addition of slightly larger polar groups (≥hydroxyethyl groups) resulted in a loss of activity where the *S*,*S*,*S*-isomers were more potent than the *S*,*S*,*R*-isomers.

5-HT_{2A} Antagonists. Among the 5-HT receptors, 5-HT_2 receptors are of significant clinical interest because of their potential involvement in mediating many of the central and peripheral physiological functions of serotonin. There are three receptor subtypes within the 5-HT_2 classes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The 5-HT_{2A} subtype is functionally the most important, the others having a much more limited distribution and functional role. Antagonists of the 5-HT_{2A} receptor are being used to treat many psychiatric disorders (e.g., depression and schizophrenia) and have also potential utility for the treatment of sleep disorders and Parkinson's disease. Scientists at Merck performed an HTS campaign using a FLIPR-based human 5-HT_{2A} receptor binding assay to identify novel structural classes of 5-HT_{2A} ligands (Figure 7).[364] Low molecular weight compounds from Merck's collection were first clustered by structural similarities. The 150 clusters containing at least 1 hit (>50% inhibition at 5 μM in the HTS assay) were then selected. The individual SMARTS (smiles arbitrary target specification) queries[364b] constructed for each cluster were used to remove structures of known 5-HT_{2A} ligands and NK_1 receptor antagonists. A final set of 17 compounds were selected for titration experiments in the 5-HT_{2A} binding assay. From this group, compound **81**, which bound to the 5-HT_{2A} receptor with an IC_{50} of 35 nM, was selected for lead optimization. Analogs of **81** were prepared by parallel synthesis (**82**; library 3.19). Acetophenones **83** reacted with ethyl formate and hydroxylamine in the presence of sodium hydride to provide the aryl isoxazolines **84**. Reaction of **84** with aliphatic alcohols in

the presence of perchloric acid, followed by reaction with diaminoethane and subsequent cyclization provided the target 1,4-diazepine derivatives **82**. Alternatively, compounds were obtained by the reaction of amines with imidate **88**. This study led to the identification of compound **89** displaying potent affinity for the human 5-HT_{2A} receptor (30-fold improvement over **81**) and excellent selectivity over a wide range of GPCRs, enzymes, and ion channels.

Carbonic Anhydrase II Inhibitors. The metalloenzyme carbonic anhydrase (CA, EC 4.2.1.1) catalyzes an important physiological reaction: the interconversion of carbon dioxide, generated in high amounts in all metabolic processes, and the bicarbonate ion. Inhibitors of these zinc-containing enzymes have a broad range of therapeutic applications as diuretic, antiglaucoma, antiobesity, and antitumor drugs. There are currently 16 known human CA isoforms that are each responsible for specific physiological functions. Most of the known CA inhibitors share as a common structural feature (fragment) a heteroaromatic sulfonamide moiety identified as a key CAII recognition element. Researchers at Griffith University (Brisbane, Australia) described a fragment-based drug discovery approach to the synthesis and identification of small molecule CAII inhibitors by dynamic combinatorial chemistry (DCC) utilizing alkene cross metathesis (CM).[310] Compound **90**, used as a scaffold building block for this study, incorporates the classical bCAII recognition element ($ArSO_2NH_2$) and a terminal alkene functionality, which under cross metathesis reaction conditions, reacts with the various olefins **91a**–**j** to afford target library 2.23 (**92**; Figure 8). The cross metathesis reaction was catalyzed by an immobilized Grubbs first-generation catalyst (20 mol%). This represents the first application of heterogeneous catalysis to DCC. The authors first demonstrated that with the exception of the symmetrical bissulfonamide **93**, the self-CM products were devoid of bCAII affinity. In order to minimize the background bCAII affinity of **93** in the dynamic combinatorial libraries (DCLs), **90** was condensed with 10 equiv of **91a**–**j**. Under these conditions, the homodimer **93** was only present in small quantities (<5% as assessed by negative ion ESI MS analysis). The library was then screened at 1 and 10 μM in a fluorescence-based bCAII enzyme binding assay. Representative compounds were resynthesized and further purified in order to confirm the binding data obtained for the library compounds. The K_i values obtained for the purified products were in full agreement with the K_i values obtained for the library compounds. This study led to the identification of the heterodimer **94** displaying nanomolar affinity toward the bCAII enzyme.

Bcl-x_L Inhibitors. Central regulators of the apoptotic pathway are proteins belonging to the Bcl-2 (B-cell lymphocyte/leukemia-2) family. Antiapoptotic Bcl-2 proteins, such as Bcl-x_L, are overexpressed in most human cancer types and therefore are very attractive targets for the development of anticancer agents. While Bcl-x_L and its close relatives such as Bcl-2, Bfl-1, Mcl-1, Bcl-W, and Bcl-B, promote cell survival, the structurally similar proapoptotic members, such as Bak, Bax, Bad, Bim, and Bid, promote cell death. The critical mechanism by which pro- and

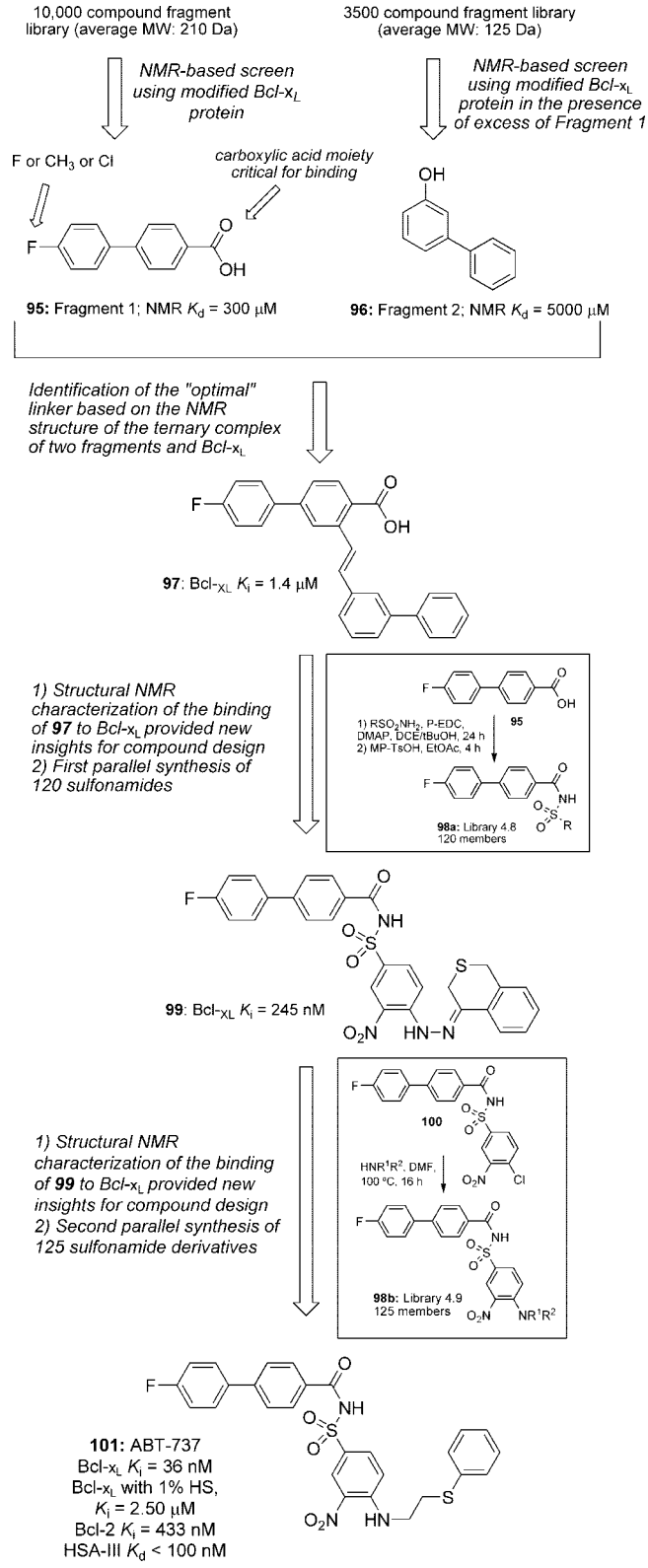


Figure 9. Bcl-x_L inhibitors via SAR by NMR.[303,384]

antiapoptotic members interact involves the hydrophobic groove on the surface of the antiapoptotic members and the BH3 dimerization domain of the proapoptotic counterparts. One approach to designing inhibitors of the antiapoptotic Bcl-2 family proteins is the discovery of small molecule BH3 mimics (inhibitors of a protein–protein interaction). Scientists

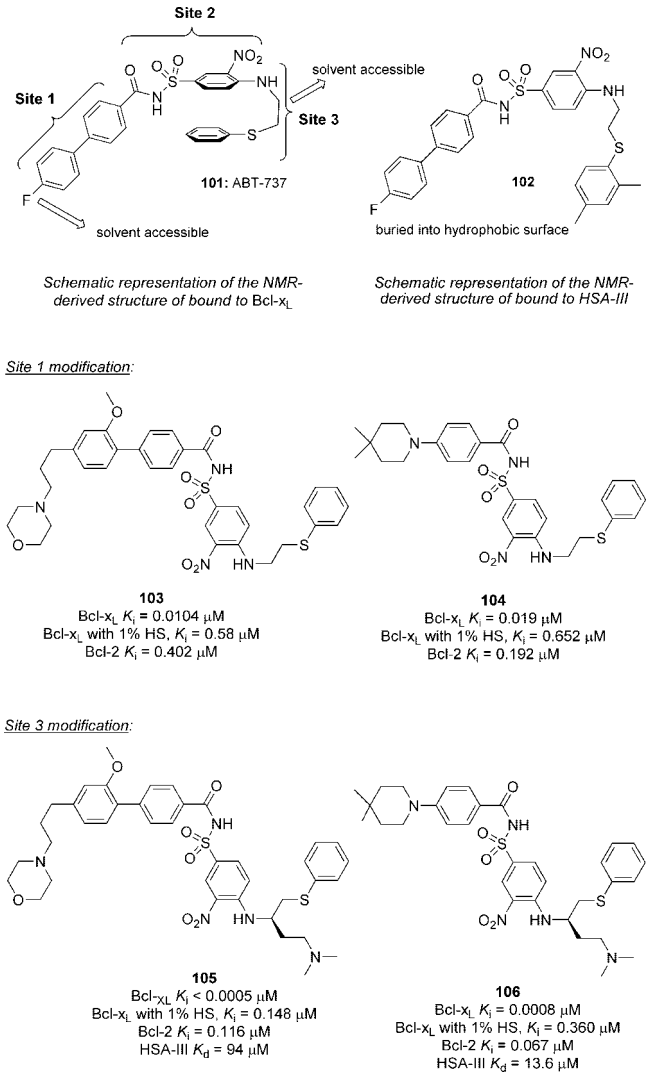


Figure 10. Bcl-x_L inhibitor optimization.[303,384]

at Abbott used a fragment-based approach, specifically SAR by NMR, and parallel synthesis to identify a potent inhibitor BH3 mimic that binds in the hydrophobic groove of Bcl-x_L (Figure 9).[303,384] A 10 000-member fragment library was screened by NMR using a modified form of Bcl-x_L. This resulted in the identification of the fluorobiaryl acid **95** as a weak ligand (fragment **95**; NMR $K_d = 300\ \mu M$) for Bcl-x_L. The SAR revealed that the presence and the orientation of the carboxylic acid functionality of **95** were critical for binding to Bcl-x_L. NMR-based structural studies were then conducted to compare the structure of Bcl-x_L complexed to **95** with the structure of Bcl-x_L/Bak peptide. This study highlighted the existence of a second potential binding site in close proximity to the fragment **95**. A 3500-member fragment library was screened by NMR to identify ligands for this second proximal site. From this screen, 5,6,7,8-tetrahydronaphthalen-1-ol (NMR $K_d = 4300\ \mu M$) and biphenyl-3-ol (**96**: NMR $K_d = 5000\ \mu M$) were identified as site 2 fragments. An appropriate linking strategy was then proposed based on the structure of the ternary complex of Bcl-x_L with the fragments. The *trans*-olefin **97** was identified from this SAR study as a low micromolar ligand for Bcl-x_L ($K_i = 1.4\ \mu M$; fluorescence polarization assay). The structural NMR characterization of the binding of **97** to Bcl-x_L provided new insights for compound design. In particular, it was envisioned that an acyl sulfonamide group, a common isostere of the carboxylic acid functionality, could be used to link the two Bcl-x_L fragments. From a 120-member acylsulfonamide library (**98a**; library 4.8), prepared by coupling various sulfonylamine derivatives to the acid **95** using resin-bound EDC, compound **99** exhibited the greatest affinity for Bcl-x_L with a $K_i = 245$ nM. Modification of isothiochroman-4-ylidenehydrazine moiety of **99** was then explored to further increase the affinity toward Bcl-x_L. A 125-member library (**98b**; library 4.9) was prepared by nucleophilic addition of various amines to the aromatic chloro substituent of **100**. Of these new derivatives, compound **101** (ABT-737) exhibited the highest binding affinity for Bcl-x_L with an inhibition constant of 36 nM. However, when the binding experiments were conducted in the presence of 1% human serum, the K_i of ABT-737 dropped to 2.5 μM. Additional studies revealed that ABT-737 bound with high affinity to the human serum albumin-III (HSA-III). Structure-based design was then conducted to decrease the affinity for HSA-III while retaining potent Bcl-x_L binding. The differences in the binding modes of **101** and the closely related analogue of **102** bound to Bcl-x_L and HSA-III, respectively, suggested a design strategy to reduce albumin binding while retaining potent affinity for Bcl-x_L (Figure 10). SAR resulting from the site 1 modification of **101** led to the identification of compounds **103** and **104**, which retained potent Bcl-x_L affinity even in the presence of human serum. Introduction of a dimethylamino group to these structures (**103** → **105**; **104** → **106**) resulted in a significant increase in the Bcl-x_L affinity combined with a greatly decreased affinity to the key HSA-III binding site. Additional experiments using a human nonsmall cell lung carcinoma line (A549) expressing large amounts of Bcl-x_L demonstrated that **106** potentiated UV-C induced cytotoxicity and enhanced the cytotoxic effect of paclitaxel. In an A549 xenograft tumor model, compound **106** enhanced the antitumor activity of paclitaxel with no increased toxicity. In this *in vivo* model, combination of **106** with paclitaxel resulted in 75% tumor growth inhibition and significantly enhanced tumor growth delay.

Dual Inhibitors of ERK-1/RasGAP-Dependent Signaling Pathways. Scientist at the Scripps Research Institute described in 2002 a combinatorial scaffold approach toward kinase-directed heterocyclic libraries.[464] The strategy involved the capture of a dichloroheterocyclic template where one chloro group is displaced selectively by a resin-bound amine nucleophile, while the other chloro substituent of the resulting resin-bound heterocycle can react with amines or participate in palladium-mediated coupling reaction with anilines, phenols, and boronic acids. To illustrate this methodology, a library of 2-, 6-, and 9-trisubstituted purine derivatives was constructed from 2,6-dichloropurine **109** (Figure 11). Addition of a PAL-amine resin **108** to the more reactive C-6 position of 2,6-dichloropurine yielded the resin-bound 6-substituted-2-chloropurine **110**. This intermediate was reacted with various alcohols under Mitsunobu condi-

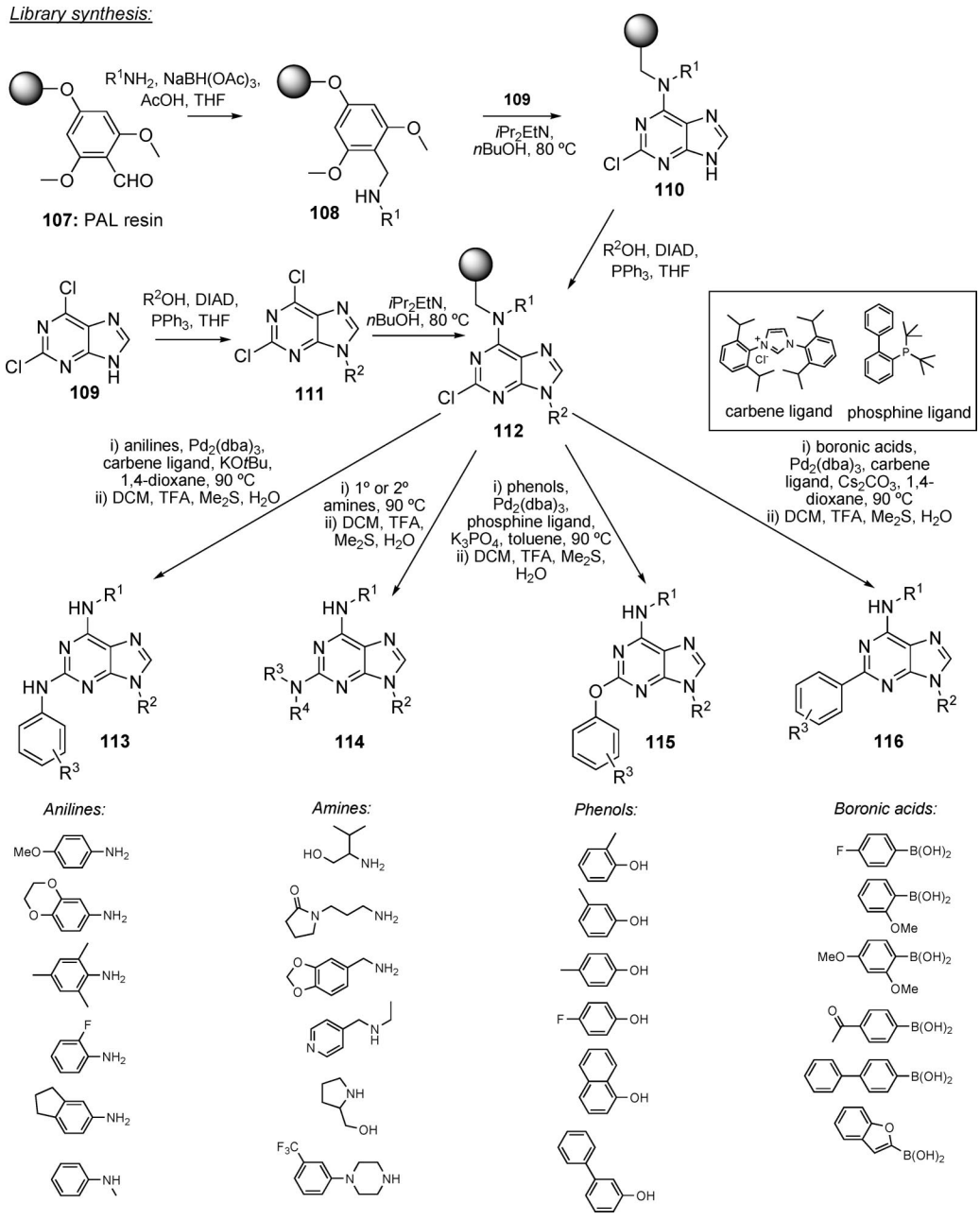


Figure 11. Kinase-directed heterocyclic libraries derived from 2,6-dichloro-9*H*-purine.[52]

tions to afford the corresponding resin-bound 9,6-disubstituted-2-chloropurine **112**. The other approach consisted of loading *N*9-substituted 2,6-dichloropurine **111**, obtained by alkylation of 2,6-dichloropurine, onto the PAL-amine resins. This second approach had the advantages of using less reagents and easy handling. Alkylation on solid support resulted in an improved *N*9/*N*7 regioselectivity. The final derivatization step consisted of a palladium-catalyzed cross-coupling reaction, or nucleophilic substitutions at the C-2 position of the resin-bound purines **112**. The palladium-catalyzed cross-coupling reactions were performed using 5 equiv of boronic acids, anilines, or phenols, 7 mol % $Pd_2(dba)_3$, 14 mol% of either 1,3-bis(2,6-di-isopropylphenyl)imidazolium chloride or biphenyl-2-yl-di-*tert*-butyl-phosphane, and 6 equiv of a base for 12 h at 80 °C using 1,4-dioxane (C–C and C–N bond formation) or toluene (C–O bond formation) as solvent. The versatility of this heterocycle resin capture strategy was demonstrated by generating heterocyclic libraries **118** (including library 2.11) starting from various dichloroheterocycles belonging to structurally diverse chemical classes, i.e. *1H*-benzo[d]imidazoles, pyrimidines, pyrimidin-2-amines, quinazolines, pyrazines, phthalazines, quinoxalines, and pyridazines (Figure 12).[52] This resulted in the generation of multiple libraries totaling some 45 140 members of discrete and highly diverse heterocyclic molecules. These libraries were used as tools to better understand the mechanisms that are controlling the self-renewal and differentiation of embryonic stem (ES) cells. Some of the most serious medical conditions, such as cancer and birth defects, are due to problems that occur during this process of self-renewal and differentiation. A better under-

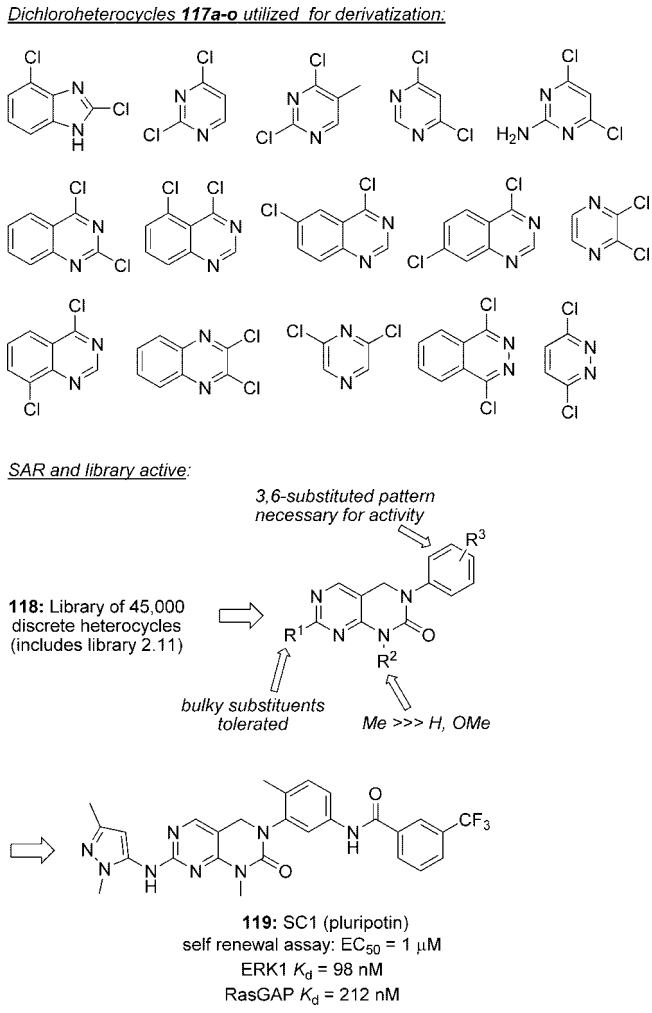


Figure 12. Kinase-directed heterocycle library screening results.[52]

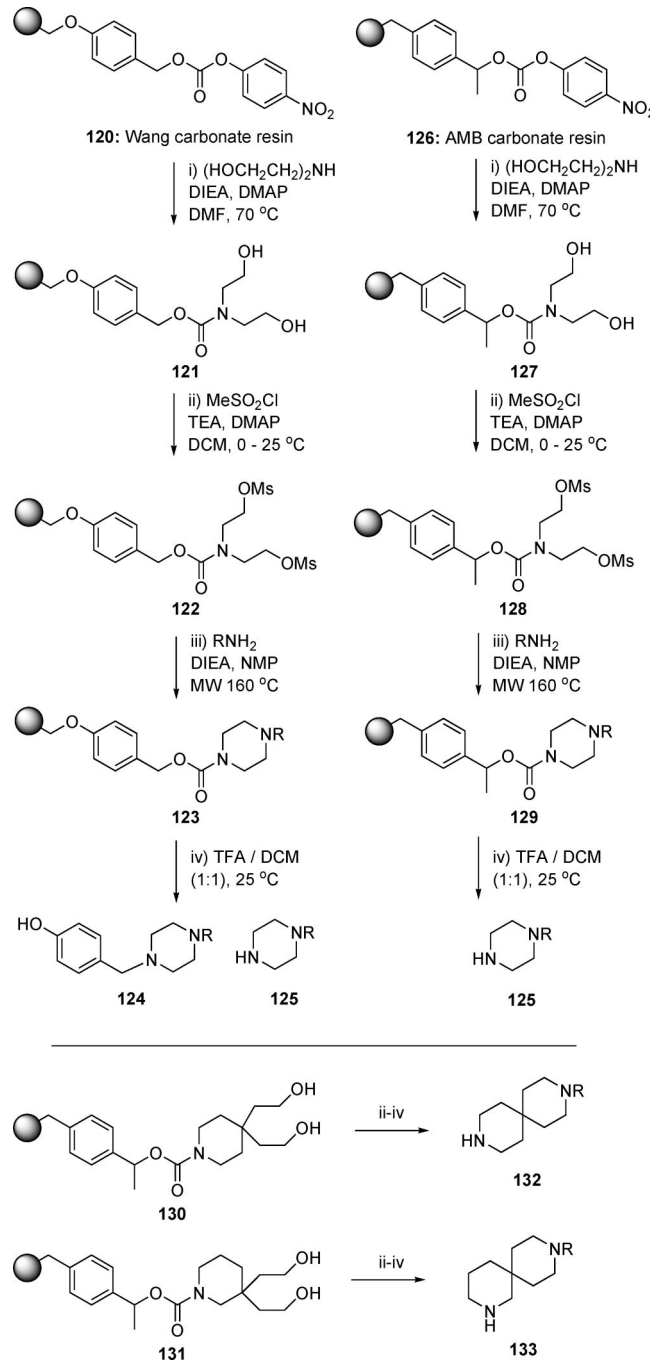


Figure 13. One-step diazacycles from primary amines and SPA*n* reagents.[250]

standing of normal cell development will allow understanding and perhaps correcting of the errors that cause these medical conditions. The library of discrete heterocycles, prepared using the methodology described previously, was screened in a high-throughput assay system for self-renewal. This screen was performed by using an established reporter mES cell line derived from transgenic OG2 mice. OG2-mES cells lose both GFP (i.e., green fluorescent protein, used as stem cell marker) expression and their colony morphology completely in 4–6 days in the absence of feeder cells and leukemia inhibitory factor (LIF). From this initial screen, 28 compounds were found to maintain colony morphology and GFP expression of OG2-mES cells. From these initial hits, members of the 3,4-dihydropyrimido[4,5-d]pyrimidine chemical class maintained the expression of multiple mES cell-specific markers. SAR for this class of compounds showed that bulky substituents are well-tolerated at the R^1 position, whereas the R^2 position tolerates only a methyl group. In addition, the 3,6-substitution pattern on the phenyl ring at the R^3 position was found to be critical for activity (Figure 12). This study led to the identification of pluripotin (**119**; SC1) displaying potent activity in the self-renewal assay ($EC_{50} = 1\ \mu M$) along with low cellular toxicity ($EC_{50} > 30\ \mu M$). Extensive mechanistic studies revealed that SC1 acts by inhibition of ERK-1 and RasGAP-dependent signaling pathways. This molecule represents the first member of a new class of agents that are dual inhibitors of a protein kinase and a small GTPase-activating protein. SC1 represents a useful pharmacological tool to study the molecular mechanisms that control stem cell self-renewal and differentiation.

Annulation of Primary Amines with Resin-Bound Bis-electrophiles. Amine derivatization is widely used to create chemical libraries for general screening or establishing SAR in a lead series. Over the past decade chemistries have focused on preparing acyclic derivatives through the reaction

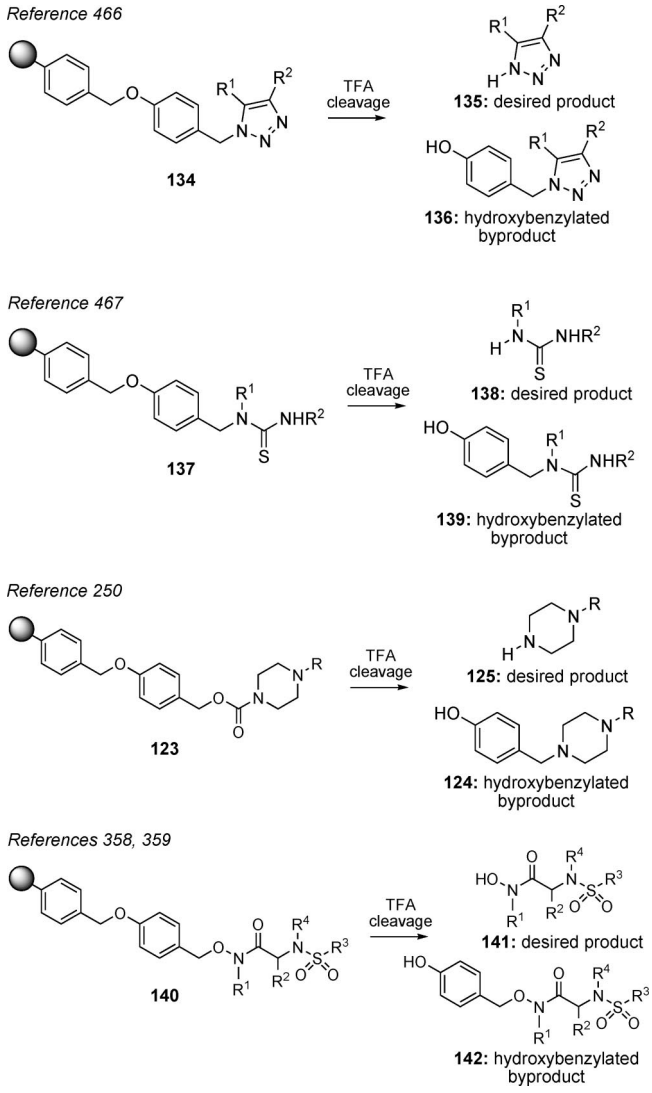


Figure 14. Quinone methide-derived byproducts from Wang resin cleavage.

of amines with acid and sulfonyl chlorides, isocyanates, and aldehydes (reductive amination) to give amides, sulfonamides, ureas, and higher order amines. The group at Adolor previously reported on a conceptually new approach to prepare cyclic derivatives from primary amines and resin-bound haloalkyl esters in a single step.[465] The reaction of primary amines with bis-electrophiles was a second reaction manifold developed to give aza-annulated derivatives (Figure 13).[250] Bis-electrophile **122** was constructed via the reaction of diethanolamine and activated carbonate Wang resin **120**. Microwave irradiation of amines and reagent **122** in NMP as solvent at 160 °C followed by TFA cleavage furnished monosubstituted piperazines **125**. Products **125** were contaminated, however, with up to 50% of the hydroxybenzylated byproducts **124**. Byproducts **124** presumably arise via anomalous cleavage of the benzyl ether bond through which the *p*-hydroxybenzyl alcohol linker is attached to resin and formation of quinine methide. This reactive species is trapped by the **125** to yield **124**. A survey of literature revealed several other cases of hydroxybenzylated byproducts formed upon Wang resin cleavage (Figure 14).[359,466,467] In the present case (Figure 13), switching to little used α-methylbenzyl (AMB)[468] carbonate resin **126** solved this byproduct issue. Preparation of reagent **128** from **127** followed by amine annulation and cleavage gave piperazines **125** in good yield and free of **124** (**128** → **129** → **125**). Analogous reagents **130** and **131** were prepared, and annulation of primary amines produced diazaspirocycles **132** and **133**.

Simultaneous Solid-Phase Synthesis. Quinoxalinone and benzimidazole cores are attractive privileged scaffolds with demonstrated activity against various enzymes and receptors. Kou and co-workers[196] described a strategy where the two distinct scaffolds are elaborated simultaneously; two scaffolds per bead are functionalized at one time (Figure 15). In early studies directed toward finding new synthetic routes to fluoroheterocycles,[469] it was discovered that the S_NAr reaction of resin-bound amines **143** with 6-nitro-2,3,4,5-tetrafluorobenzoic acid **144** proceeds to give resin **145**, where each bead formally displays a 1:1 mixture of regioisomers (**145a**) and (**145b**) after decarboxylation. The fluorine atoms para to the nitro group (**145a**) and ortho to the nitro group in (**145b**) are activated for a second S_NAr amine displacement to give resin **146**. Nitro group reduction was accomplished using 2 M $SnCl_2 \cdot 2H_2O$/2 M *N*-methylmorpholine (NMM) in DMF at ambient temperature for 12 h (**146** → **147**). Condensation of resin **147** possessing the two distinct regioisomers with aldehydes followed by cyanoborohydride reduction (**147** → **148**) and TFA-mediated cleavage processed simultaneously a library of benzimidazole and quinoxalinone analogs in approximately a 1:1 ratio (**148** → **150/151**). The IRORI system in a 4 × 5 × 6 × 2 array containing 3 substituent diversity points and 2 scaffold diversity elements was employed in the 240-membered library construction.

Multicomponent Condensations. Ilyin and co-workers describe the postfunctionalization of a set of tricyclic compounds **153** created by Ugi four-component condensation (Ugi 4-CC) followed by intramolecular Diels–Alder reaction (IMDA; Figure 16).[159] In an effort to produce isoindol-1-ones by H_3PO_4-promoted dehydrative aromatization, the authors experienced an unexpected rearrangement. Treatment of **153** with 85% H_3PO_4 at 80–100 °C for 2 h led to natural product-like tricyclic bis-lactam lactones **158**. Recrystallization of the products from methanol produced diastereomerically pure compounds **160–163** in 60–70% yields. A tentative mechanism for the diastereoselective production of the lactones was proposed. It is hypothesized that the heterolytic disruption of the C6–C7 bond is assisted by the C3-carboxamide side chain leading to the new lactam ring and hydrolytically prone cyclic enol ether moiety **159a**. The cyclic enol ether is then opened in an acid-promoted process generating the C-3a tertiary carbocation **159b** which is intercepted by the C-7a carboxamide side chain to give the iminolactam **159c**. Elimination of an amino fragment through hydrolysis of the protonated iminolactam leads to production of the bis-lactam lactone products. From this proposed mechanism, it was further hypothesized that treatment of the Ugi 4-CC/IMDA products **153** with a Lewis acid in nonpolar solvents should yield the desired isoindol-1-ones. This was confirmed upon treatment of compound **164** with trifluo-

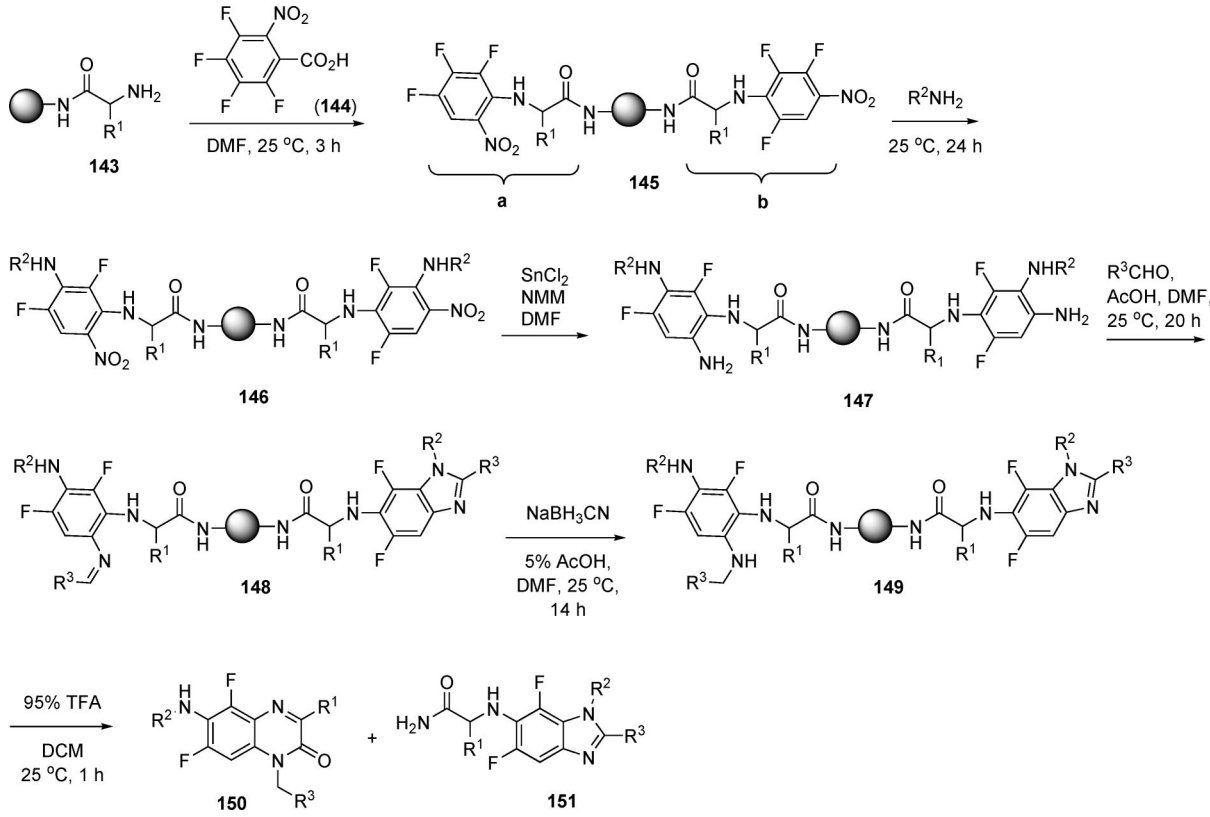


Figure 15. Simultaneous solid-phase processing of two heterocycles.[196]

roborane etherate which furnished product **165** by dehydrative aromatization.

An improved synthesis of dibenz[*b*,*f*][1,4]oxazepines **171** using Ugi 4-CC followed by microwave-assisted S_NAr cyclization, using 2-chloro-5-nitrobenzoic acid **168** in place of the previously employed 2-fluoro-5-nitrobenzoic acid, was reported by Xing and co-workers (Figure 17).[398] Optimization of the reaction time and temperature in the synthesis of compound **172** resulted in an almost quantitative yield of the desired product. The optimized reaction conditions were then employed in the preparation of several analogs in excellent yield **173**–**175** (81–96% yield). In an extension of the research, 2-chloro-5-nitrobenzaldehyde **168** and various benzoic acids were used to prepare compounds of general structure **178**. However, the yields of the desired compounds were greatly reduced. This was due to an inefficient production of the intermediates **177** prepared from the Ugi 4-CC. The low yield of the condensation was attributed to the production of an electron-deficient imine which is not easily protonated by the carboxylic acid. To validate this assertion, the Ugi 4-CC reactions with **168** and benzoic acids of varying pK_as were performed. It was determined that decreasing the pK_a of the benzoic acid resulted in improved overall yields. Intramolecular amidation (*N*-arylation) preparation using the amides of general structure **171** was also conducted. Attempts to prepare the 2-oxindole **184** from **183** using copper catalysts were unsuccessful. However, using palladium acetate and BINAP, the transformation was carried out in good yield. Further optimization of the reaction conditions led to almost quantitative production of the desired 2-oxindoles. Application of these reaction conditions produced a series of novel compounds **185**–**187** in excellent yield.

New four- and five-component Ugi reactions using metalated ketimines as intermediates were reported (Figure 18).[350] Simoneau and co-workers condensed nitriles **188/190** with organometallic reagents **189/191** to form metalated ketimine species **192**. It was reasoned that protonation of the metalated species might provide a route to *N*-unsubstituted ketimines **193** for the synthesis of diamides **194**, as previous studies have shown that the use of preformed imines in Ugi reactions is higher yielding than those performed with imines formed from ammonia–aldehyde condensations. The metalated imines were protonated with methanol before treatment with carboxylic acid and nitrile components to produce the diamides **197**–**199** in 45–70% yield. Reaction of the metalated imines **192** with a methanolic solution of carboxylic acid and a substituted amine led to an amine–imine interchange (**192** → **195**). The equilibrium of the interchange was expected to favor formation of the substituted imines **195**. Reaction of **195** with isonitriles formally giving rise to an Ugi 5-CC process generated substituted diamides **196**. However, this procedure resulted in an 85:15 mixture of **196** to the corresponding four-component products **194**. Attempts to remove the ammonia generated as a byproduct from the reaction in situ were unsuccessful, but separation of the mixtures was easily achieved by flash chromatography to give **200**–**202** in good yield.

The use of ammonia as the amine component of Ugi 4-CC reactions is not well tolerated. Sung and colleagues reported

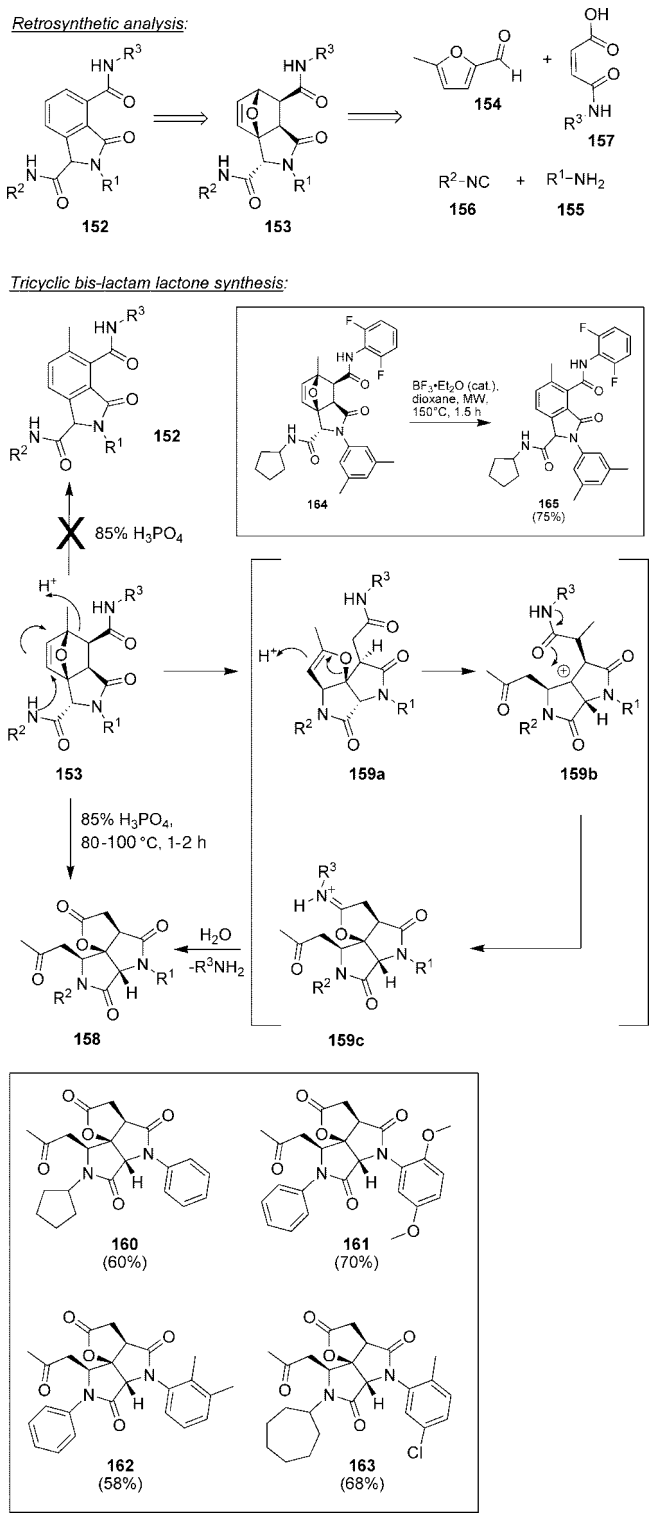


Figure 16. Multicomponent condensation to bis-lactam lactones.[159]

the successful use of 2-nitrobenzylamine **203** as an ammonia equivalent in the reaction (Figure 19).[363] In this study, the authors describe an efficient one-pot, two-step process in the generation of diamides **208** from four components, **203**–**206**. The free base of the benzylamine was required for successful transformation as use of the hydrochloride salt resulted in P-3CR products. Irradiation of the Ugi-4CC products **207** afforded the desired compounds **209**–**213** in 68–93% yield.

In a typical Ugi 4-CC reaction, a primary amine plays multiple roles during the reaction sequence, i.e. simultaneous acylation, alkylation, and double proton loss. The use of secondary amines in the Ugi 4-CC has been reported, but the reaction requires 2 equiv of the amine to the other reagents. Giovenzana and co-workers described a novel and efficient extension of the Ugi 4-CC reaction whereby the 2 equiv of secondary amine is contained in the same molecule (Figure 20).[109] When piperazine was employed as the amine, the desired compounds **219**–**221** were prepared in 30–95% yield. The low yield observed for compound **221** was attributed to the formation of a crowded, fully alkylated iminium ion intermediate. Extension of the study using a variety of diamines was performed. The use of acyclic diamines generated compounds such as **222** and **223**. It was noted that the good yield observed for compound **223** was unexpected as rearrangement of the intermediate involves an 11-membered metacyclophane. Compound **224** is a known vasodilator and is traditionally prepared in a four-step procedure starting from piperazine. Using the new methodology, a high yield preparation of **224** was achieved via a one-pot single-step procedure.

Natural Product-Based and DOS Libraries. Mitchell and Shaw[271] emphasize the need for the efficient preparation of compounds with different core atom connectivity within the same library resulting in small molecule collections with extensive skeletal and stereochemical diversity. These types of libraries are believed to offer the greatest discovery opportunity when applied to chemical biology screening approaches.[470] These researchers devised a strategy to produce complex libraries using a minimum of chemical manipulations from a single solid-phase starting point by exploiting bond construction between proximal ester/azide functional groups. An enantioselective solid-phase variant of the Suga–Ibata reaction[471,472] was developed as a platform to incorporate these two functionalities into a single template (Figure 21). Enantioselective addition of resin-bound, methoxy-substituted oxazoles **225** to aromatic aldehydes **226** was carried out using chiral complex **227** furnishing esters **228**. High diasteroselectivity (>94%) was achieved. The required azido group was introduced by using either *ortho*-azido- or *ortho*-azidomethyl-substituted aromatic aldehydes in the Suga–Ibata reaction or by alkylating esters **228** with azide substituted benzyl or allyl halides. Michael addition was also possible using phenyl vinyl sulfones and *tert*-butyl acrylate. Once the ester/azide functionality was in place, intermediates **230a**,**b** were subjected to a Staudinger-type reduction resulting in the formation of spiro- and fused lactams. By way of demonstration, the key reductive/cyclization sequence was used to generate all four chiral lactam cyclization products **231**–**234** under a single set of conditions in >95% conversion. Lactam products were optionally *N*-alkylated (**231**–**234** → **235**–**238**) to add additional diversity to the molecules. Methyl esters **230a** may also be converted to amides **239** generating an additional series of related structures. A pilot library of 529 analogs was completed using the IRORI X-microkans.

Aigialomycin D **240** is a representative member of a family of resorcyclide natural products, which are potent kinase

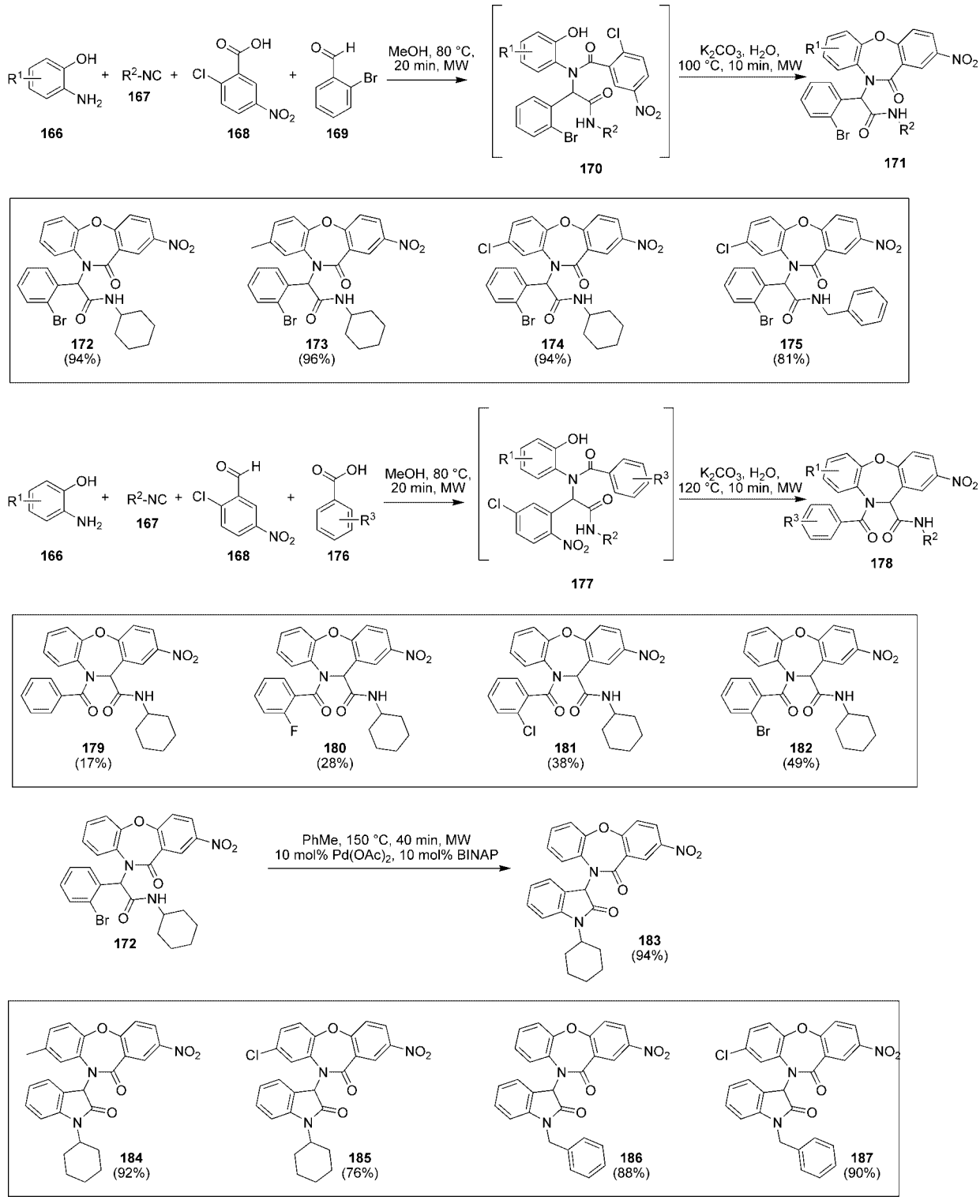


Figure 17. Four-component reaction to dibenzoxapines.[398]

inhibitors. Barluenga and co-workers[19] envisioned a solid-phase approach to this class of natural products amenable to the preparation of libraries extending beyond the existing natural products (Figure 22). The key point in their approach is the use of benzyl-disposed thio- or selenoether intermediate **241** to facilitate alkylation chemistry and provide a point of attachment to resin. The macrocycle would be formed by a metathesis reaction, and the diol would then be installed from a *trans*-epoxide obtained via Sharpless asymmetric epoxidation. The authors achieved several solution-phase routes to the macrocyclic core and generated analogs of Aigialomycin D. In the interest of streamlining the synthesis and to facilitate the preparation of libraries, the synthesis was optimized on the solid phase. The phenyl selinide in **241** was replaced by a resin-bound thioether linkage (**246** → **247** → **248**). Notably, the ring closing metathesis failed under optimized solution-phase conditions: 80

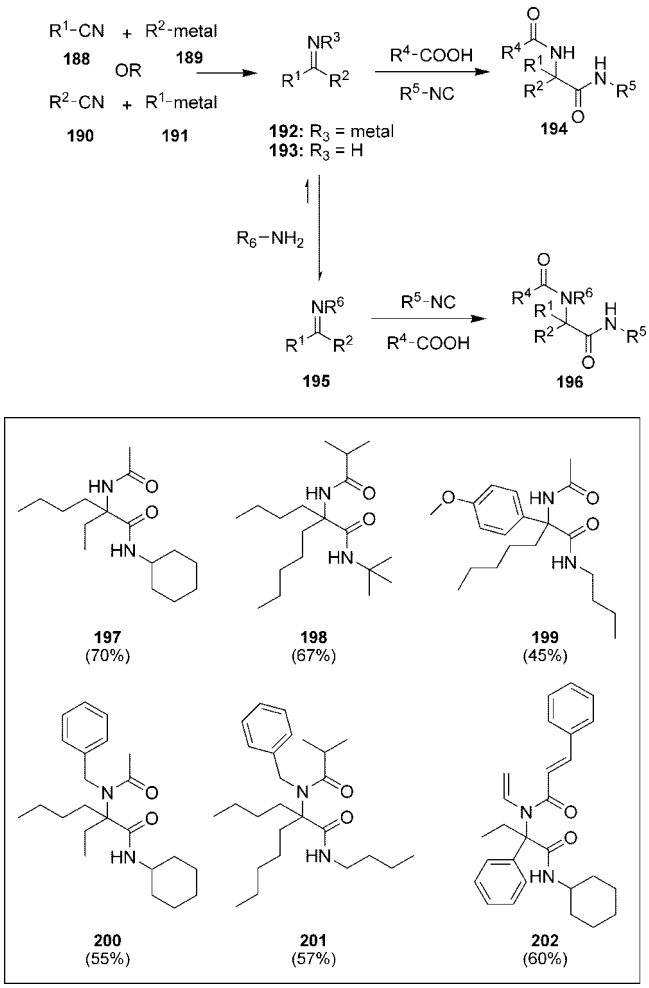


Figure 18. Ugi 4- and 5-component condensations.[350]

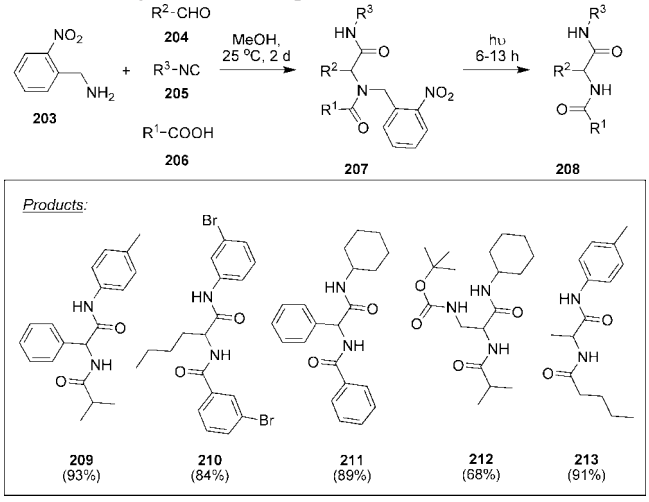


Figure 19. Ugi 4-CR with "ammonia" equivalent.[363]

°C for 12 h using second generation Grubbs catalyst. Successful solid-phase conditions required heating in a microwave at 120 °C for 75 min in CH_2Cl_2 and adding catalyst in three 6 mol% portions (**248** → **249**). Compounds **250a**,**b** were released from the resin using both oxidative elimination (H_2O_2/hexafluoroisopropanone) and free radical cleavage (Bu_3SnH/AIBN).

Kumagi and co-workers[200] described an intramolecular cyclization strategy directed towards the generation of densely

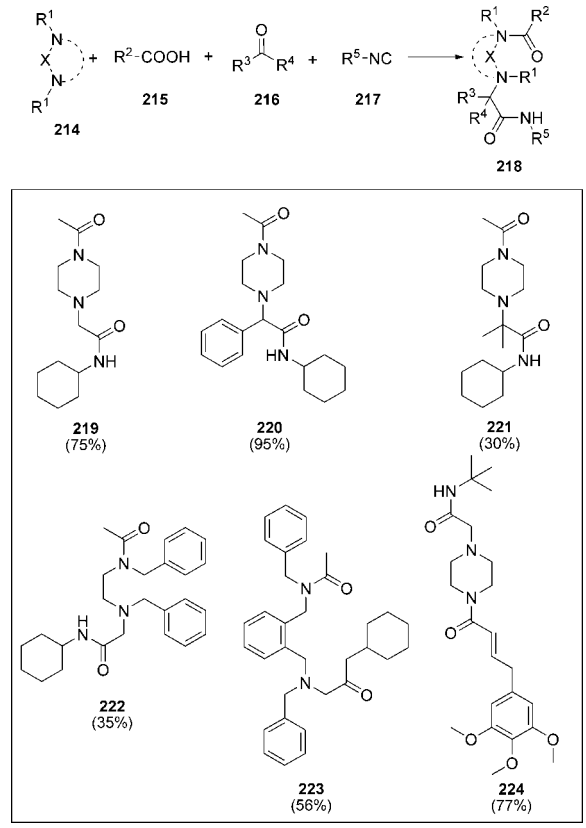


Figure 20. Modified Ugi 4-CR with diamine.[109]

functionalized amino alcohols (Figure 23). The Petasis three-component boronic acid Mannich[473] reaction was employed followed by amine propargylation to yield β-amino alcohols **256**. The resulting β-amino alcohols bear handles for subsequent elaboration. A series of skeletal diversification reactions were demonstrated using the functionalized β-amino alcohol **257**. Palladium-catalyzed cycloisomerization resulted in cyclopropyl ring opening to afford triene **258** via a β-hydride elimination/reductive elimination sequence.[474] Cycloisomerization using a ruthenium catalyst results in a [5+2] reaction to afford cyclic diene **259** via a cyclopropyl ring opening/reduction elimination sequence.[475] Both reactions proceed to afford a single diastereomer. Pauson–Khand reaction of **257**, $Co_2(CO)_8$/trimethylamine *N*-oxide,[476] provided azabicyclo derivative **260**. Enyne metathesis of **257** provided diene **261** which underwent Diels–Alder cycloaddition chemistry to generate **264**. Electrophilic activation of the alkyne functionality in **257** by gold salts led to morpholine derivative **263**. Treatment of **257** with NaH gave lactone **262** which may be further elaborated into a tricyclic diene **265**, or other fused tricyclic [5+2] products, fused tricyclic enones, and bicyclic dienes in good yields. A range of amines were used in the Petasis reaction to produce variations in the initial scaffold. These molecules undergo the same skeletal diversification to provide corresponding products, demonstrating an efficient approach to skeletally distinct compounds in good yield with high diastereoselectivity. The diversification reactions described are mild and sufficiently chemoselective to permit the use of complex building blocks. This DOS pathway provides densely substituted stereochemically defined diverse small molecules.

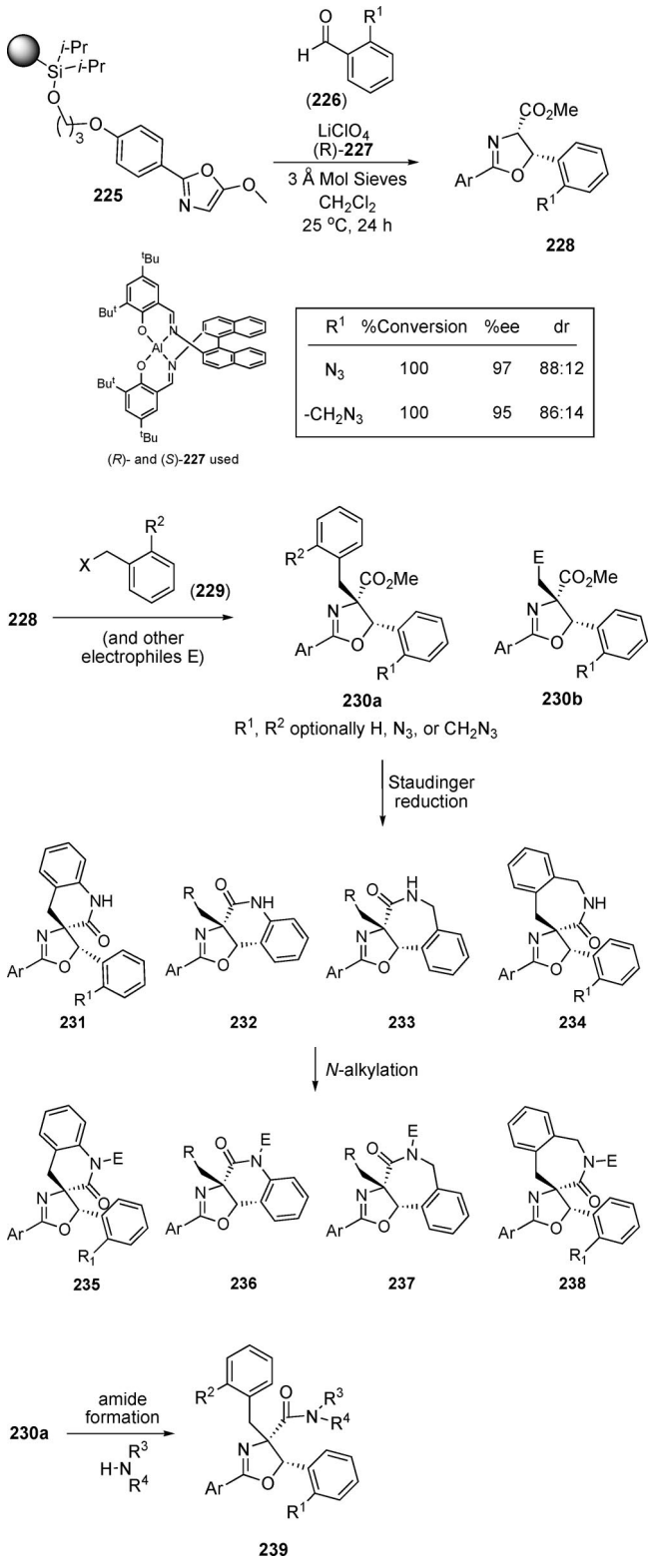


Figure 21. DOS library based on Suga–Ibata/Staudinger reactions.[271]

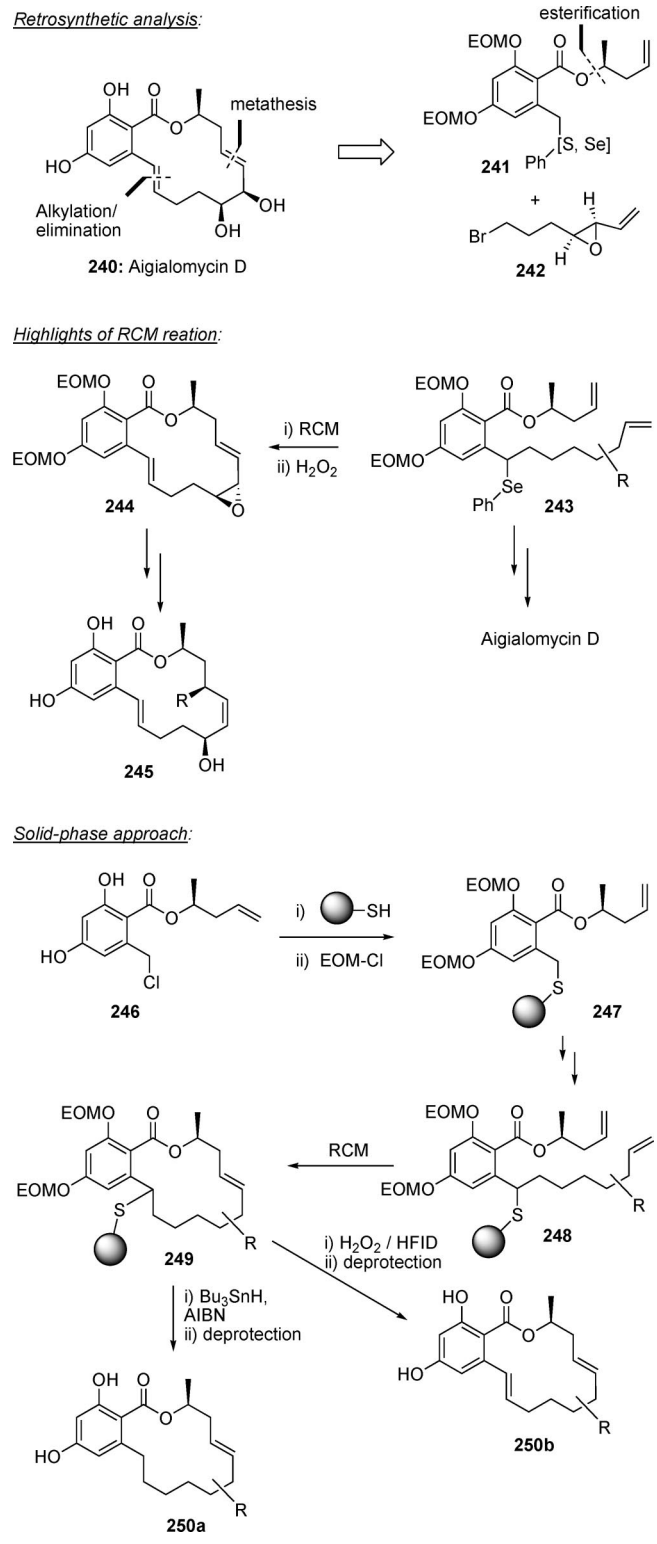


Figure 22. Aigialomycin D analog library.[19]

Looper and co-workers[240] emphasize the benefit of macrocyclic, conformationally restricted small molecules with regard to assay performance and outcome.[477] Their approach towards the synthesis of this class of molecules is to use the Cu-catalyzed cycloaddition of azides with alkynes as the penultimate macrocyclic ring forming reaction (Figure 24). This macrocycloaddition strategy deployed in the context of a modular system enabled the facile variation of stereochemistries and substituents. Three interchangable modules were established to incorporate diversity: bifunctional isocyanate/carboxylic acids **267**, amino azides **266**, and propargylamines **268**. To exemplify this approach, optically active isocyanate **272** was coupled with either amino azides **266** or propargylamines **268**, followed by selective ester deprotection and coupling to the appropriate third

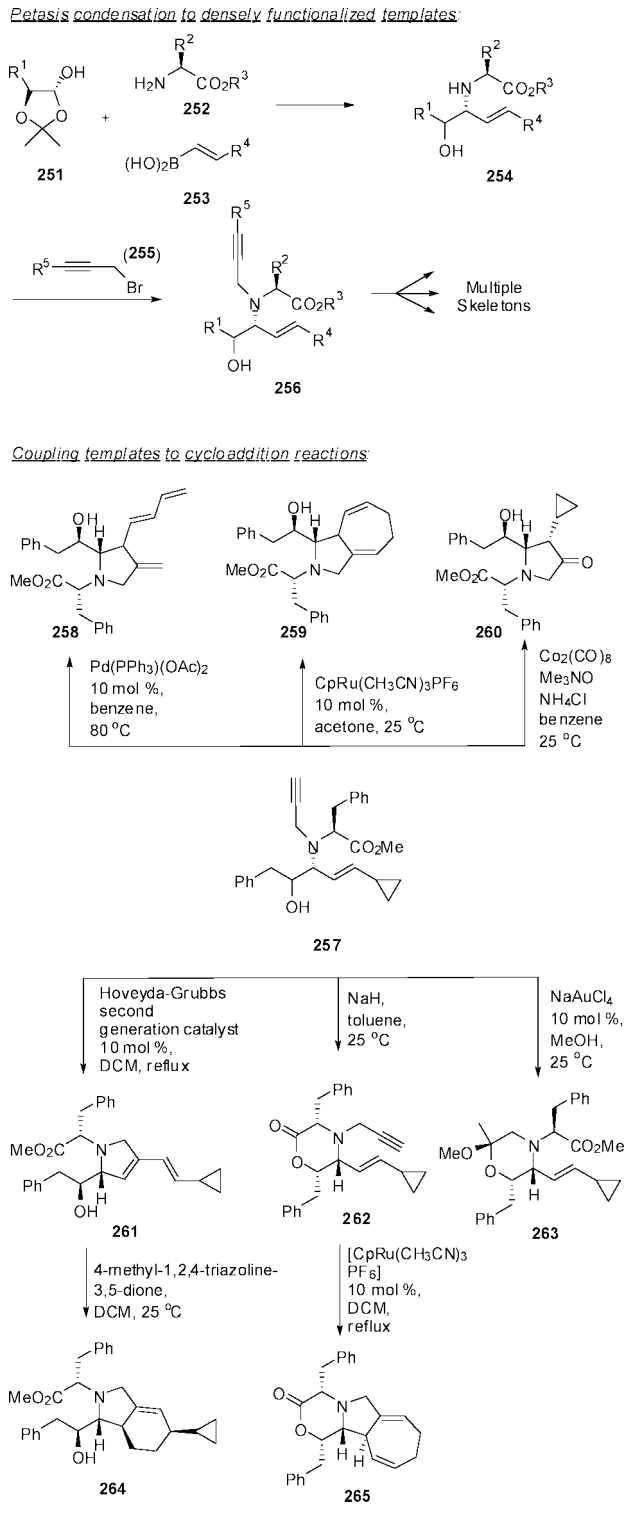


Figure 23. DOS libraries coupling Petasis condensation and cyclization reactions.[200]

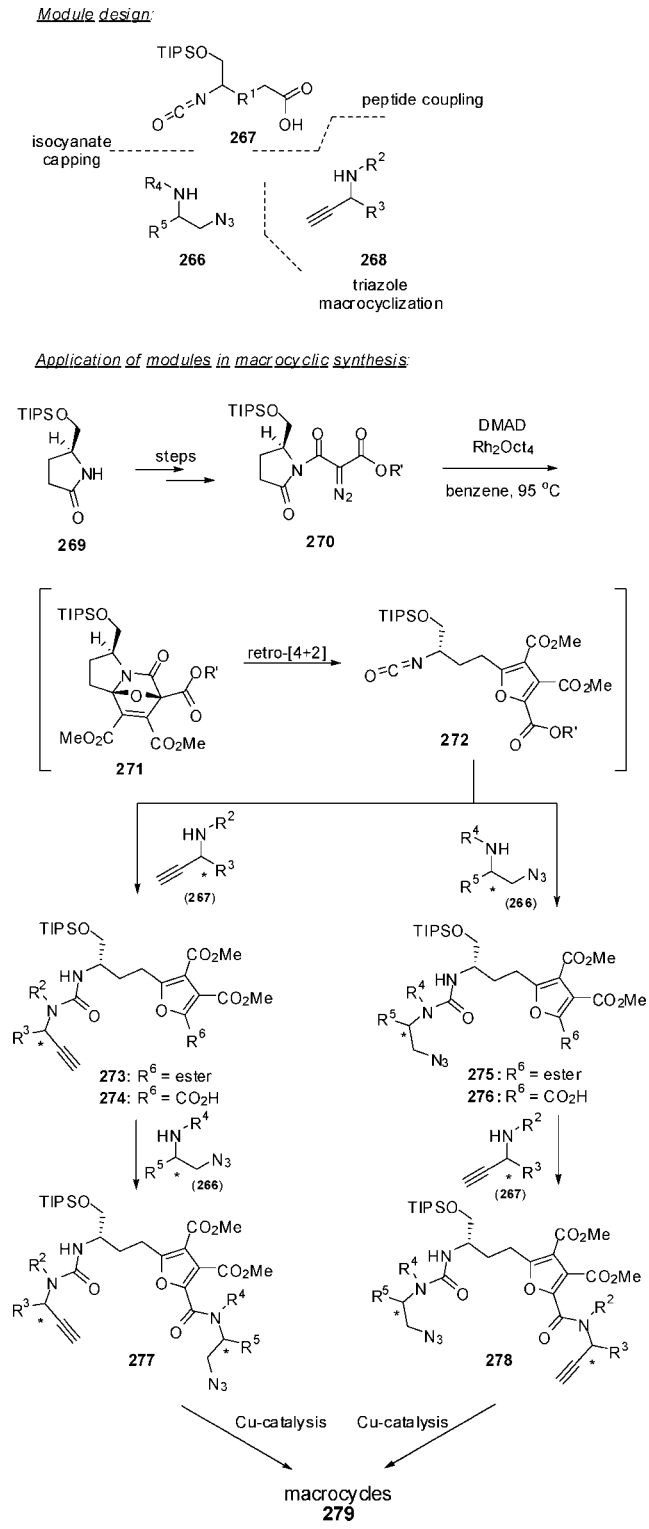


Figure 24. Modular approach to a macrocyclic DOS library.[240]

module to afford macrocyclic precursors **277** and **278** (**272** → **273** → **274** → **277**; **272** → **275** → **276** → **278**). The critical Cu(I)-catalyzed macrocycloaddition (**277**/**278** → **279**) reactions were optimized, and toluene was found to be the solvent of choice to minimize the inclusion of Cu within the macrocycle. The stereochemistry within the macrocycle was largely indeterminate of the macrocycloaddition outcome, and all the stereoisomers of acyclic azido alkynes participated in the macrocyclization affording macrocycles in good isolated yields (Figure 25). The diversity of the isocyanate module **267** was expanded to include other cycloaddition–cycloreversion sequences.

Methodology which offers flexibility for the synthesis of small molecules as well as more complex natural productlike molecules was sought by Masse and co-workers.[262] To this end, the researchers investigated the largely unexplored cycloaddition

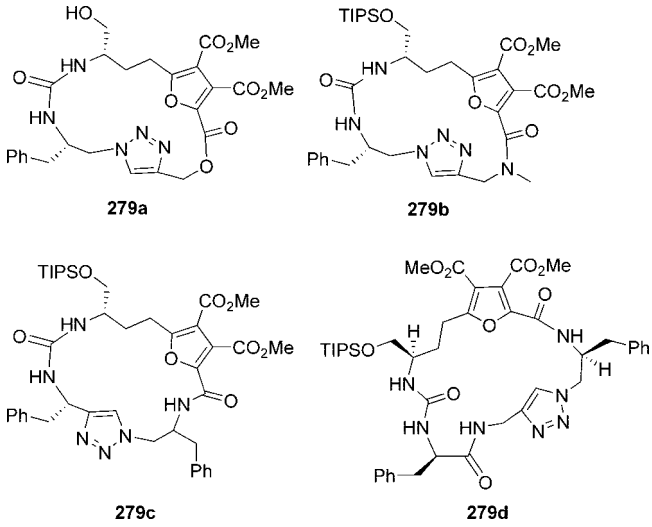
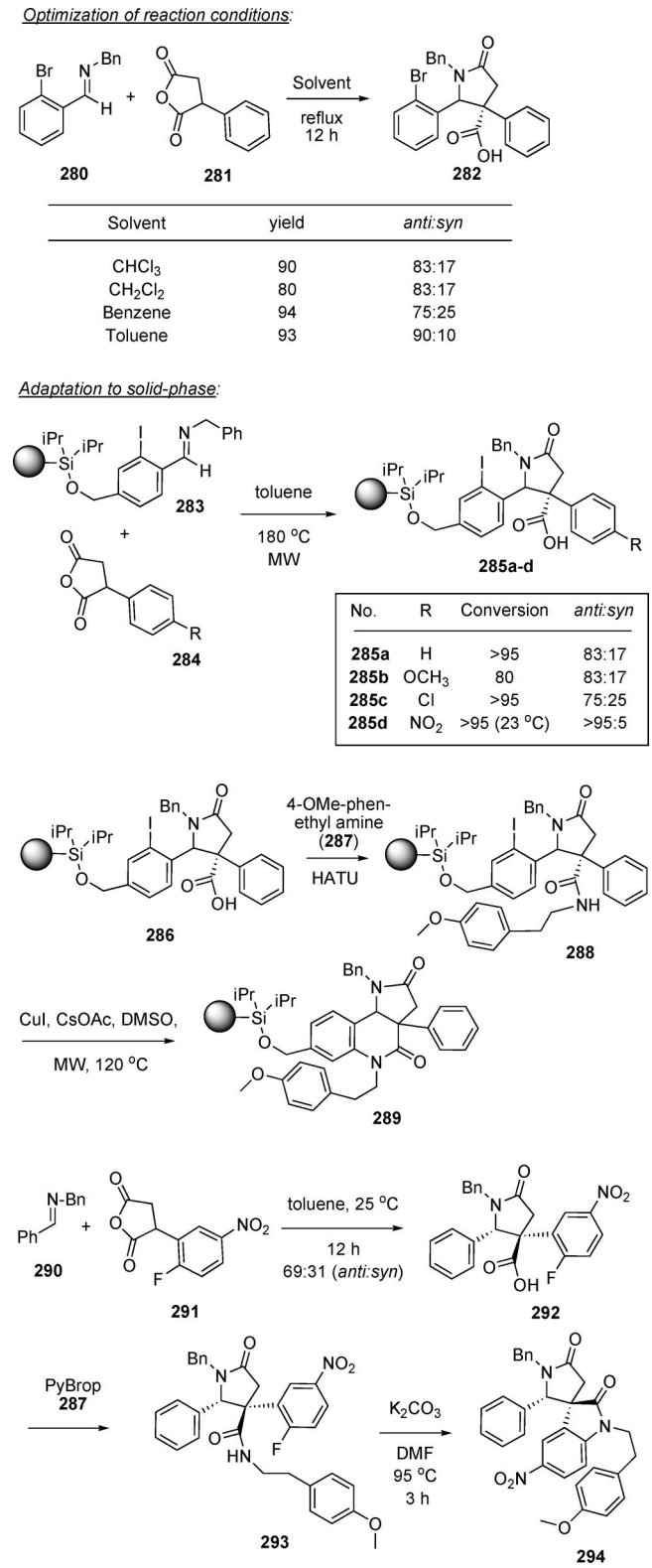


Figure 25. Macrocycles via a modular approach.[240]

reaction between imines and cyclic anhydrides[478] to generate lactams (Figure 26). Initial research examined selectivities in the reaction of the imine **280** derived from benzyl amine and bromobenzaldehyde and phenyl succinic anhydride **281**. The highest yield and selectivity was found using toluene as solvent. In this and subsequent reactions with other substrate pairs, the *anti* product was obtained as the major product as evident from NOE experiments. Translation of the chemistry from the solution to solid phase required a higher temperature to secure the cycloaddition reaction. The reactions on the solid phase were performed under microwave irradiation, albeit with reduced diastereoselectivity. A study of the effect of *para*-substitution in the phenyl succinic anhydrides **285a–d** revealed that methoxy impeded the reaction slightly, whereas inductively electron-withdrawing substituents had little effect on the conversion or diastereoselection. Notably the reaction of *p*-nitrophenyl succinic anhydride **285d** resulted in a high conversion and high selectivity at room temperature. Tricyclic products **289** were produced in high yield from resin-bound lactam acid **285a** by first generating its amide **288** and then reacting **288** with a stoichiometric amount of ligandless CuI to cyclize the aryl iodide (**288** → **289**).[479] The iodide used as the corresponding aryl bromide did not react. Spirobicyclic lactam was obtained from lactam acid **292** derived from 2-fluoro-5-nitrophenyl succinic anhydride **291** and imine **290**. Acid **292** was converted to the amide **293**, which cyclized to form the spirocyclic oxindole **294** in the presence of K_2CO_3 in DMF. The chemistry was used to produce a library of 570 structurally diverse products for biological screening.

Libraries Using Fluorous Technology. (-)-Dictyostatin is a marine macrolactone that has potent anticancer activity. Its stereostructure was confirmed by total synthesis accomplished by the Paterson and Curran groups in 2004. Further biological testing on the synthetic sample shows that dictyostatin has equal or better activity against the paclitaxel-resistant cell line versus open-chain analog discodermolide, radiolabeled paclitaxel, or epothilone B. The Curran group modified their total synthesis route (over 20 steps) and designed a fluorous mixture synthesis (FMS) to make (-)-dictyostatin and three C6 and C7 diastereomers

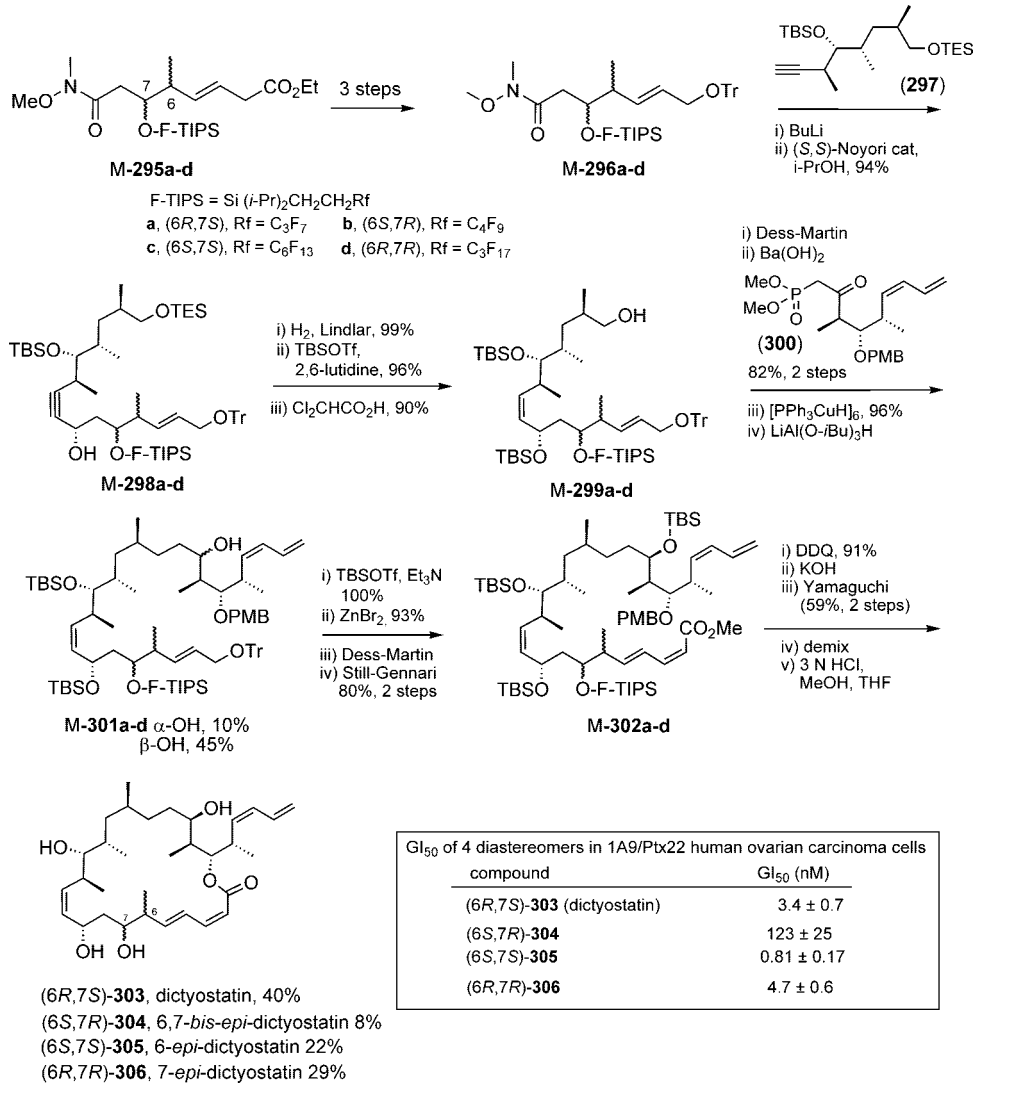


Solvent	yield	*anti:syn*
$CHCl_3$	90	83:17
CH_2Cl_2	80	83:17
Benzene	94	75:25
Toluene	93	90:10

No.	R	Conversion	*anti:syn*
285a	H	>95	83:17
285b	OCH_3	80	83:17
285c	Cl	>95	75:25
285d	NO_2	>95 (23 °C)	>95:5

Figure 26. Structurally diverse spirobicyclic lactams.[262]

for SAR studies (Figure 27).[98] Instead of making those diastereomers in four parallel multistep syntheses, the FMS is able to produce those compounds in a single set. This represents a good example of FMS for making complex molecules and analogs without a proportional increase in work. At the premix stage, a set of four enantiopure



GI50 of 4 diastereomers in 1A9/Ptx22 human ovarian carcinoma cells

compound	GI50 (nM)
(6*R*,7*S*)-**303** (dictyostatin)	3.4 ± 0.7
(6*S*,7*R*)-**304**	123 ± 25
(6*S*,7*S*)-**305**	0.81 ± 0.17
(6*R*,7*R*)-**306**	4.7 ± 0.6

Figure 27. Fluorous mixture synthesis of (-)-dictyostatin and stereoisomers.[98]

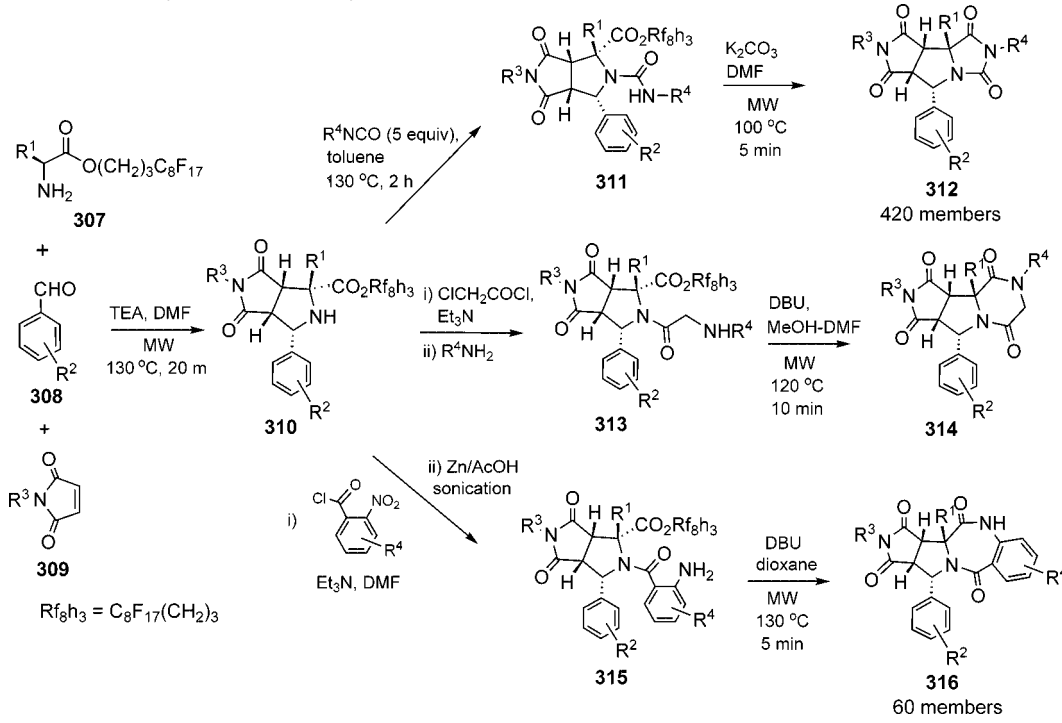


Figure 28. Fluorous DOS of novel heterocyclic scaffolds.[419,420]

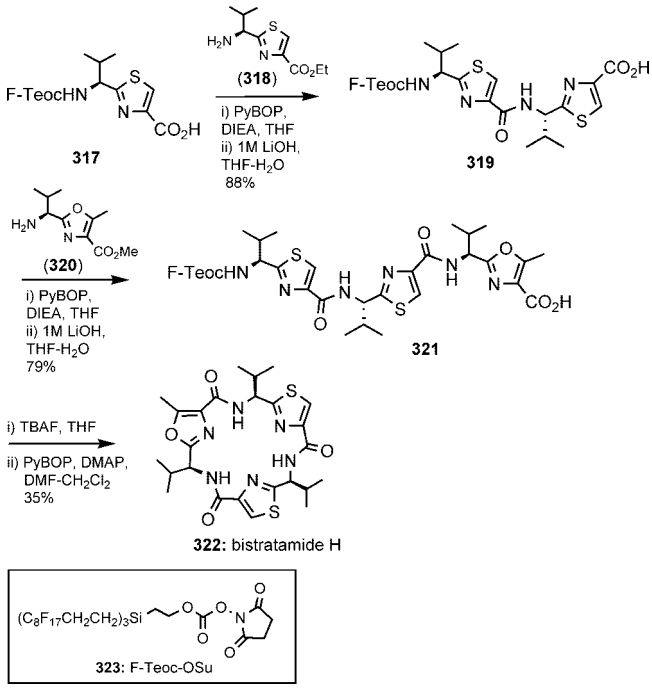


Figure 29. Synthesis of bistratamide H using the F-Teoc tag.[282]

alcohols with chiral centers at C6 and C7 were individually tagged with a set of four fluorous TIPS-type silanes containing C_3F_7, C_4F_9, C_6F_{13}, and C_8F_{17} tags, respectively. The coded alcohols were then converted to fluorous esters **295a**–**d**. These four esters were blended in a ratio of 1.5:1:1:1.5, and then, the resulting mixture M-**295a**–**d** was converted to M-**296** in three steps of FMS. The products from these reaction mixtures were purified by standard flash chromatography without demixing. M-**296** was coupled with alkynyllithium and then reduced by (*S*,*S*)-Noyori catalyst to give M-**298**. The alkyne group of M-**298** was reduced to the *cis*-alkene by Lindlar hydrogenation, and the resulting secondary hydroxy group was protected with the TBS group. The cleavage of TES with dichloroacetic acid gave M-**299**. Dess–Martin oxidation of the primary alcohol followed by Horner–Wadsworh–Emmons coupling with **300** gave the α,β-unsaturated ketone. The reduction of C17–C18 alkene with Stryker's reagent followed by reduction of the C19 ketone with LiAl(O*t*-Bu)$_3$H gave β-alcohol M-**301** as the major product which was isolated by silica gel chromatography of the mixture. TBS protection of the C19 hydroxy group, removal of the trityl group with $ZnBr_2$, oxidation of the allylic alcohol with the Dess–Martin reagent, and then Still–Gennari reaction provided (*E*),(*Z*)-diene M-**302**. The removal of PMB with DDQ, basic hydrolysis of the conjugated ester, followed by macrolactonization under Yamaguchi conditions gave a mixture of major (2*Z*),(4*E*) and minor (2*E*),(4*E*) macrolactones. Demixing of the final mixture was accomplished by a preparative F-HPLC to provide the four individual components. Desilylation using 3 N HCl in MeOH afforded dictyostatin (6*R*,7*S*)-**303** and the other three C6,C7-*epi*-dictyostatin

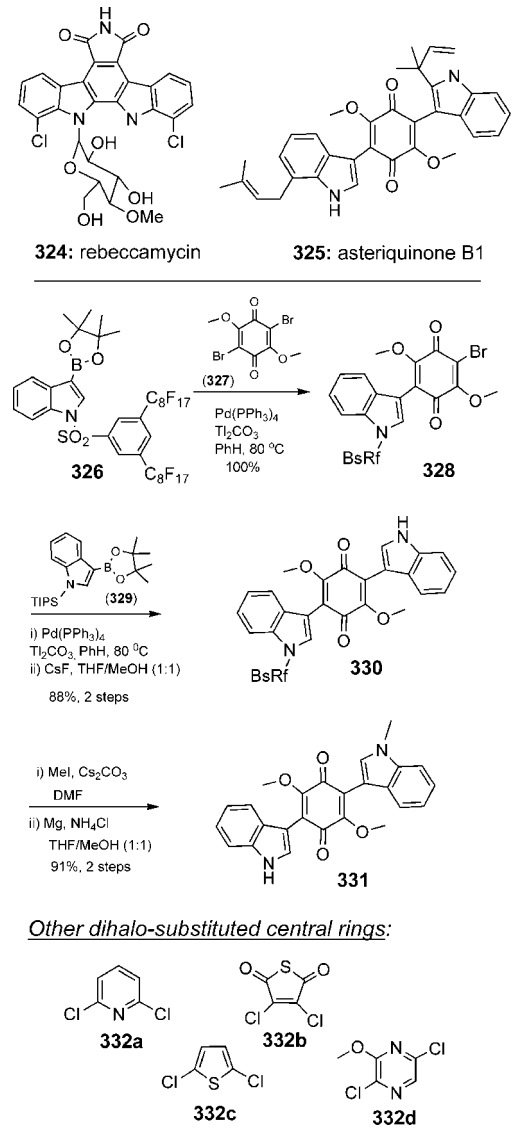


Figure 30. Double Pd-catalyzed coupling for making bisindoles.[185]

diastereomers after HPLC purification. These four compounds were assayed against human ovarian carcinoma cells for the antiproliferative effects. The bis-*epi*-diastereomer (6*S*,7*R*)-**304** was found to be less active than the other isomers, while the monoepimer (6*R*,7*R*)-**306** was found to be equipotent to dictyostatin (6*R*,7*S*)-**306**, and another monoepimer (6*S*,7*S*)-**305** was found to be four times more potent.

Zhang and co-workers at Fluorous Technologies developed a [3+2] cycloaddition/detag/cyclization protocol for making novel heterocyclic library scaffolds (Figure 28).[419] This fluorous-based synthetic method has the following features: (1) all the intermediate purifications were facilitated by fluorous solid-phase extraction (F-SPE) without conducting flash chromatography, (2) each reaction step could be closely followed by LC-MS analysis, and (3) the libraries were produced by FMS with high synthetic efficiency. The key intermediate **310** for DOS was made by one-pot [3+2] cycloaddition of fluorous aminoester **307** with slightly excess (1.2–1.5 equiv)

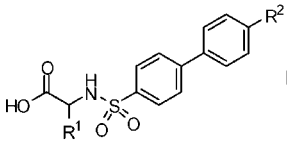
aldehyde and alkene. The reaction was conducted under conventional or microwave heating to give highly stereoselective bicyclic pyrrolidine derivative **310**. The cycloaddition product was easily separated by F-SPE. Its structure was confirmed by X-ray crystal structure analysis. The cycloaddition product was then used for DOS of hydantoin-, piperazinedione-, and benzodiazepine-fused heterocyclic scaffolds **312**, **314**, and **316**. Each of these three scaffolds has four stereocenters on the central pyrrolidine ring and up to four points of diversity (R^1–R^4). These compounds resemble the structures of some known biologically active compounds. The structure of compound **312** is similar to tricyclic thrombin inhibitors, the structure of compound **314** is similar to diketopiperazine-based inhibitors of human hormone-sensitive lipase, and compound **316** contains a privileged benzodiazepine moiety which exists in numerous pharmaceutically interesting compounds. Synthesis of scaffold **312** was accomplished by reaction of **310** with excess phenylisocyanate in the presence of a catalytic amount of *N,N*-4-dimethylaminopyridine (DMAP) to give urea **311**. Compound **311** was then mixed with K_2CO_3 and heated under microwave for fluorous tag cleavage and formation of hydantoin-fused product **312**. Piperazinedione-fused tricyclic scaffold **314** was synthesized by acylation of **310** with chloroacetyl chloride followed by chlorine displacement with a primary amine to form **313**. The detag/cyclization reaction was promoted by 1,8-diazabicyclo[4.3.0]non-5-ene (DBU) under microwave heating to give **314**. Synthesis of benzodiazepine-fused scaffold **316** was accomplished by a three-step post-MCR modification. *N*-acylation of **310** with 2-nitrobenzoyl chloride followed by zinc–acetic acid reduction under sonication gave compound **315**. The cyclative tag cleavage promoted by DBU produced benzodiazepinedione-fused scaffold **316**. The chemistry developed for making scaffolds **312** and **316** has been applied to FMS of compound libraries.[420] A 420-member library of scaffold **312** was produced by a 5-component fluorous mixture synthesis by incorporating 5 amino esters (R^1), 7 benzaldehydes (R^2), 4 maleimides (R^3), and 12 isocyanates (R^4). A total of 380 out of 420 final products were obtained in >90% purities. The amount of each final product was in the range of 5–30 mg. A 60-member library of scaffold **316** was prepared by a two-component FMS by incorporating 2 amino esters (R^1), 10 benzaldehydes (R^2), and 3 maleimides (R^3). A total of 58 compounds were obtained in >90% after C18 reverse-phase prep-HPLC purification.

Bistratamides are isolated from ascidians *Lissoclinum bistratum*. Bistratamides and related compounds such as didmolamides and tenuecyclamides have shown moderate cytotoxic activity, antidrug resistance, and antimicrobial properties and inhibition of the division of sea urchin embryos. Bistratamides have a unique macrolactam structure that contains amino acids, thiazole, and oxazole. The Kelly and Shin groups have developed synthetic routes to bistratamides and applied them to solid-phase synthesis. Takeuchi and co-workers developed a "heavy fluorous" 2-[tri(perfluorodecyl)-silyl]ethoxycarbonyl (F-Teoc) protecting group and employed it in the fluorous synthesis of bistratamide H (Figure 29).[282] The F-Teoc has three $C_8F_{17}CH_2CH_2$ chains with a total of 51 fluorine atoms. The high fluorine content of F-Teoc increases the partition coefficiency of Teoc-tagged intermediates from the organic reaction phase to the fluorous phase during the fluorous liquid–liquid extraction (F-LLE) with a fluorous solvent such as FC-72 (perfluorohexanes). Alternative to the F-SPE, F-LLE is also an efficient technique for purification of heavy fluorous compounds. Fluorous synthesis of bistratamide H involved the coupling of F-Teoc-tagged thiazole amino acid **317** with thiazole amino acid ester **318** in the presence of benzotriazol-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP) and *i*-Pr_2EtN. The resulting thiazole dipeptide ester was treated with 1 M LiOH aqueous solution followed by extraction of the crude product with FC-72 to afford **319**. The thiazole dipeptide **319** was coupled with the oxazole amino acid methyl ester **320** followed by hydrolysis and FC-72 extraction to give tripeptide methyl acid **321**. Cleavage of the F-Teoc protecting group with TBAF followed by the intramolecular coupling reaction and preparative TLC gave bistratamide H in 35% yield.

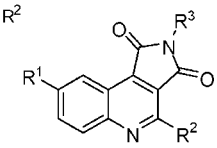
Many bisindole natural alkaloids have a unique structure where two indole units are linked through a central five- or six-membered heterocyclic ring. Rebeccamycin **324** and asteriquinone B1 **325** are the representative compounds which have antitumor and insulin receptor activator activities (Figure 30). One of the non-natural bisindole derivatives with a bisindolylpyridine skeleton also exhibits potent cytotoxity. To generate synthetic bisindole analogs for biological testing, Kasahara and Kondo developed a concise fluorous route that involves consecutive cross-coupling reactions of fluorous-tagged indolylborons with dichloro- or dibromosubstituted heterocyclic compounds.[185] The fluorous sulfonyl tag was introduced to 3-iodoindole under a basic reaction condition, followed by Pd-catalyzed borylation to give fluor ous boronate **326**. Pd-catalyzed cross-coupling of **326** with dibromosubstituted central ring **327** using Tl_2CO_3 as a base afforded the monocoupling product **328**. This compound was subjected to the second cross-coupling with TIPS-protected indolylboron **329**, followed by cleavage of TIPS to give **330**. Methylation and sequential Mg-promoted fluorous tag cleavage afforded bisindole **331**. The fluorous intermediates in the multistep synthesis were purified by F-SPE. This protocol has been used to make symmetrical and asymmetrical bisindolyl-substituted heterocycle scaffolds by double cross-coupling reactions of indolylborons with different kinds of dihalo central rings **332a–d**.

Table 1. Chemical Libraries Targeting Proteases[a]

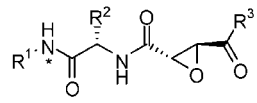
Alphabetical listing



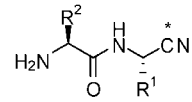
- Library 1.1
- multiple small arrays
- Xiang [393]
- aggrecanase-1 inhibitors



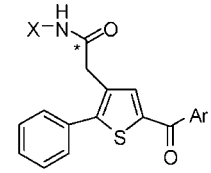
- Library 1.2
- 1231 members
- Kravchenko [198]
- caspase-3 inhibitors



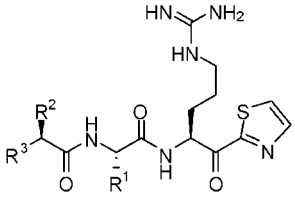
- Library 1.3
- size not defined
- Sadaghiani [332]
- cathepsin B inhibitors



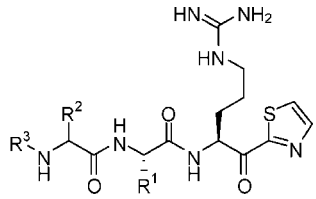
- Library 1.4
- size not defined
- Bondebjerg [31]
- dipeptidyl peptidase I inhibitors



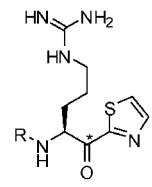
- Library 1.5
- 10 members
- Park [299]
- Botulinum neurotoxin serotype A endo-peptidase inhibitors



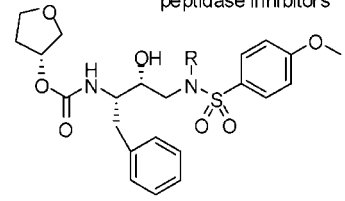
- Library 1.6
- *ca.* 24 members
- Lin [228]
- Factor XIa inhibitors



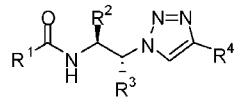
- Library 1.7
- size not defined
- Lin [228]
- Factor XIa inhibitors



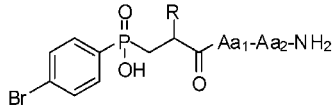
- Library 1.8
- multiple arrays
- Deng [71]
- Factor XIa inhibitors



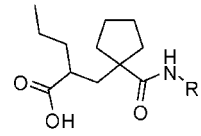
- Library 1.9
- 90 members
- Liang [225]
- HIV protease inhibitors



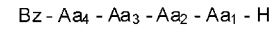
- Library 1.10
- size not defined
- Whiting [387]
- HIV type-I protease inhibitors



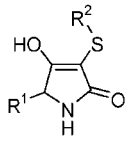
- Library 1.11
- > 10,000 members
- Devel [116]
- MMP-12 inhibitors



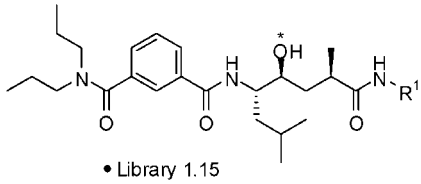
- Library 1.12
- size not defined
- Pryde [314]
- neutral endopeptidase (NEP) inhibitors



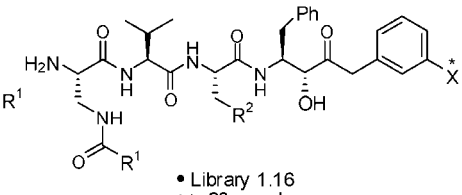
- Library 1.13
- 22 members
- Yin [410]
- NS3 protease inhibitors



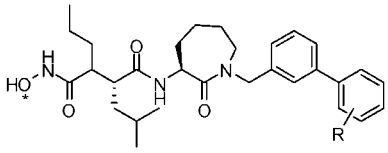
- Library 1.14
- 42 members
- Larbig [208]
- β-secretase inhibitors



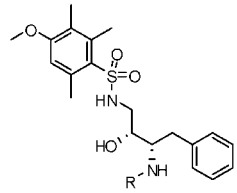
- Library 1.15
- 50 members
- Xiao [394]
- β-secretase (BACE) inhibitors



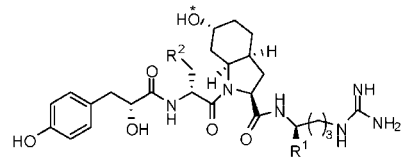
- Library 1.16
- > 20 members
- Hamada [126]
- β-secretase inhibitors; X = COOH; tetrazole



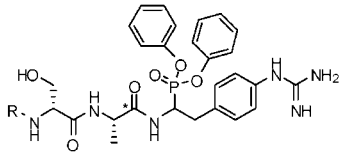
- Library 1.17
- multiple arrays
- Thompson [368]
- γ-secretase inhibitors



- Library 1.18
- 3 members
- Howard [148]
- thrombin inhibitors



- Library 1.19
- 24 members
- Doi [81]
- trypsin inhibitors

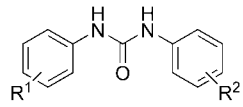


- Library 1.20
- 14 members
- Joossens [172]
- urokinase-type plasminogen activator inhibitors

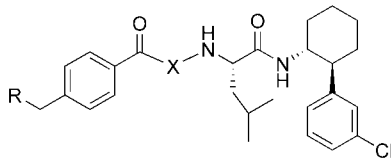
[a] The asterisk is the point of attachment to resin.

Table 2. Chemical Libraries Targeting Nonproteolytic Enzymes[a]

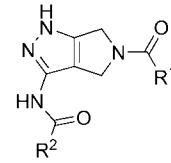
Kinases and phosphatases



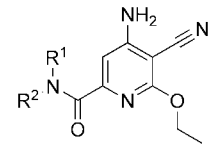
- Library 2.1
- *ca.* 100 members
- Anderson [11]
- insulin-like growth factor receptor tyrosine kinase inhibitors



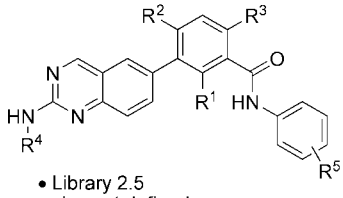
- Library 2.2
- size not defined
- Castanedo [43]
- CDK2/cyclinA inhibitors



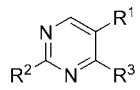
- Library 2.3
- size not defined
- Pevarello [304]
- CDK2 inhibitors



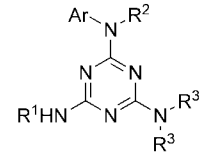
- Library 2.4
- > 7 members
- Zhao [422]
- c-Jun NH_2 terminal kinase inhibitors



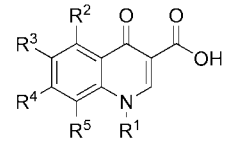
- Library 2.5
- size not defined
- DiMauro [73]
- Lck inhibitors



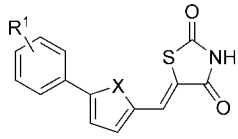
- Library 2.6
- 100 members
- Peters [302]
- polo-like kinase (Plks) inhibitors



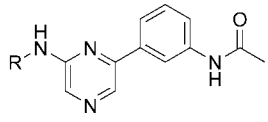
- Library 2.7
- ECLiPS-242,172 members
- Metzger [269]
- p38 MAP kinase inhibitors



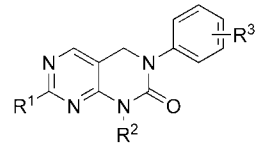
- Library 2.8
- 70,000 members
- Golub [112]
- protein kinase CK2 inhibitors



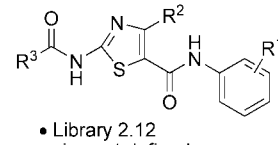
- Library 2.9
- 41 members
- Pomel [307]
- phosphoinositide 3-kinase γ



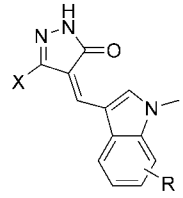
- Library 2.10
- 39 members
- Niculescu-Duvaz [287]
- B-RAF protein kinase inhibitors



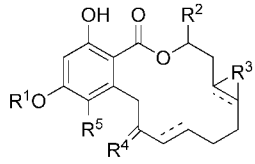
- Library 2.11
- size not defined
- Chen [52]
- dual inhibitor of RasGAP and ERK1 effecting self-renewal embryonic stem cells



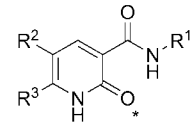
- Library 2.12
- size not defined
- Das [70]
- *pan*-Src kinase inhibitors



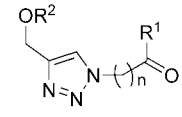
- Library 2.13
- > 15 members
- Tripathy [371]
- VEGFR-2 kinase inhibitors



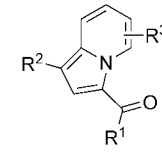
- Library 2.14
- 103 members
- Moulin [275]
- non-selective kinase inhibitors



- Library 2.15
- 24 members
- Li [223]
- anaplastic lymphoma kinase inhibitors

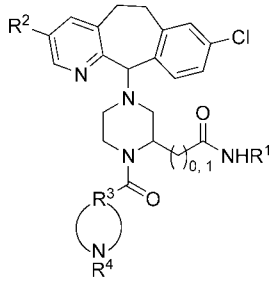


- Library 2.16
- 66 members
- Srinivasan [357]
- protein tyrosine phosphatase 1B inhibitors

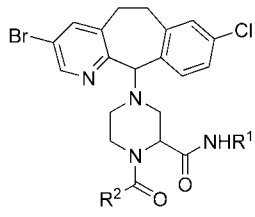


- Library 2.17
- size not defined
- Weide [383]
- PTB-1b inhibitors

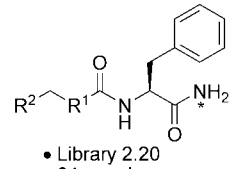
Farnesyltransferases



- Library 2.18
- ECLiPS-26,908 members
- Rokosz [328]
- FTase inhibitors



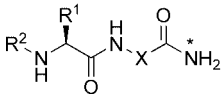
- Library 2.19
- size not defined (multiple arrays)
- Huang [150]
- FTase inhibitors



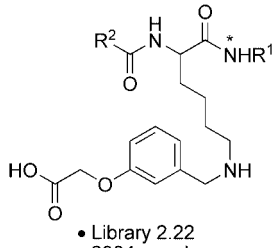
- Library 2.20
- 64 members
- Gilleron [108]
- FTase inhibitors

Table 2. Continued

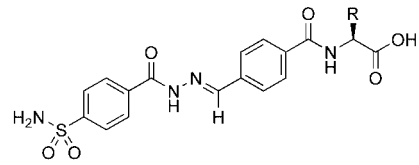
Alphabetical listing



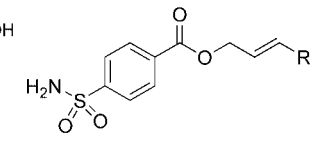
- Library 2.21
- size not defined
- Robins [324]
- aldose reductase inhibitors



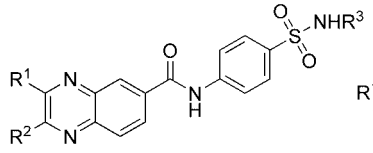
- Library 2.22
- 2304 members
- Dixon [76]
- aminodeoxychorismate synthase inhibitors



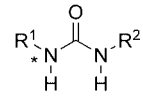
- Library 2.23
- dynamic library
- Poulsen [309]
- carbonic anhydrase II inhibitors



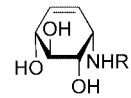
- Library 2.24
- >20 members
- Poulsen [310]
- carbonic anhydrase II inhibitors



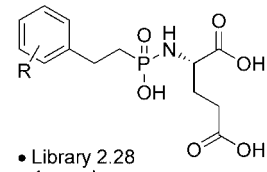
- Library 2.25
- > 16 members
- Li [221]
- cyclophilin A inhibitors



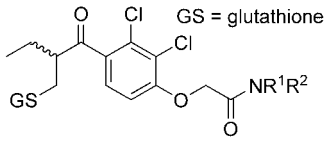
- Library 2.26
- 192 members
- Hwang [157]
- soluble epoxide hydrolase inhibitors



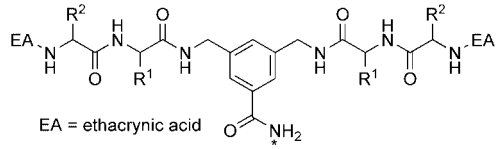
- Library 2.27
- 18 members
- Lysek [246]
- α-glucosidase inhibitors



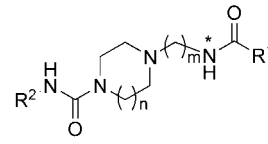
- Library 2.28
- 4 members
- Wone [390]
- glutamate carboxy-peptidase inhibitors



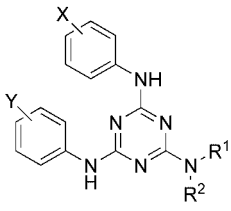
- Library 2.29
- *ca.* 14 members
- Shi [348]
- glutathione *S*-transferase inhibitors



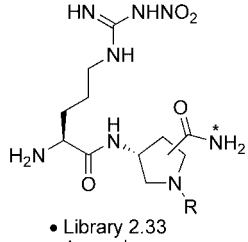
- Library 2.30
- *ca.* 400 members
- Mahajan [253]
- glutathione *S*-transferase inhibitors



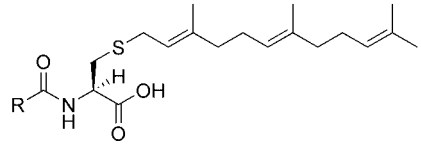
- Library 2.31
- size not defined
- Li [224]
- glycogen phosphorylase A inhibitors



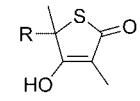
- Library 2.32
- >15 members
- McKay [268]
- *P. aeruginosa* DNA helicase inhibitors



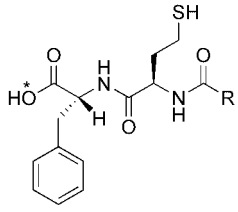
- Library 2.33
- 4 members
- Ji [170]
- iNOS inhibitors



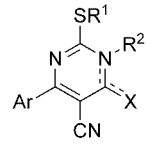
- Library 2.34
- *ca.* 23 members
- Donelson [82]
- isoprenylcysteine carboxyl methytransferase inhibitors



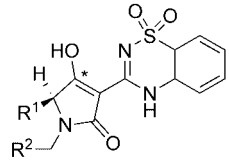
- Library 2.35
- 77 members
- Kim [192]
- β-ketoacyl-ACP synthase of type II fatty acid synthase inhibitors



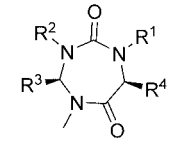
- Library 2.36
- *ca.* 80 members
- Sun [362]
- L1 metallo-β-lactamase inhibitors



- Library 2.37
- *ca.* 65 members
- Ding [75]
- *hepatitis C* viral NS5B RNA-dependent RNA polymerase

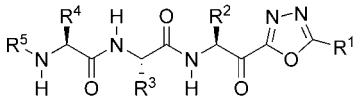


- Library 2.38
- 2 x 96 members
- Evans [91]
- *hepatitis C* virus RNA-dependent RNA polymerase

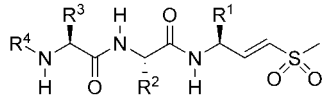


- Library 2.39
- *ca.* 34 members
- Muller [276]
- phospholipase A2 inhibitors

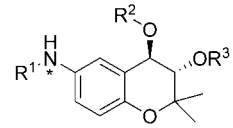
Table 2. Continued



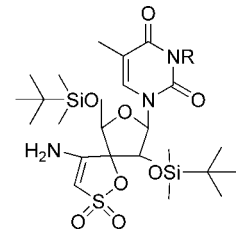
- Library 2.40
- 12 members
- Rydzewski [331]
- proteosome inhibitors



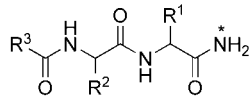
- Library 2.41
- *ca.* 35 members
- Rydzewski [331]
- proteosome inhibitors



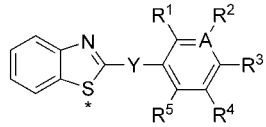
- Library 2.42
- 200 members
- Seo [338]
- prolyl 4-hydrolase inhibitors



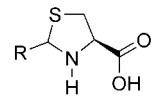
- Library 2.43
- *ca.* 64 members
- Sluis-Cremer [351]
- HIV-1 reverse transcriptase inhibitors



- Library 2.44
- 74,088 members
- Dixon [77]
- serine racemase inhibitors



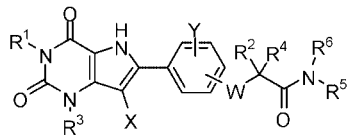
- Library 2.45
- 25 members
- Choi [55]
- topoisomerase II inhibitors



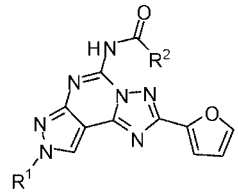
- Library 2.46
- 10 members
- Khan [188]
- *B. pasteurii* urease inhibitors

[a] The asterisk is the point of attachment to resin.

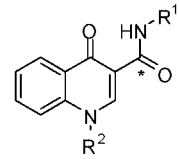
Table 3. Chemical Libraries Targeting G-Protein-Coupled Receptors[a]



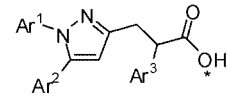
- Library 3.1
- > 150 members
- Carotti [49]
- A_{2B} adenosine receptor antagonists



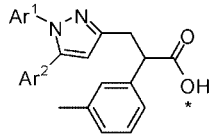
- Library 3.2
- 9 members
- Moro [273]
- Adenosine A3 antagonists



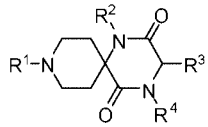
- Library 3.3
- 25 members
- Stern [360]
- CB_2 cannabinoid receptor agonists



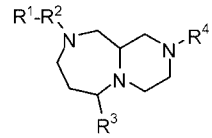
- Library 3.4
- size not defined
- McClure [265]
- CCK_1 receptor antagonists



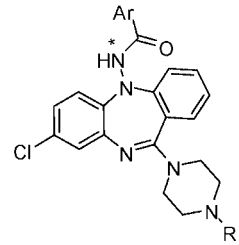
- Library 3.5
- *ca.* 30 members
- Sehon [336]
- CCK_1 receptor antagonists



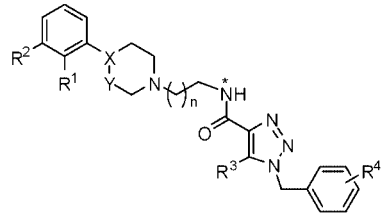
- Library 3.6
- size not defined
- Habashita [125]
- CCR_5 antagonists



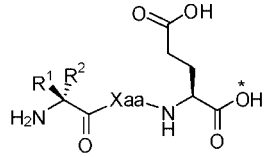
- Library 3.7
- large ECLiPS encoded library
- Stroke [266]
- $CXCR_3$ receptor agonists



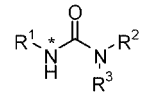
- Library 3.8
- multiple small arrays
- Su [361]
- dopamine-1 (D_1) receptor agonists



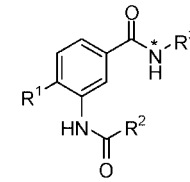
- Library 3.9
- >50 members
- Loaiza [239]
- dopamine D_3 ligands



- Library 3.10
- 15 members
- Alonso De Diego [7]
- glutamate receptor ligands

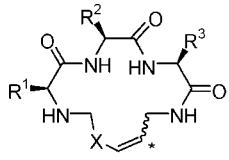


- Library 3.11
- > 300 members
- Lau [211]
- histamine H_3 receptor antagonists

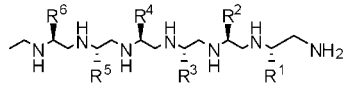


- Library 3.12
- *ca.* 22 members
- Ma [248]
- melanin-concentrating hormone receptor-1 antagonists

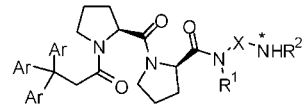
Table 3. Continued



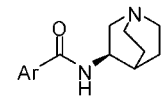
- Library 3.13
- *ca.* 56 members
- Marsault [258]
- motilin receptor antagonists



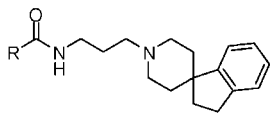
- Library 3.14
- 34M members
- Nefzi [283]
- μ opioid receptor ligands



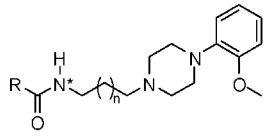
- Library 3.15
- size not defined
- Sagara [333]
- M_3 muscarinic receptor antagonists



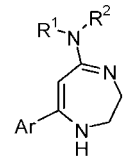
- Library 3.16
- > 100 members
- Wishka [389]
- α7 nicotinate acetylcholine receptor agonists



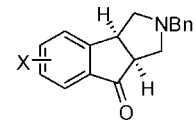
- Library 3.17
- >12 members
- Goto [117]
- ORL-1 antagonists



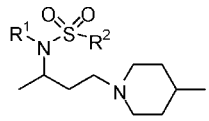
- Library 3.18
- 60 members
- Zajdel [415]
- 5-HT_{1A} receptor ligands



- Library 3.19
- *ca.* 260 members
- Swain [364]
- 5-HT_{2A} ligands



- Library 3.20
- > 50 members
- Huck [152]
- 5-HT_{2C} receptor agonists

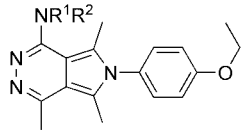


- Library 3.21
- 384 members
- Lattmann [210]
- 5-HT_7 agonists

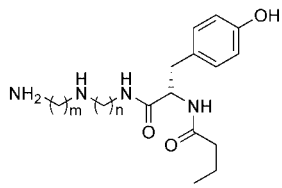
[a] The asterisk is the point of attachment to resin.

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

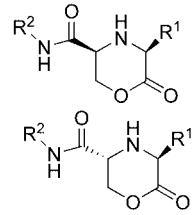
Ion channels



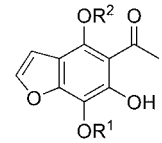
- Library 4.1
- 374 members
- Chen [51]
- $\alpha_2\delta$ ligands for calcium channel



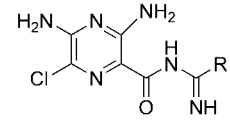
- Library 4.2
- Multiple libraries
- Andersen [9]
- AMPA antagonists



- Library 4.3
- *ca.* 16 members
- Ku [199]
- T-type Ca^{2+} channel blockers

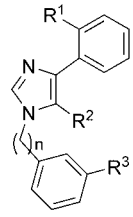


- Library 4.4
- size not defined
- Harvey [130]
- Kv 1.3 channel blockers

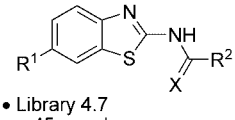


- Library 4.5
- *ca.* 32 members
- Hirsh [142]
- epithelial sodium channel (ENaC) blockers

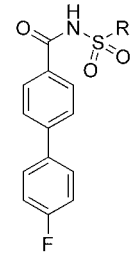
Protein-protein interactions



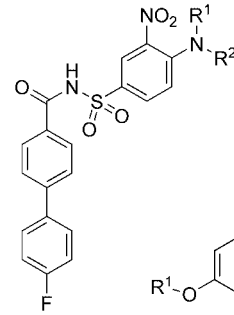
- Library 4.6
- 60 members
- Antuch [12]
- apoptosis regulation protein-protein inhibitors



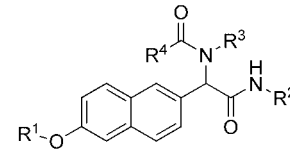
- Library 4.7
- > 45 members
- Xie [396]
- amyloid beta peptide (Aβ) and Aβ-binding alcohol dehydrogenase (ABAD) interaction inhibitors



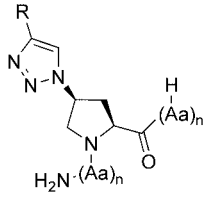
- Library 4.8
- 120 members
- Petros [303, 384]
- Bcl-x_L inhibitors



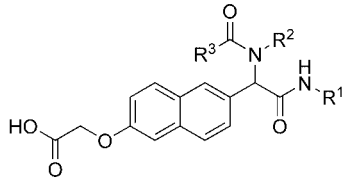
- Library 4.9
- 125 members
- Petros [303, 384]
- Bcl-x_L inhibitors



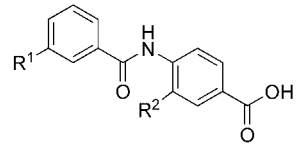
- Library 4.10
- 285 members
- Xu [402]
- HIV-1 gp41 protein-protein inhibitors



- Library 4.11
- *ca.* 22 members
- Gopi [115]
- HIV-1 envelope glycoprotein gp120 antagonists



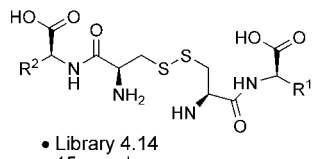
- Library 4.12
- 285 members
- Xu [404]
- c-Myc-Max protein-protein inhibitors



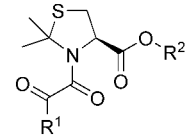
- Library 4.13
- 173 members
- Lu [241]
- p53-MDM2 protein-protein inhibitors

Table 4. Continued

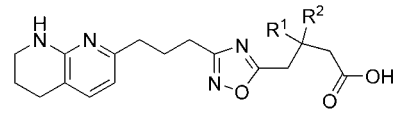
Alphabetical listing



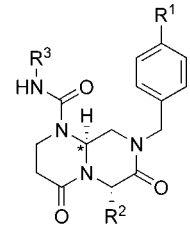
- Library 4.14
- 15 members
- Milanesi [270]
- calmodulin ligands



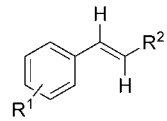
- Library 4.15
- 57120 virtual members
- Zhao [423]
- FK 506-binding protein ligands



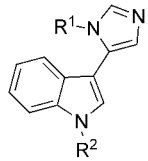
- Library 4.16
- size not defined
- Boys [33]
- $\alpha_v\beta_3$ integrin receptor antagonists



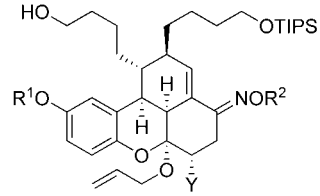
- Library 4.17
- 35 members
- Kim [191]
- nuclear factor-kB (NF-κB) inhibitors



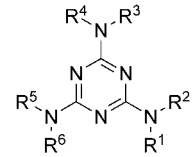
- Library 4.18
- 75 members
- Heynekamp [140]
- NF-κB activation inhibitors



- Library 4.19
- size not defined
- Beck [25]
- neurite outgrowth stimulators



- Library 4.20
- 8670 members
- Goess [111]
- vesicular traffic inhibitors

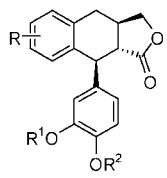


- Library 4.21
- >1000 members
- Pipalia [305]
- inhibitors of cholesterol accumulation in Niemann-Pick C cells

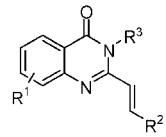
[a] The asterisk is the point of attachment to resin.

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

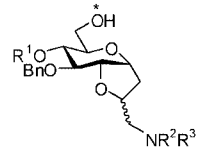
Oncolytics



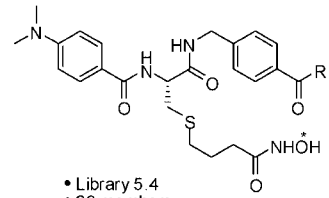
- Library 5.1
- >10 members
- Zhao [426]
- BEL-7404 cell proliferation inhibitors



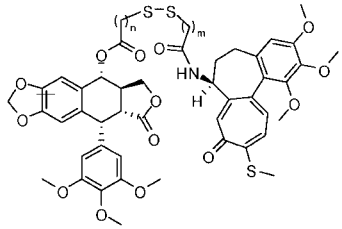
- Library 5.2
- *ca.* 120 members
- Liu [235]
- NCI-H460 cell proliferation inhibitors



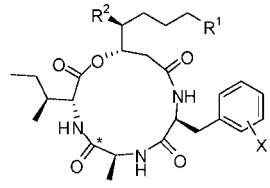
- Library 5.3
- 37 members
- Cervi [46]
- HT29 proliferation inhibitors



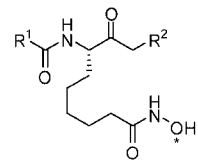
- Library 5.4
- 26 members
- Lucke [244]
- MM96L cell growth inhibitors (possible histone deacetylase inhibitor)



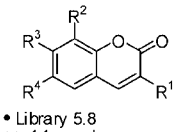
- Library 5.5
- dynamic combinatorial library
- Danieli [69]
- human lung carcinoma NCI-H460 growth inhibitors



- Library 5.6
- 77 members
- Nagai [281]
- macrophages droplet accumulation inhibitors

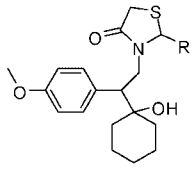


- Library 5.7
- 43 members
- Kahnberg [189]
- cytotoxic against MM96L melanoma cells

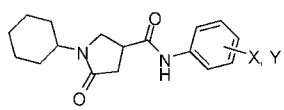


- Library 5.8
- > 14 members
- Lee [214]
- human umbilical vein endothelial cell (HUVEC) growth inhibitors (anti-angiogenic agents)

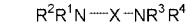
Antiinfectives



- Library 5.9
- 10 members
- Kavitha [187]
- *E. coli* growth inhibitors

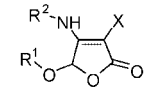


- Library 5.10
- 37 members
- He [133]
- *M. tuberculosis* growth inhibitors



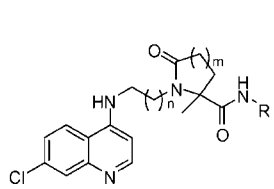
- Library 5.11
- 5000 members
- Bogatgheva [29]
- *M. tuberculosis* growth inhibitors

- Library 5.12
- 16 members
- Gupta [124]
- *P. aeroginosa* growth inhibitors

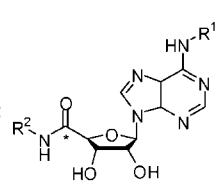


- Library 5.13
- >256 members
- Lattmann [209]
- *P. aeroginosa* growth inhibitors

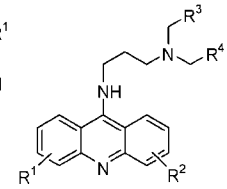
Table 5. Continued



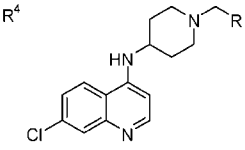
- Library 5.14
- 16 members
- Musonda [278]
- *P. falciparum* growth inhibitors



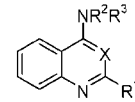
- Library 5.15
- 20 members
- Rodenko [325]
- *P. falciparum* growth inhibitors



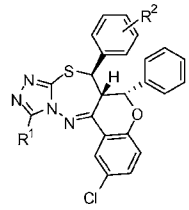
- Library 5.16
- 31 members
- Anderson [10]
- *P. falciparum* growth inhibitors



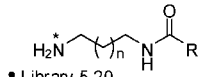
- Library 5.17
- 116 members
- Madrid [251]
- *P. falciparum* growth inhibitors



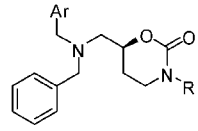
- Library 5.18
- size not defined
- Cope [61]
- suppression of protease resistant protein (anti-prion agents)



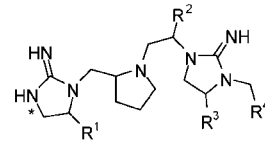
- Library 5.19
- 11 members
- Dandia [68]
- *R. Solani* growth inhibitors



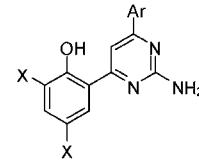
- Library 5.20
- *ca.* 48 members
- Yingyongnarongkul [411]
- *S. aureus* (MRSA) inhibitors



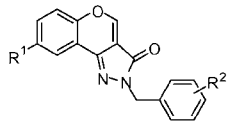
- Library 5.21
- *ca.* 30 members
- Wang [380]
- *S. aureus 2913* growth inhibitors



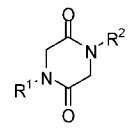
- Library 5.22
- 738,192 members
- Hensler [136]
- *S. aureus* (MRSA) growth inhibitors



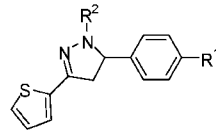
- Library 5.23
- 6 members
- Jhala [169]
- *S. fecalis* growth inhibitors



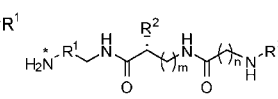
- Library 5.24
- 36 members
- Zhou [429]
- *T. cinnabarinus* insecticidal activity



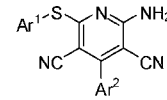
- Library 5.25
- 98 members
- Mas [259]
- *viral haemorragic septicemia* virus (VHSV) inhibitors



- Library 5.26
- 24 members
- Goodell [114]
- *West Nile Virus* inhibitors



- Library 5.27
- 540 members
- Burns [37]
- lipopolysaccharide neutralizers

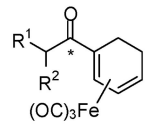


- Library 5.28
- 45 members from 1050 member virtual library
- Reddy [323]
- prion protein binders

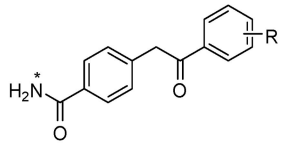
[a] The asterisk is the point of attachment to resin.

Table 6. Scaffold Derivatization[a]

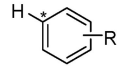
Part A: Solid-phase



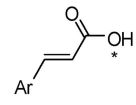
- Eriksson [88]
- reaction of resin-bound cyclohexadienoic acid active esters with amines



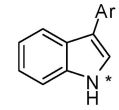
- Limbeck [227]
- Pd-catalyzed α-arylation of ketones on solid support



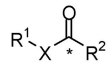
- Tsukamoto [372]
- Pd-catalyzed reductive cleavage of resin-bound benzenesulfonates



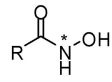
- Sheng [343]
- Heck reaction of PEG-bound acrylate and ArI



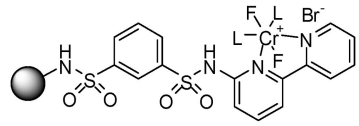
- Kasahara [186]
- Suzuki coupling of resin-bound indole boronate ester and ArX



- He [134]
- *N*-acylsulfonamide linker activation by Pd-catalyzed allylation

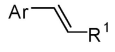


- Porcheddu [308]
- Angeli-Rimini's reaction from aldehydes and solid-supported *N*-hydroxybenzenesulfonamide

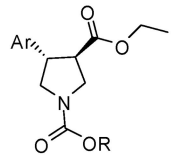


- Kurosu [203]
- for allylation of aldehydes

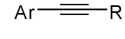
Part B: Solution-phase



- Shokouhimehr [349]
- Heck reaction using aryliodides alkenes and polymer-bound catalyst



- Hamilton [127]
- *N,N*-disuccinimidyl carbonate (DSC)-mediated carbamate synthesis

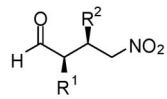


- Rahman [317]
- Sonogashira reaction in ionic liquids using novel array reaction

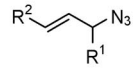
- Kurosu [204]
- from 2° amines using DIAD, PS-TPP and R^3-X

- Cardullo [40]
- alkylation of primary amines using Fukuyama methodology with resin-bound thiol and MW for deprotection

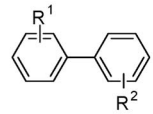
Table 6. Continued



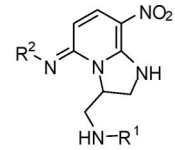
• Zu [155]
• fluorous organocatalyst-promoted Michael addition reactions of aldehydes to nitroolefins



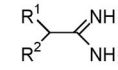
• Uozumi [376]
• π-allylic azidation of allyl carbonates with resin-bound Pd catalyst



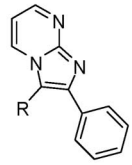
• Zhang [417]
• desulfitative Suzuki cross-couplings of arylsulfonyl chlorides and boronic acids in the presence of polymer-supported NHC-Pd complex



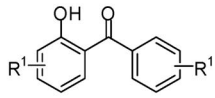
• Schmid [334]
• two consecutive reactions of primary amines to 3-bromomethyl-5-chloro-2,3-dihydroimidazopyrimidine



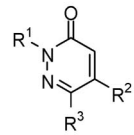
• Solodenko [353]
• amidination of amines with resin-bound 1*H*-pyrazole-1-carboxamidine



• Ermolat'ev [90]
• MW-assisted Heck reaction of 2-phenyl-imidazopyrimidine and RBr

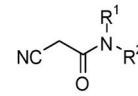


• Zhang [416]
• MW-assisted BCl_3-catalyzed acylation of phenols

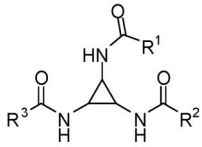


• Coelho [60]
• 3-CR Pd-catalyzed functionalization of 2-hydroxymethylpiridazin-3-ones

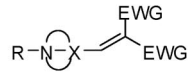
• Baxendale [24]
• MW-assisted Suzuki coupling reactions using encapsulated Pd (Pd EnCat™)



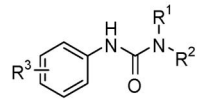
• Domling [78]
• reaction of secondary amines with isocyanoacetic acid methyl ester



• Guarise [122]
• functionalization of 1,2,3-triaminopropane

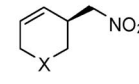


• Coelho [58]
• condensation of heterocyclic aldehydes with active methylenes and base; X = heterocycle; EWG = COOR, CN

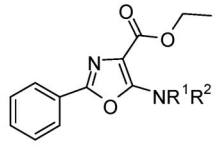


• Zhang [418]
• amine and ArNCO then fluorous scavenging

• Zhang [418]
• Mitsunobu reaction then fluorous scavenging



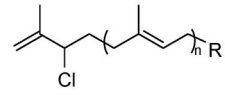
• Uozumi [375]
• Pd-mediated π-allylic substitution



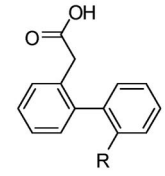
• Nolt [292]
• Cornforth rearrangement products by MW irradiation of 5-alkoxy-oxazole-4-carboxamides

• Morwick [274]
• ester hydrolysis with catch-and-release isolation of carboxylic acids

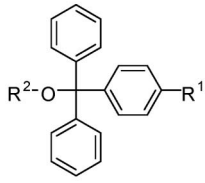
• Wiles [388]
• oxidation of aromatic alcohols using silica-supported Jones' reagent in a pressure-driven flow reactor



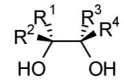
• Barrero [21]
• allylic chlorination using catalytic resin-bound selenenyl bromide and NCS



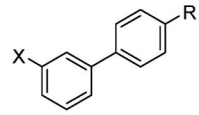
• Zheng [428]
• use of magnetic nanoparticles as an orthogonal support of polymer resins



• Lundquist [245]
• AgOTf-assisted tritylation of alcohols



• Reddy [322]
• asymmetric dihydroxylation of olefins using polysulfone-MC-OsO_4

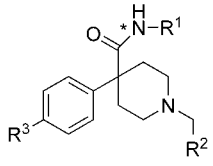


• Rasmussen [320]
• application of resin-bound triarylbismuthanes

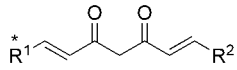
[a] The asterisk is the point of attachment to resin.

Table 7. Acyclic Synthesis[a]

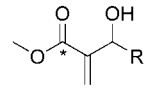
P:art A; Solid-phase



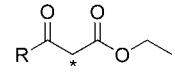
• Zhu [294]
• multi-step sequence



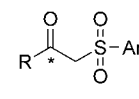
• Shao [340]
• multi-step sequence from resin-bound hydroxybenzaldehydes



• Sheng [344, 149]
• alkylation of PEG-supported α-phenylselenopropionate ester with aldehydes then oxidative elimination

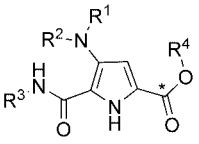


• Qian [315]
• alkylation of resin-bound α-seleno acetate with RCHO then selenoxide elimination

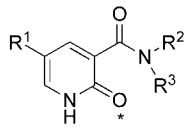


• Qian [316]
• addition of alkynes to resin-bound toluenesulfonate then hydrolysis

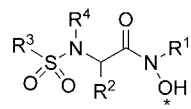
Table 7. Continued



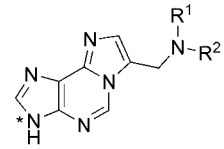
• Brouillette [35]
• multi-step sequence from resin-bound 4-aminopyrrole carboxylic acid



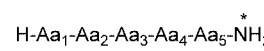
• Zhu [174]
• from resin-bound 5-bromo-2-hydroxylpyridine-3-carboxylic acid ester



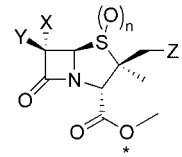
• Stanger [358, 359]
• *N*-derivatization of resin-bound amino acid hydroxamates



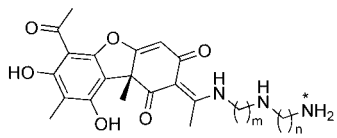
• Karskela [184]
• multi-step sequence derived from a resin-bound deoxyadenosine derivative



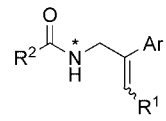
• Gebinoga [103]
• pentapeptides prepared using "Syn&Sort" chip-based tool



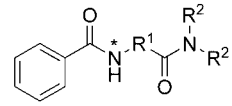
• Boggian [30]
• derived from resin-bound penicillin



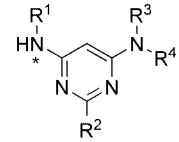
• Tomasi [369]
• SynPhase-supported amino alcohols, *O*-mesylation, reaction with diamines then urnic acid



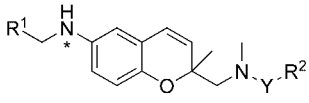
• Grigg [118]
• Pd-catalyzed multi-component cascade reaction



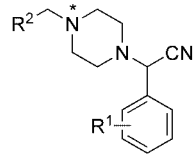
• Ruan [330]
• use of $PhSiH_3$ as active amidation reagent



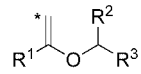
• Weber [382]
• from resin-bound aminochloro-pyrimidines



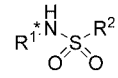
• Hwang [154]
• multi-step sequence from resin-bound 6-amino-2-methyl-2-(*N*-methyl)aminobenzopyran



• Probst [313]
• 3-CR of REM resin-bound piperazine, RCHO and cyanohydrin then *N*-benzylation and release

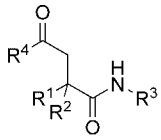


• Liu [236]
• epoxide ring-opening with resin-bound lithium selenide, *O*-alkylation then oxidation elimination/cleavage

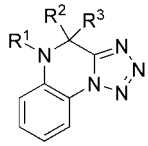


• Kumar [202]
• derived from amine, sulfonyl chloride using novel quinone methide release linker

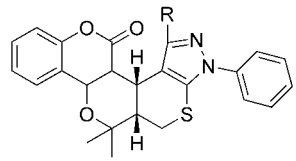
Part B: Solution-phase



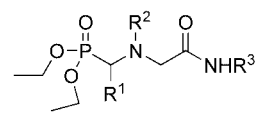
• Simoneau [350]
• Ugi condensation based on the reaction of organometallic reagents with nitriles



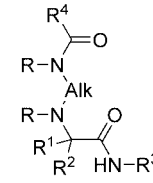
• Kalinski [177]
• 2-fluorophenylisocyanide in the Ugi-tetrazole reaction followed by a nucleophilic aromatic substitution



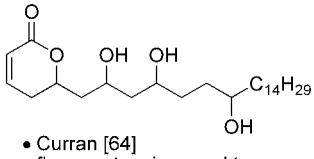
• Jayashankaran [165]
• intramolecular domino Knoevenagel hetero Diels-Alder reaction of 4-hydroxy coumarin and its benzo-analogous with *S*-prenylated aromatic aldehydes



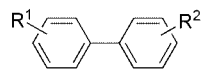
• El Kaim [87]
• two-step Mannich/Ugi one-pot procedure from isocyanides



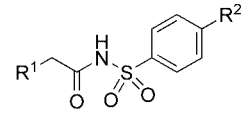
• Giovenzana [109]
• Ugi 4-CR



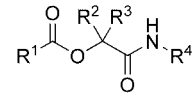
• Curran [64]
• fluorous tagging used to prepare 8-member stereoisomer library



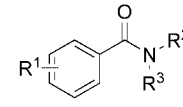
• Thiot [367]
• Pd-catalyzed Suzuki cross-coupling reaction of aryl bromides using polyionic gels



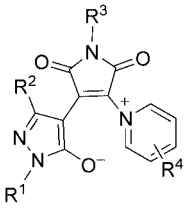
• Cassidy [42]
• from *in situ* generated copper(I) acetylides and sulfonyl azides



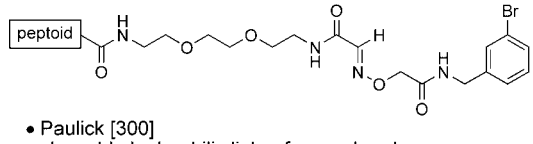
• Extance [93]
• Passerini reaction in water



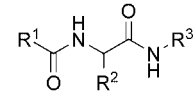
• Lagerlund [207]
• MW-assisted amino-carbonylation of ArCl



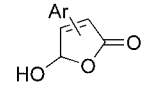
• Varga [377]
• 3-CR with pyridines, dichloromaleimides and pyrazolones



• Paulick [300]
• cleavable hydrophilic linker for one-bead-one-compound sequencing of oligomer libraries by tandem mass spectrometry

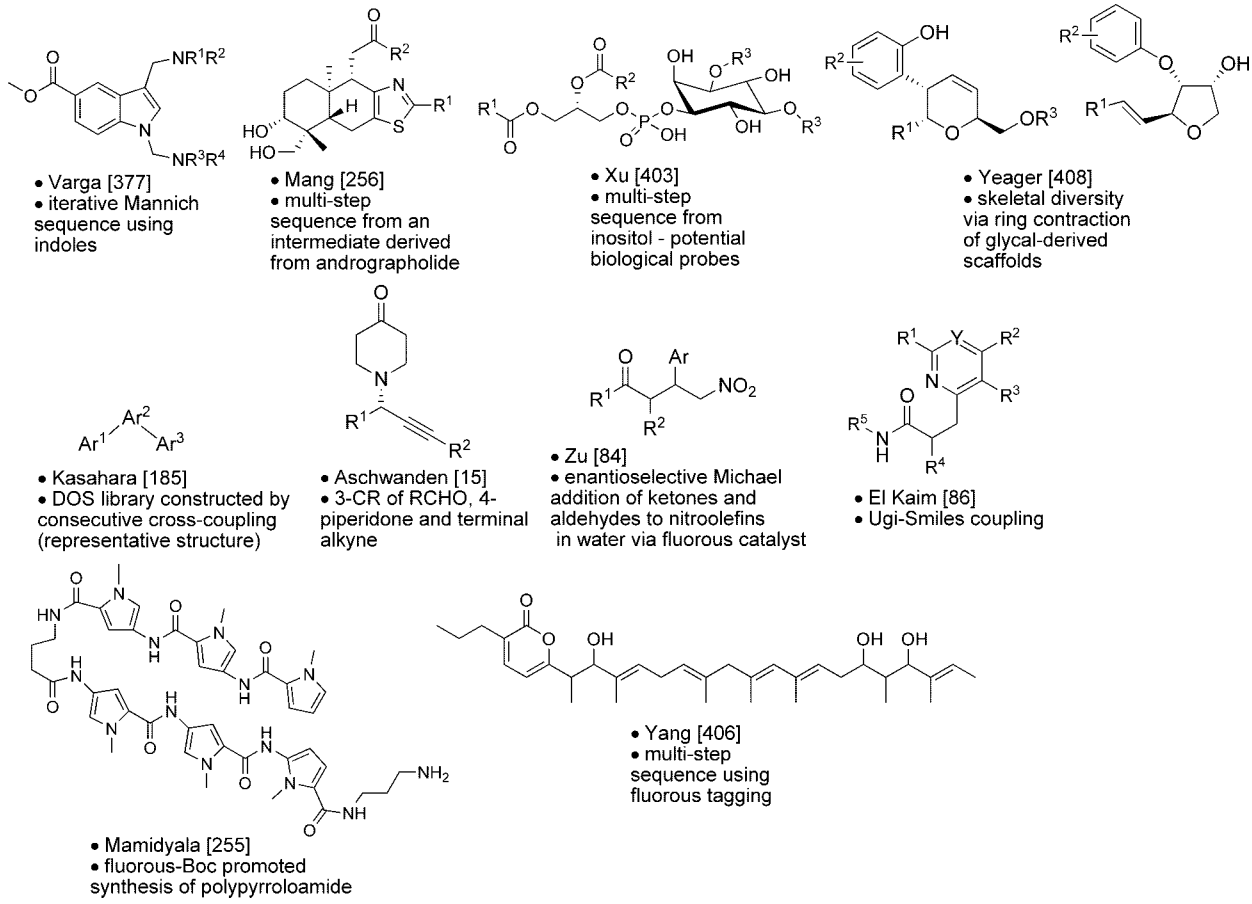


• Sung [363]
• Ugi 4-CR using 2-nitrobenzylamine as an ammonia equivalent



• Aquino [13]
• photooxidation of 3-bromofuran then Suzuki coupling

Table 7. Continued



[a] The asterisk is the point of attachment to resin.

Table 8. Monocyclic Synthesis[a]

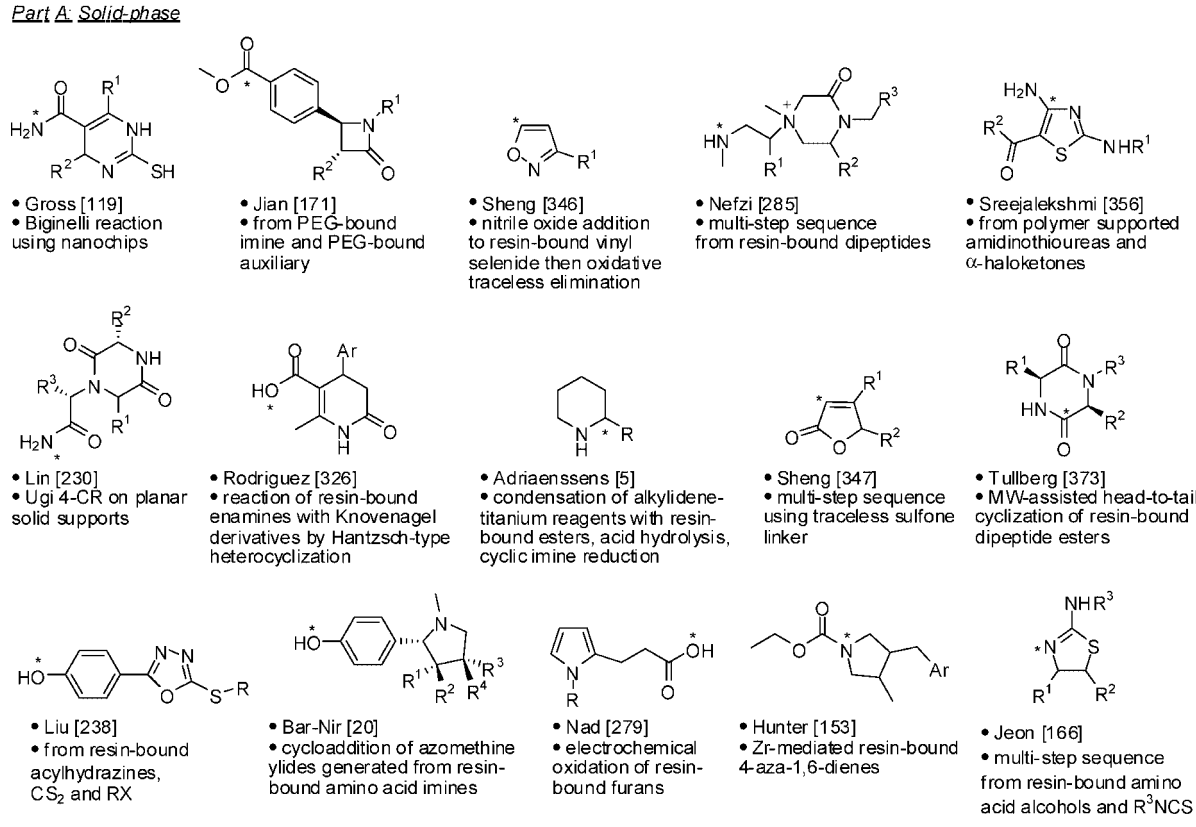
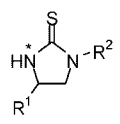
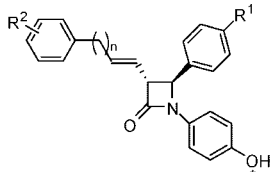


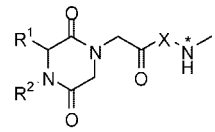
Table 8. Continued



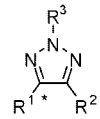
• Jeon [167]
• multi-step sequence from resin-bound amino acid alcohols and R^2NCS



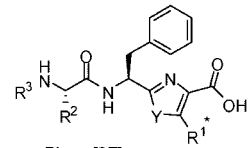
• Testero [366]
• cross-metathesis of resin-bound vinyl-β-lactams



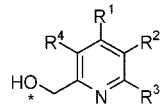
• Gong [113]
• derived from resin-bound iminodiacetate and second amino acid



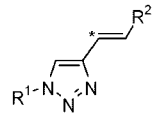
• Gao [101]
• [3+2] cycloaddition of resin-bound vinyl sulfone and sodium azide



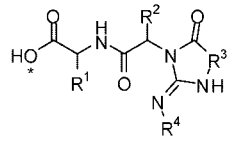
• Biron [27]
• cyclodehydration of resin-bound *C*-terminal threonine, serine, cysteine or diaminopropionic acid



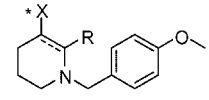
• Senaiar [337]
• solid supported [2+2+2] cyclotrimerization



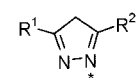
• Xu [400]
• 1,3-dipolar cycloaddition of resin-bound propargyl selenide with RN_3 then oxidative cleavage



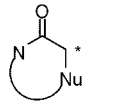
• Gavrilyuk [102]
• dehydrothiolation/ iminohydantoin formation from resin-bound dipeptides



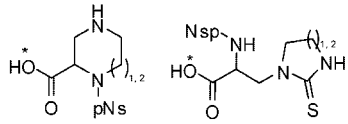
• Back [16]
• cyclization of resin-bound acetylenic sulfones with chloroalkylamines
X = SO_2R; H



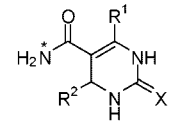
• Cesarini [47]
• from resin-bound acylhydrazines



• McAllister [264]
• application of sulfur α-hetero-atom substituted carbonyl linker and cleavage with SmI_2

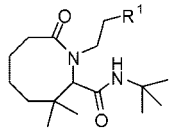


• Olsen [293]
• aminolysis of resin-bound *N*-nosylaziridine-2-carboxylic acids

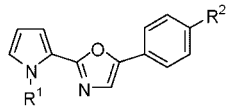


• Gross [121]
• 3-CR with resin-bound β-ketoamides

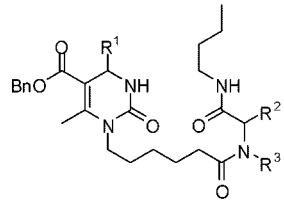
Part B: Solution-phase



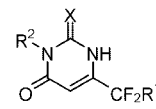
• El Kaim [85]
• radical cyclization of xanthate Ugi products



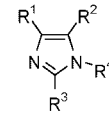
• Loughlin [392]
• acylation of acylaminoketone salts with pyrrole acid chlorides then dehydration



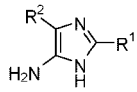
• Werner [386]
• tandem Biginelli-Ugi MCR



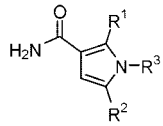
• Fustero [99]
• fluorous synthesis from fluoro-substituted enamino esters and iso(thio)cyanates



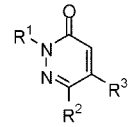
• Gelens [104]
• synthesis from R^3CHO, R^1COCOR^2, NH_4OAc and R^4NH_2



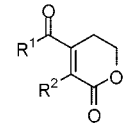
• Soh [352]
• MW-assisted condensation of thioamides, RCH_2Br, and α-aminonitriles



• Gross [121]
• multiple core structures based on resin-bound 3-oxo-propanamides prepared using novel micro reactor

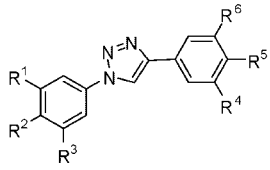


• Coelho [60]
• Pd-catalyzed 3-CR

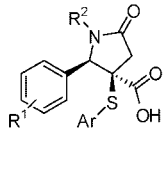


• Yang [407]
• reaction of cyclopropyl aryl ketones with α-ketoacetic acids using $C_8F_{17}SO_3H$ in fluorous phase

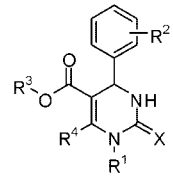
• Beck [25]
• 3-CR of Tosmic, indole carboxaldehydes and primary amines in a van Leusen reaction



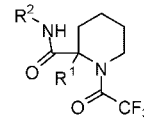
• Pagliai [298]
• Huisgen [3+2] cycloaddition reaction



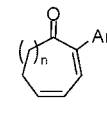
• Ng [280]
• cycloaddition reaction of imines with 3-thiosuccinic anhydrides



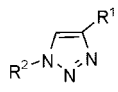
• Desai [72]
• MW-assisted multi-component Biginelli reaction



• Nenajdenko [286]
• Ugi 3-CR using 2,3,4,5-tetrahydropyridine, CF_3CO_2H and R^2NC

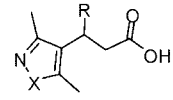


• Hok [145]
• multi-step sequence using sulfone-based methodology

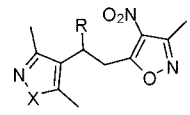


• Girard [110]
• [3+2] Huisgen cycloaddition of alkyne and azide using Amberlyst-derived Cu catalyst

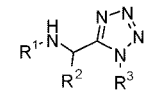
• Baumann [23]
• condensation of RCOCl and isonitrile in mesofluidic flow reactor



• Adamo [3]
• 4-CR from nitroheteroaromatic, RCHO, H_2N-X, and $MeCOCH_2COMe$

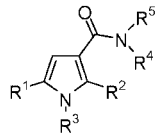


• Adamo [3]
• 4-CR from nitroheteroaromatic, RCHO, H_2N-X, and $MeCOCH_2COMe$

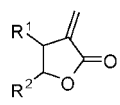


• Achatz [2]
• 4-CR of R^1NH_2, R^2CHO, R^3-NC and $TMSN_3$

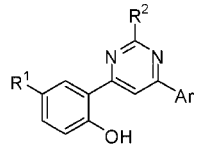
Table 8. Continued



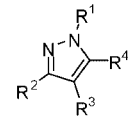
• Bianchi [26]
• homologation of β-ketoesters with aldehydes then oxidation to 1,4-dicarbonyls, MW-assisted Paal-Knorr reaction



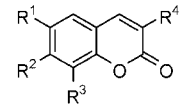
• Le Lamer [212]
• from fluorous Baylis-Hillman intermediates



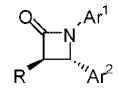
• Nie [289]
• MW-assisted condensation of 2'-hydroxychalcones with amidines or guanidine



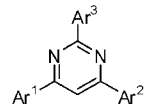
• Xie [395]
• 3-CR from iodochromone, $ArB(OH)_2$ and hydrazine



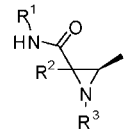
• Polito [306]
• RCM of acrylate esters of 2-vinylphenols



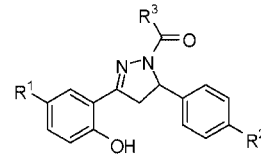
• Kikuchi [190]
• PS-TPP mediated condensation of α-bromo carboxylic acids and imines



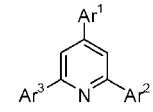
• Adib [4]
• MW-assisted 4-CR between aryl methyl ketones, benzaldehydes, aromatic nitriles and hydroxylamine



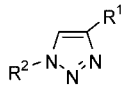
• Banfi [17]
• Ugi 4-CR with lactate-derived *O*-protected α-hydroxycarbonyl derivatives



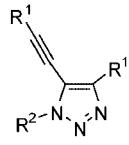
• Nie [288]
• 2'-hydroxychalcones and acylhydrazines in MW at 200 °C



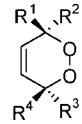
• Kumar [201]
• from benzlidene-acetophenones and urea or thiourea using $Bi(NO_3)_3$ Al_2O_3



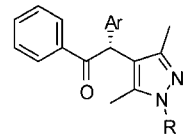
• Gerard [105]
• 1,3-dipolar cycloaddition-coupling of azides with an excess of alkyne in the presence of $Cu(CH_3CN)_4PF_6$ as catalyst



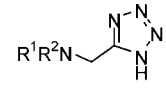
• Gerard [105]
• 1,3-dipolar cycloaddition-coupling of azides with an excess of alkyne in the presence of $Cu(CH_3CN)_4PF_6$ as catalyst



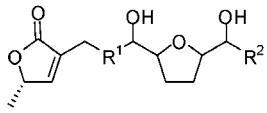
• Fuchter [97]
• ring-opening metathesis polymer sphere-supported *seco*-porphyrazines as photooxygenation catalysts



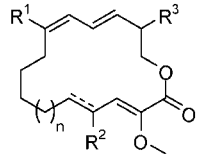
• Blay [28]
• enantioselective DOS of densely substituted pyrazoles



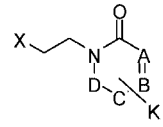
• Domling [79]
• Ugi tryp reaction from 1-isocyano-methylbenzotriazole and 2,2,4,4-tetramethylbutyl-isocyanide



• Curran [66] and Gudipati 123]
• multi-step reaction using fluorous tagging



• Lu [242]
• DOS approach to plecomacrolides

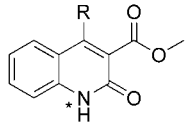


• Coelho [59]
• multi-step sequence from substituted pyridones and Michael acceptors

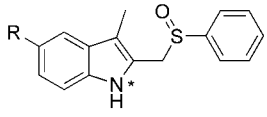
[a] The asterisk is the point of attachment to resin.

Table 9. Bicyclic and Spirocyclic Synthesis[a]

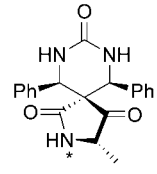
Part A: Solid-phase



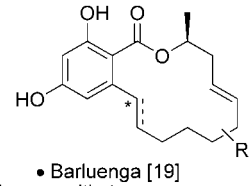
• Xu [399]
• resin-bound 4-tosyl quinolinone



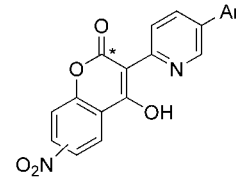
• Hoenke [143]
• intramolecular addition of resin-bound amides to allenyl sulfoxides



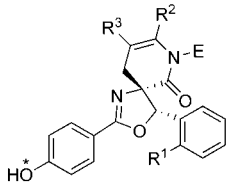
• Byk [38]
• 3-CR from resin-bound β-keto-γ-lactam, ArCHO and urea



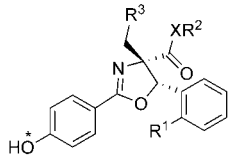
• Barluenga [19]
• multi-step sequence via a resin-bound thioether intermediate



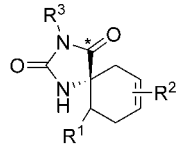
• Liu [237]
• multi-step sequence



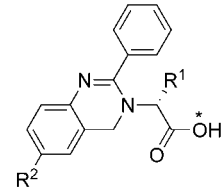
• Mitchell [271]
• multi-step DOS library



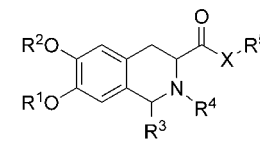
• Mitchell [271]
• multi-step DOS library



• Kuster [205]
• multi-step sequence

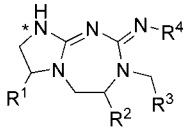


• Ortega [297]
• multi-step sequence using perfluorous solvents

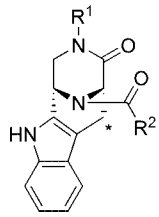


• Lesma [219]
• Pictet-Spengler condensation

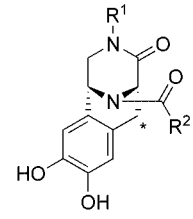
Table 9. Continued



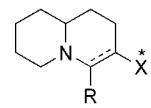
• Hoesl [144]
• from resin-bound exhaustively reduced dipeptides



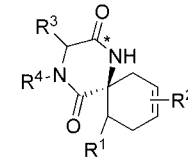
• Lee [216]
• tandem acidolytic cleavage, *in situ* iminium formation then Pictet-Spengler intramolecular cyclization



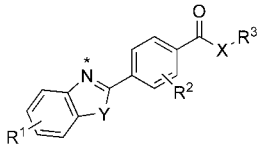
• Lee [216]
• tandem acidolytic cleavage, *in situ* iminium formation then Pictet-Spengler intramolecular cyclization



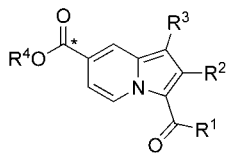
• Back [16]
• cyclization of resin-bound acetylenic sulfones with chloroalkylamines
X = SO_2R; H



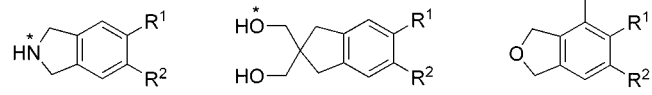
• Kuster [205]
• multi-step sequence



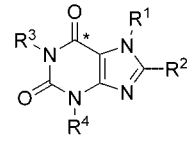
• Hioki [141]
• imine-exchange of resin-bound imine and 1,2-diamines or 2-thioanilines



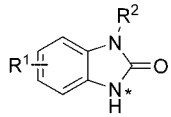
• Yue [414]
• from resin-bound pyridium salts and alkynes



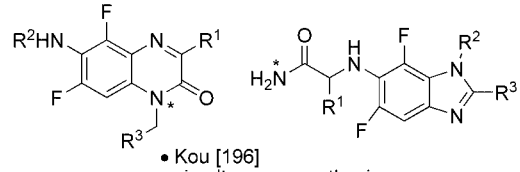
• Young [412]
• cyclotrimerization reaction with resin-bound diynes and alkynes



• He [132]
• multi-step sequence from resin-bound *N*-substituted glycines, ethoxymethylene cyanamide isocyanates then intracyclative cleavage

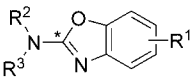


• Xu [401]
• Pd-catalyzed intramolecular cyclization of the resin-bound primary ureas then *N*-alkylation and cleavage

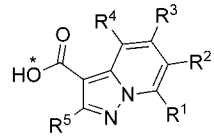


• Kou [196]
• simultaneous synthesis of quinoxalines and benzimidazoles from resin-bound Fmoc-amino acids

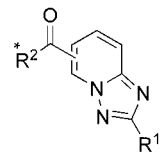
• Cebasek [44]
• from resin-bound enaminones



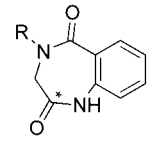
• Hwang [156]
• reaction of Merrifield resin with 2-aminophenols and CS_2, oxidation then treatment with amines



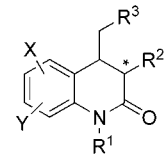
• Harju [129]
• cycloaddition of resin-bound propargyl esters and *N*-aminopyridine iodides



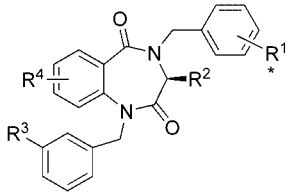
• Fernandez [94]
• *N*-electrophilic amination of 2-amino-pyridines



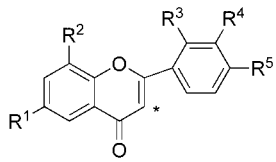
• Rao [319]
• multi-step sequence from PEG-bound *N*-substituted glycines



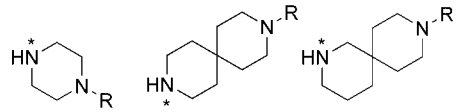
• Turner [374]
• multi-step sequence using sulfur linker cleaved by SmI_2



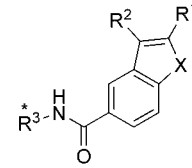
• Cheng [54]
• multi-step sequence from PEG-bound aryl aldehydes, amino acid esters, 2-nitrobenzoyl chlorides and benzyl bromides



• Cao [39]
• Lewis acid-mediated resin-supported selenium induced intramolecular cyclization of chalcones and oxidative cleavage of selenium resins

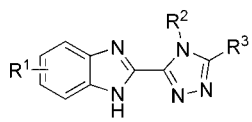


• Macleod [250]
• annulation of primary amines using bis-electrophilic (SPA*n*) reagents

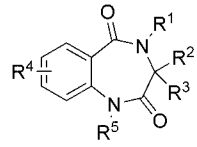


• Bui [36]
• Pd-mediated coupling and iodocyclization

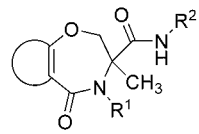
Part B: Solution-phase



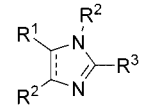
• Ivanova [163]
• from triazole aldehydes and *ortho*-phenylenediamines



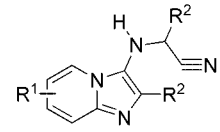
• Kalinski [178]
• 4-CR then Pd-mediated cyclization



• Ilyin [160]
• multi-step sequence

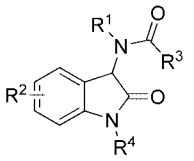


• Lin [231]
• from diamines and carboxylic acids under microwave irradiation

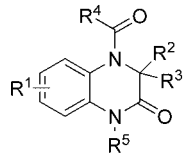


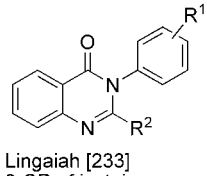
• Masquelin [261]
• sequential Ugi/Strecker reactions

Table 9. Continued

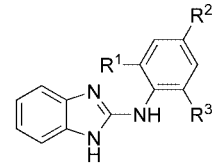


• Kalinski [178]
• 4-CR then Pd-mediated intramolecular *N*-aryl amidation reaction

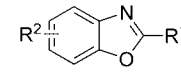




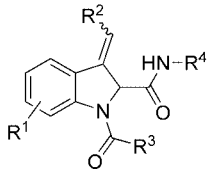
• Lingaiah [233]
• 3-CR of isatoic anhydride/anthranilic acid, orthoesters, and amines in the presence of Nafion-H



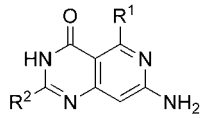
• Cee [45]
• diamines, isothiocyanates and PS-carbodiimide



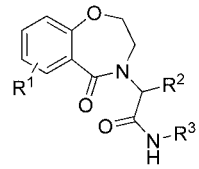
• Wang [381]
• from carboxylic acids and 1,2-aminophenol with PS-PPh_3/CCl_3CN



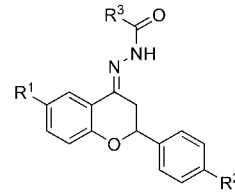
• Kalinski [178]
• Ugi 4-CR then intramolecular Heck



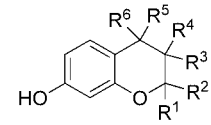
• Jang [164]
• from pyrido[4,3-*d*] pyrimidin-4(3*H*)-ones



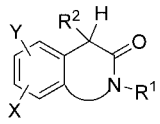
• Banfi [18]
• Ugi condensation followed by intramolecular Mitsunobu cyclization



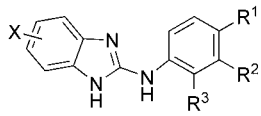
• Nie [288]
• 2'-hydroxychalcones and acylhydrazines in MW at 120 °C



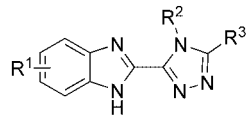
• Ko [193]
• DOS library incorporating benzopyran motif



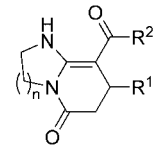
• McCormick [267]
• fluorous phase Pummerer cyclative-capture then oxidative cleavage



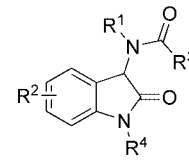
• Carpenter [41]
• one-pot synthesis from ArNCS, *O*-phenylenediamines and DIEA-mediated cyclization



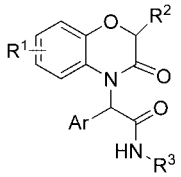
• Ivanova [163]
• *O*-phenyldiamines and 1,2,4-triazole carboxaldehydes



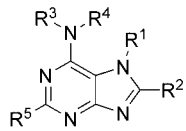
• Yu [413]
• 3-CR of heterocyclic ketene amines, Meldrum's acids and R^1CHO



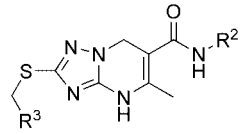
• Bonnaterre [32]
• tandem Ugi 4-CR MW-assisted intramolecular Buchwald-Hartwig amidation



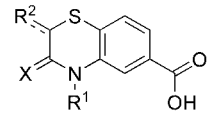
• Xing [397]
• Ugi 4-CR and intramolecular *O*-alkylation where α-bromo acids are one component



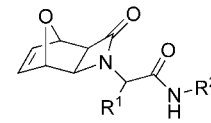
• Liu [234]
• cyclization reactions of substituted pyrimidines with either carboxylic acid or aldehyde



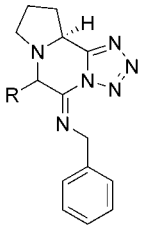
• Chebanov [50]
• 3-CR of 3-amino-2-alkylthio-1,2,4-triazoles with aromatic aldehydes and acetoacetamides



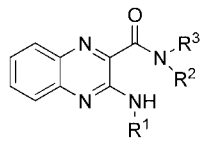
• Trifilenkov [370]
• multiple derivatives of dihydrobenzothiazines from 4-fluoro-3-nitro benzoic acid



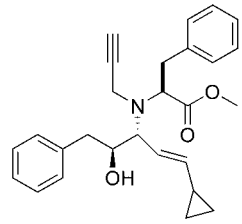
• Kanizsai [183]
• Ugi 4-CR from oxabicycloheptane-based amino acid



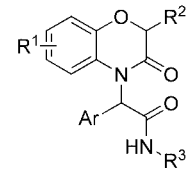
• Franckevicius [96]
• Ugi-type 3-CR between an aldehyde, an isocyanide and proline tetrazole



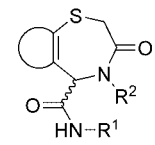
• Kowalski [197]
• from 1,2-diamines and 1,2-dicarbonyls



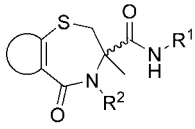
• Kumagai [200]
• densely functionalized template for constructing DOS libraries



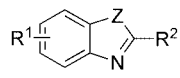
• Xing [397]
• Ugi 4-CR then intramolecular *O*-alkylation



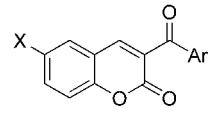
• Ilyn [161]
• Ugi 4-CR



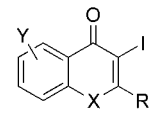
• Ilyn [161]
• Ugi 4-CR



• Evindar [92]
• copper-catalyzed cyclization of *ortho*-haloanilides



• Rao [318]
• condensation of α-aroylketene dithioacetals and salicylaldehydes/2-hydroxy-1-naphthaldehyde and catalytic piperidine

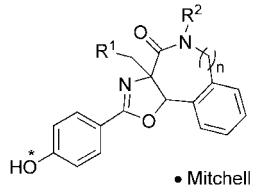


• Zhou [425]
• DOS of 3-iodochromones and heteroatom analogues via ICl-induced cyclization

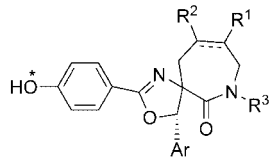
[a] The asterisk is the point of attachment to resin.

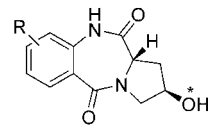
Table 10. Polycyclic and Macrocyclic Synthesis[a]

Part A: Solid-phase

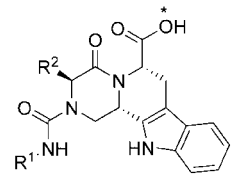


• Mitchell [271]
• multi-step DOC library

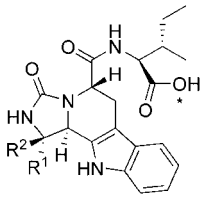




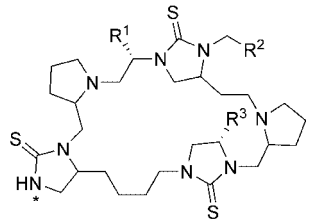
• Kamal [182]
• reduction of resin-bound arylazides with BF_3-Et_2O/Et_3SiH



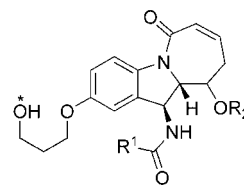
• Lee [215]
• tandem intramolecular Pictet-Spengler cyclization

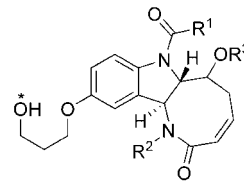


• Diness [74]
• intramolecular *N*-carbamyliminium Pictet-Spengler reaction

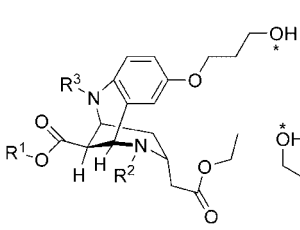


• Nefzi [284]
• treatment of exhaustively reduced polyamides on resin with bifunctional reagents then cleavage

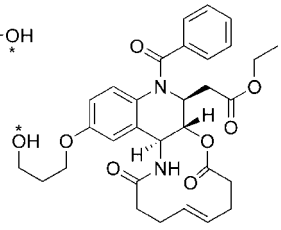




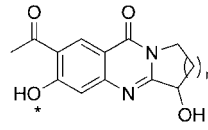
• Reddy [321]
• RCM-derived products from resin-bound indole diolefin

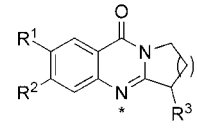


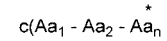
• Prakesch [311]
• DOS library (representative structure)



• Prakesch [311]
• DOS from an orthogonal-protected tetrahydro-aminoquinoline (representative structure)

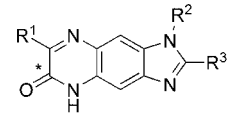




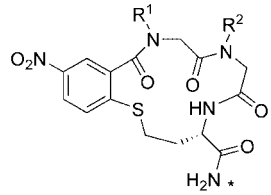


• Kamal [181]
• from resin-bound anthranilic acid and lactams

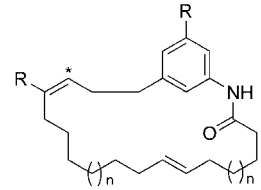
• Monroc [272]
• MW-assisted cyclic synthesis on SynPhase Lanterns



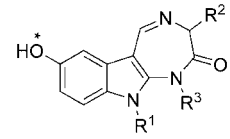
• Lin [229]
• multi-step sequence from PEG-bound amino acid esters, *N*-heteroarylation with difluorodinitrobenzene



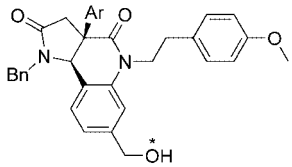
• Nnanabu [291]
• intramolecular ring closure of homocysteine and 2-fluoro-4-nitrobenzamide then cleavage



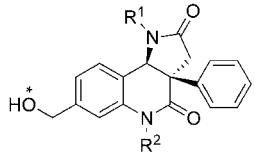
• Peng [301]
• multi-step sequence *via* resin-bound triphenylphosphonium salts



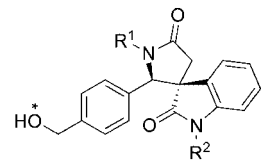
• Lee [213]
• multi-step sequence from resin-bound 2-amino-3-formyl indole and Fmoc-amino acids



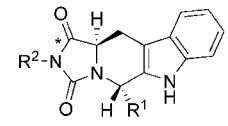
• Masse [262]
• condensation of resin-bound *ortho*-iodobenzaldehydes with imines, cycloaddition with succinic anhydrides, then amide formation and cyclization



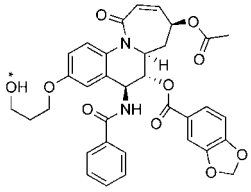
• Masse [262]
• DOS library from resin-bound aryl imines and substituted succinate anhydrides



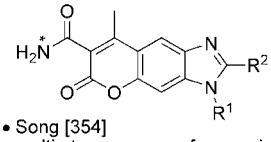
• Masse [262]
• DOS library from resin-bound aryl imines and substituted succinate anhydrides



• Chang [48]
• MW-assisted Pictet-Spengler reaction



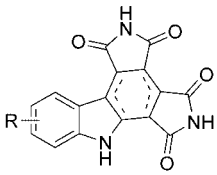
• Sharma [341]
• DOS library from an orthogonal-protected tetrahydroaminoquinoline (representative structure)



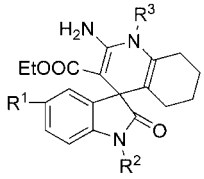
• Song [354]
• multi-step sequence from resin-bound 7-fluoro-4-methyl-6-nitro-2*H*-1-benzopyran-3-carboxylic acid

Table 10. Continued

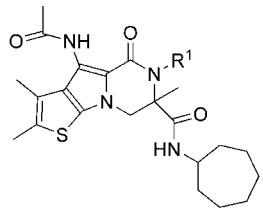
Part B: Solution-phase



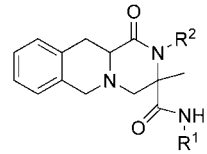
• Henon [134]
• four-step sequence from substituted indoles



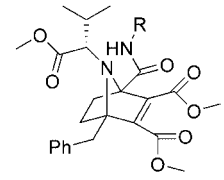
• Hatamjafari [131]
• 4-CR



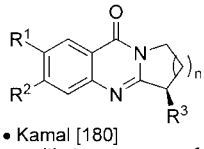
• Ilyin [158]
• Ugi 4-CR



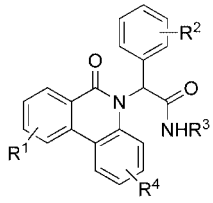
• Ilyin [162]
• Ugi 4-CR

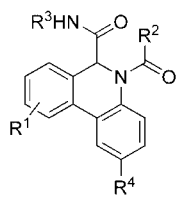


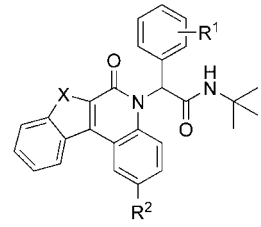
• Kadzimirsz [173]
• gold-catalyzed intramolecular hydroamination of alkynes derived from Ugi 4-CR products



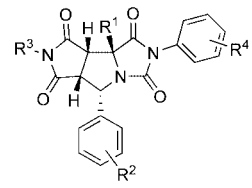
• Kamal [180]
• multi-step sequence from lactams and 2-azidobenzoic acids using solid phase reagents



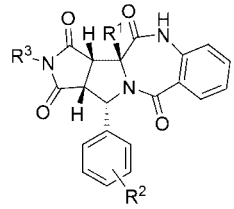




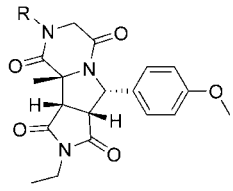
• Ma [249]
• Ugi 4-CR/Pd-catalyzed intramolecular arylation



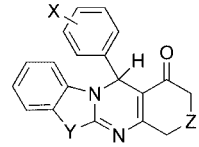
• Zhang [420]
• multi-step sequence using fluorous amino acid esters



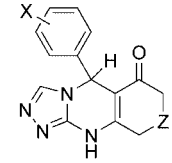
• Zhang [420]
• multi-step sequence using fluorous amino acid esters



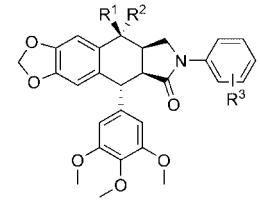
• Zhang [419]
• multi-step sequence with fluorous amino acid esters (several other related structures)



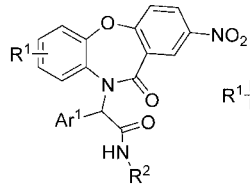
• Shaabani [339]
• 3-CR with ArCHO, 1,3-diketones and aminoheterocycle

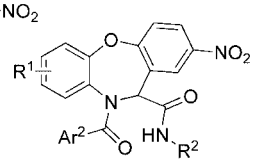


• Shaabani [339]
• 3-CR with ArCHO, 1,3-diketones and aminoheterocycle

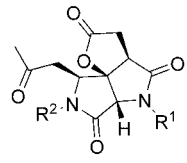


• Dorbec [83]
• from methyl ester thuriferic acid *via* $InCl_3$-tandem aza-Michael addition-cyclization reaction of anilines

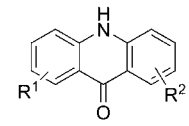




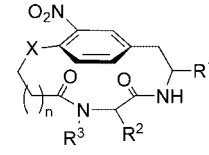
• Xing [398]
• Ugi 4-CR and intramolecular *O*-arylation



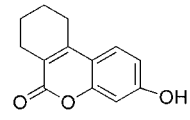
• Ilyin [159]
• Ugi 4-CR then 85% H_3PO_4 at 100 °C



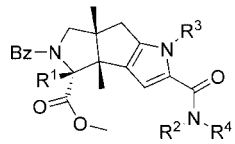
• Nishio [290]
• multi-step sequence from 2-bromobenzoic acids and anilines



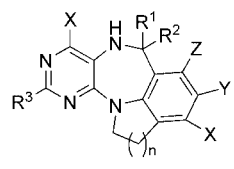
• Cristau [63]
• Ugi 4-CR and intramolecular S_NAr-based macrocyclization reaction



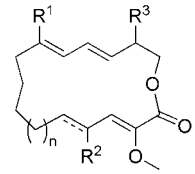
• Wyatt [391]
• DOS library derived from fluorous α-diazoacetate and cycloaddition chemistry (representative structure)



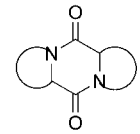
• Werner [385]
• multi-step sequence from *N*-benzyl amino acid esters



• Zheng [427]
• multi-step sequence from 2,4-dichloro-3-nitro-pyrimidine and amines

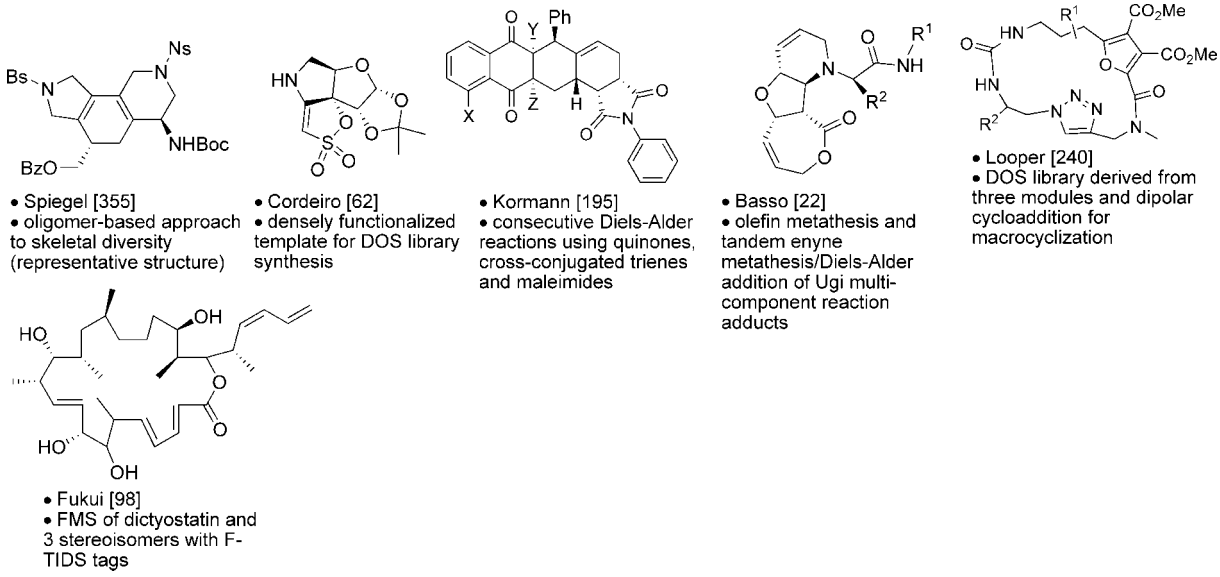


• Lu [242]
• DOS approach of plecomacrolides *via* diene-ene ring-closing metathesis



• Dandapani [67]
• one-pot cyclodimerization of pipecolic acids

Table 10. Continued



[a] The asterisk is the point of attachment to resin.

Table 11. Polymer-Supported and Fluorous Reagents and Scavengers

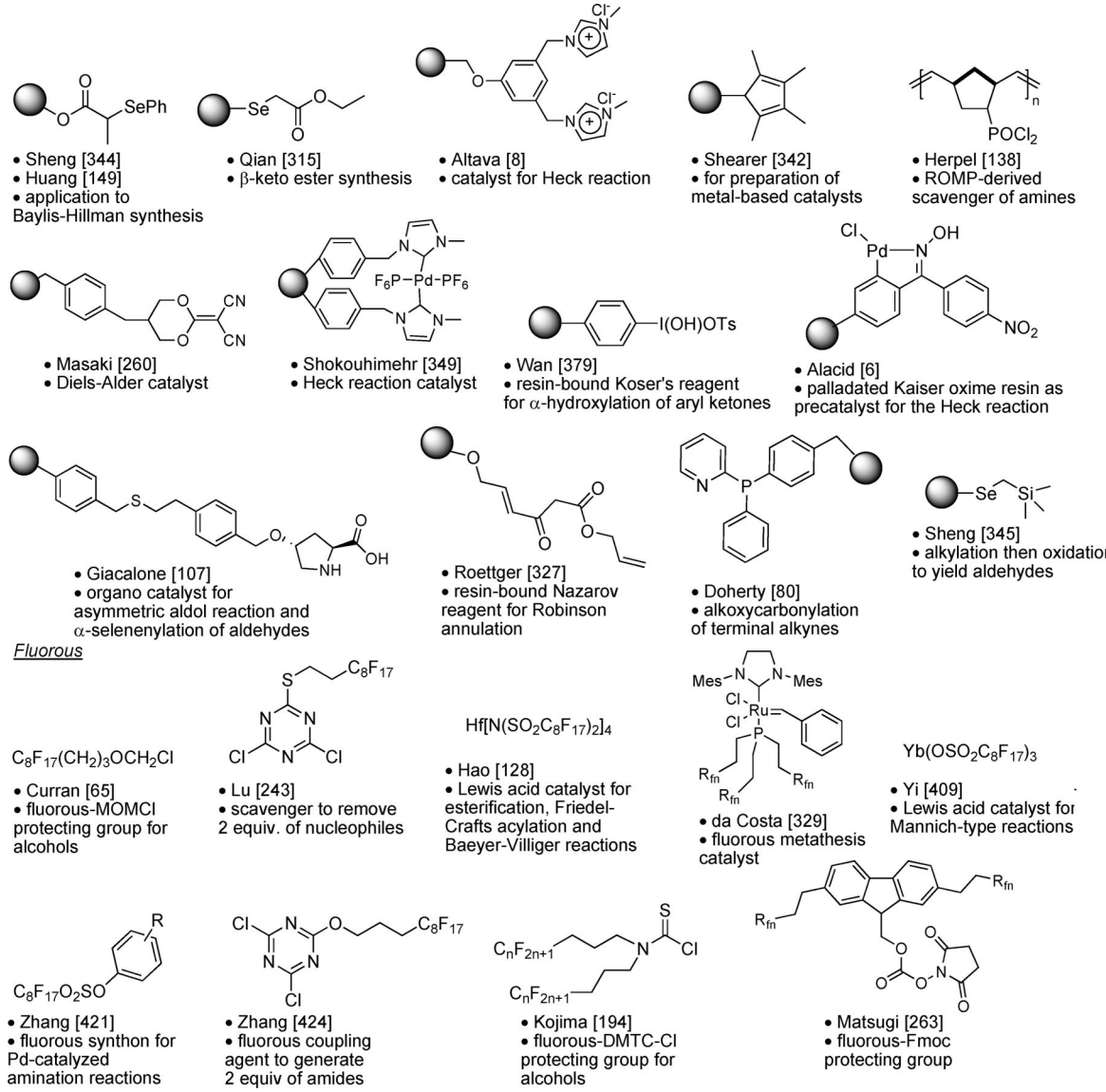


Table 11. Continued

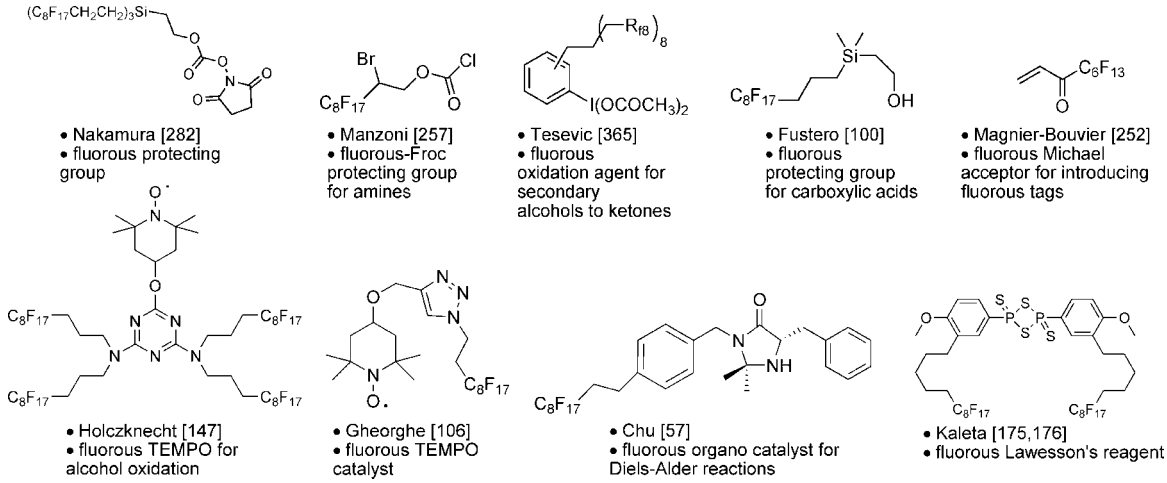


Table 12. Polymer-Supported and Fluorous Linkers

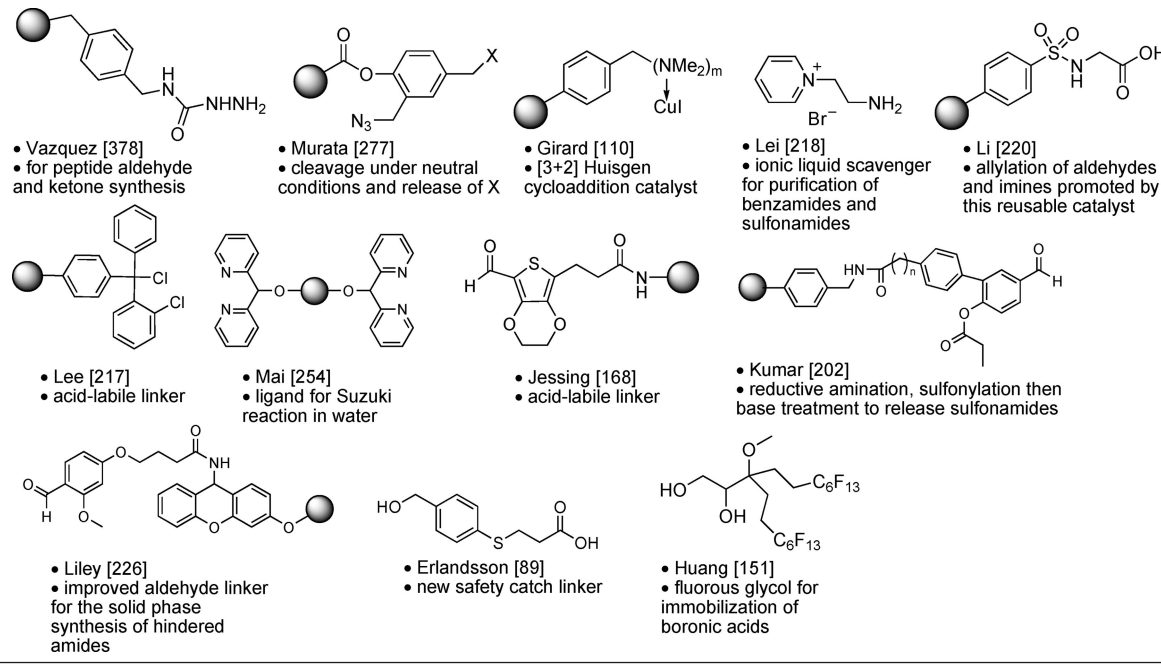
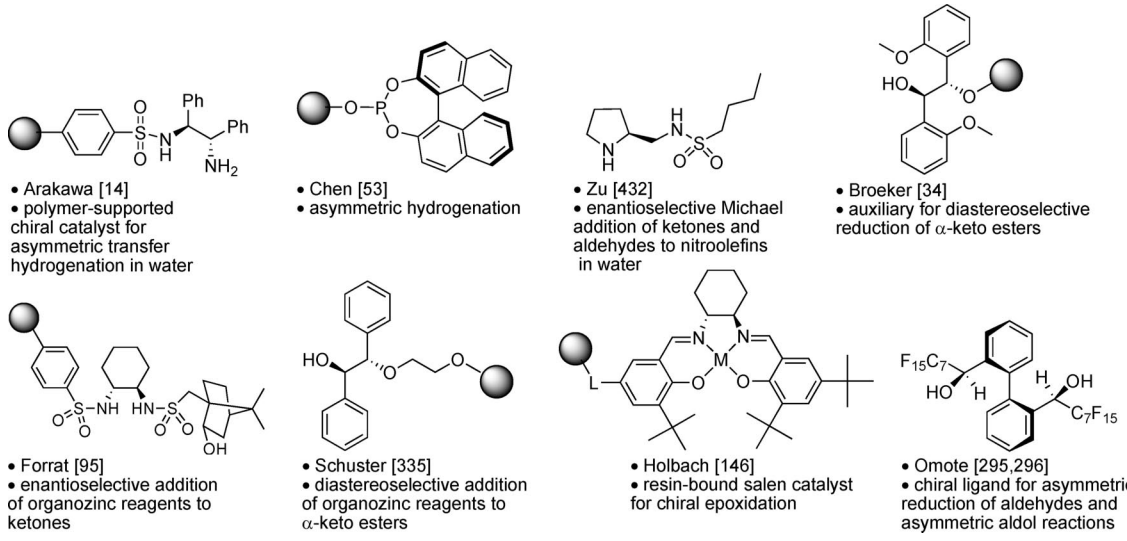


Table 13. Polymer-Supported and Fluorous Chiral Ligands



References and Notes

(1) Dolle, R. E.; Le Bourdonnec, B.; Morales, G. A.; Moriarty, K. J.; Salvino, J. M. *J. Comb. Chem.* **2006**, *8*, 597–635.
(2) Achatz, S.; Doemling, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6360–6362.
(3) Adamo, M. F. A.; Duffy, E. F. *Org. Lett.* **2006**, *8*, 5157–5159.
(4) Adib, M.; Mahmoodi, N.; Mahdavi, M.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 9365–9368.
(5) Adriaenssens, L. V.; Austin, C. A.; Gibson, M.; Smith, D.; Hartley, R. C. *Eur. J. Med. Chem.* **2006**, 4998–5001.
(6) Alacid, E.; Najera, C. *Synlett* **2006**, 2959–2964.
(7) Alonso De Diego, S. A.; Gutierrez-Rodriguez, M.; Perez de Vega, M. J.; Casabona, D.; Cativiela, C.; Gonzalez-Muniz, R.; Herranz, R.; Cenarruzabeitia, E.; Frechilla, D.; Del Rio, J.; Luisa Jimeno, M.; Teresa Garcia-Lopez, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1392–1396.
(8) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Karbass, N.; Luis, S. V.; Puzary, A.; Sans, V. *Tetrahedron Lett.* **2006**, *47*, 2311–2314.
(9) Andersen, T. F.; Tikhonov, D. B.; Bolcho, U.; Bolshakov, K.; Nelson, J. K.; Pluteanu, F.; Mellor, I. R.; Egebjerg, J.; Stromgaard, K. *J. Med. Chem.* **2006**, *49*, 5414–5423.
(10) Anderson, M. O.; Sherrill, J.; Madrid, P. B.; Liou, A. P.; Weisman, J. L.; DeRisi, J. L.; Guy, R. K. *Bioorg. Med. Chem.* **2006**, *14*, 334–343.
(11) Anderson, M. O.; Yu, H.; Penaranda, C.; Maddux, B. A.; Goldfine, I. D.; Youngren, J. F.; Guy, R. K. *J. Comb. Chem.* **2006**, *8*, 784–790.
(12) Antuch, W.; Menon, S.; Chen, Q.-Z.; Lu, Y.; Sakamuri, S.; Beck, B.; Schauer-Vukasinovic, V.; Agarwal, S.; Hess, S.; Doemling, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1740–1743.
(13) Aquino, M.; Bruno, I.; Riccio, R.; Gomez-Paloma, L. *Org. Lett.* **2006**, *8*, 4831–4834.
(14) Arakawa, Y.; Haraguchi, N.; Itsuno, S. *Tetrahedron Lett.* **2006**, *47*, 3239–3243.
(15) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437–2440.
(16) Back, T. G.; Zhai, H. *Chem. Commun.* **2006**, 326–328.
(17) Banfi, L.; Basso, A.; Guanti, G.; Paravidino, M.; Riva, R. *QSAR Comb. Sci.* **2006**, *25*, 457–460.
(18) Banfi, L.; Guanti, A. B. G.; Lecinska, P.; Riva, R. *Org. Biomol. Screening* **2006**, *4*, 4236–4240.
(19) Barluenga, S.; Dakas, P.-Y.; Ferandin, Y.; Meijer, L.; Winssinger, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 3951–3954.
(20) Bar-Nir, B. B.-A.; Portnoy, M. *Heterocycles* **2006**, *68*, 511–518.
(21) Barrero, A. F.; Quilez del Moral, J. F.; Herrador, M. M.; Cortes, M.; Arteaga, P.; Catalan, J. V.; Sanchez, E. M.; Arteaga, J. F. *J. Org. Chem.* **2006**, *71*, 5811–5814.
(22) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron* **2006**, *62*, 8830–8837.
(23) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. *Org. Lett.* **2006**, *8*, 5231–5234.
(24) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Chem.—Eur. J.* **2006**, *12*, 4407–4416.
(25) Beck, B.; Leppert, C. A.; Mueller, B. K.; Doemling, A. *QSAR Comb. Sci.* **2006**, *25*, 527–535.
(26) Bianchi, I.; Forlani, R.; Minetto, G.; Peretto, I.; Regalia, N.; Taddei, M.; Raveglia, L. F. *J. Comb. Chem.* **2006**, *8*, 491–499.
(27) Biron, E.; Chatterjee, J.; Kessler, H. *Org. Lett.* **2006**, *8*, 2417–2420.
(28) Blay, G.; Fernandez, I.; Molina, E.; Munoz, M. C.; Pedro, J. R.; Vila, C. *Tetrahedron* **2006**, *62*, 8069–8076.
(29) Bogatcheva, E.; Hanrahan, C.; Nikonenko, B.; Samala, R.; Chen, P.; Gearhart, J.; Barbosa, F.; Einck, L.; Nacy, C. A.; Protopopova, M. *J. Med. Chem.* **2006**, *49*, 3045–3048.
(30) Boggian, D. B.; Mata, E. G. *Synthesis* **2006**, 3397–3404.
(31) Bondebjerg, J.; Fuglsang, H.; Valeur, K. R.; Pedersen, J.; Naerum, L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3614–3617.
(32) Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2006**, *8*, 4351–4354.
(33) Boys, M. L.; Schretzman, L. A.; Chandrakumar, N. S.; Tollefson, M. B.; Mohler, S. B.; Downs, V. L.; Penning, T. D.; Russell, M. A.; Wendt, J. A.; Chen, B. B.; Stenmark, H. G.; Wu, H.; Spangler, D. P.; Clare, M.; Desai, B. N.; Khanna, I. K.; Nguyen, M. N.; Duffin, T.; Engleman, V. W.; Finn, M. B.; Freeman, S. K.; Hanneke, M. L.; Keene, J. L.; Klover, J. A.; Nickols, G. A.; Nickols, M. A.; Steininger, C. N.; Westlin, M.; Westlin, W.; Yu, Y. X.; Wang, Y.; Dalton, C. R.; Norring, S. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 839–844.
(34) Broeker, J.; Knollmueller, M.; Gaertner, P. *Tetrahedron: Asymmetry* **2006**, *17*, 2413–2429.
(35) Brouillette, Y.; Rombouts, F. J. R.; Lubell, W. D. *J. Comb. Chem.* **2006**, *8*, 117–126.
(36) Bui, C. T.; Flynn, B. L. *J. Comb. Chem.* **2006**, *8*, 163–167.
(37) Burns, M. R.; Jenkins, S. A.; Wood, S. J.; Miller, K.; David, S. A. *J. Comb. Chem.* **2006**, *8*, 32–43.
(38) Byk, G.; Kabha, E. *Synlett* **2006**, 747–748.
(39) Cao, J.; Tang, E.; Huang, X.; Wu, L. L.; Huang, X. *Chin. Chem. Lett.* **2006**, *17*, 857–858.
(40) Cardullo, F.; Donati, D.; Fusillo, V.; Merlo, G.; Paio, A.; Salaris, M.; Solinas, A.; Taddei, M. *J. Comb. Chem.* **2006**, *8*, 834–840.
(41) Carpenter, R. D.; DeBerdt, P. B.; Lam, K. S.; Kurth, M. J. *J. Comb. Chem.* **2006**, *8*, 907–914.
(42) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154–3157.
(43) Castanedo, G.; Clark, K.; Wang, S.; Tsui, V.; Wong, M.; Nicholas, J.; Wickramasinghe, D.; Marsters, J. C.; Sutherlin, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1716–1720.
(44) Cebasek, P.; Bevk, D.; Pirc, S.; Stanovnik, B.; Svete, J. *J. Comb. Chem.* **2006**, *8*, 95–102.
(45) Cee, V. J.; Downing, N. S. *Tetrahedron Lett.* **2006**, *47*, 3747–3750.
(46) Cervi, G.; Peri, F.; Battistini, C.; Gennari, C.; Nicotra, F. *Bioorg. Med. Chem.* **2006**, *14*, 3349–3367.
(47) Cesarini, S.; Colombo, N.; Pulici, M.; Felder, E. R.; Brill, W. K. D. *Tetrahedron* **2006**, *62*, 10223–10236.
(48) Chang, W.-J.; Kulkarni, M. V.; Sun, C.-M. *J. Comb. Chem.* **2006**, *8*, 141–144.
(49) Carotti, A.; Cadavid, M. I.; Centeno, N. B.; Esteve, C.; Loza, M. I.; Martinez, A.; Nieto, R.; Ravina, E.; Sanz, F.; Segarra, V.; Sotelo, E.; Stefanachi, A.; Vidal, B. *J. Med. Chem.* **2006**, *49*, 282–299.
(50) Chebanov, V. A.; Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Kappe, C. O. *J. Comb. Chem.* **2006**, *8*, 427–434.
(51) Chen, C.; Stearns, B.; Hu, T.; Anker, N.; Santini, A.; Arruda, J. M.; Campbell, B. T.; Datta, P.; Aiyar, J.; Munoz, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 746–749.
(52) Chen, S.; Do Jeong, T.; Zhang, Q.; Yao, S.; Yan, F.; Peters, E. C.; Scholer, H. R.; Schultz, P. G.; Ding, S. *Proc. Natl. Acad. Sci.* **2006**, *103*, 17266–17271.
(53) Chen, W.; Roberts, S. M.; Whittall, J. *Tetrahedron Lett.* **2006**, *47*, 4263–4266.
(54) Cheng, M.-F.; Yu, H.-M.; Ko, B.-W.; Chang, Y.; Chen, M.-Y.; Ho, T.-I.; Tsai, Y.-M.; Fang, J.-M. *Org. Biomol. Screening* **2006**, *4*, 510–518.
(55) Choi, S.-J.; Park, H. J.; Lee, S. K.; Kim, S. W.; Han, G.; Choo, H.-Y. P. *Bioorg. Med. Chem.* **2006**, *14*, 1229–1235.
(56) Chretien, J.-M.; Zammattio, F.; Gauthier, D.; Le Grognec, E.; Paris, M.; Quintard, J.-P. *Chem.—Eur. J.* **2006**, *12*, 6816–6828.
(57) Chu, Q.; Zhang, W.; Curran, D. P. *Tetrahedron Lett.* **2006**, *47*, 9287–9290.
(58) Coelho, A.; El-Maatougui, A.; Ravina, E.; Cavaleiro, J. A. S.; Silva, A. M. S. *Synlett* **2006**, 3324–3328.
(59) Coelho, A.; Sotelo, E. *J. Comb. Chem.* **2006**, *8*, 388–400.
(60) Coelho, A.; Sotelo, E. *Comb. Chem. High Throughput Screening* **2006**, *9*, 15–19.
(61) Cope, H.; Mutter, R.; Heal, W.; Pascoe, C.; Brown, P.; Pratt, S.; Chen, B. *Eur. J. Med. Chem.* **2006**, *41*, 1124–1143.
(62) Cordeiro, A.; Quesada, E.; Bonache, M.; Velazquez, S.; Camarasa, M.; Felix, A. *J. Org. Chem.* **2006**, *71*, 7224–7235.
(63) Cristau, P.; Vors, J.-P.; Zhu, J. *QSAR Comb. Sci.* **2006**, *25*, 519–526.

(64) Curran, D. P.; Moura-Letts, G.; Pohlman, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2423–2426.
(65) Curran, D. P.; Ogoe, C. *QSAR Comb. Sci.* **2006**, *25*, 732–735.
(66) Curran, D. P.; Zhang, Q.; Richard, C.; Lu, H.; Gudipati, V.; Wilcox, C. S. *J. Am. Chem. Soc.* **2006**, *128*, 9561–9573.
(67) Dandapani, S.; Lan, P.; Beeler, A. B.; Beischel, S.; Abbas, A.; Roth, B. L.; Porco, J. A., Jr.; Panek, J. S. *J. Org. Chem.* **2006**, *71*, 8934–8945.
(68) Dandia, A.; Singh, R.; Khaturia, S. *Bioorg. Med. Chem.* **2006**, *14*, 1303–8.
(69) Danieli, B.; Giardini, A.; Lesma, G.; Passarella, D.; Peretto, B.; Sacchetti, A.; Silvani, A.; Pratesi, G.; Zunino, F. *J. Org. Chem.* **2006**, *71*, 2848–2853.
(70) Das, J.; Chen, P.; Norris, D.; Padmanabha, R.; Lin, J.; Moquin, R. V.; Shen, Z.; Cook, L. S.; Doweyko, A. M.; Pitt, S.; Pang, S.; Shen, D. R.; Fang, Q.; de Fex, H. F.; McIntyre, K. W.; Shuster, D. J.; Gillooly, K. M.; Behnia, K.; Schieven, G. L.; Wityak, J.; Barrish, J. C. *J. Med. Chem.* **2006**, *49*, 6819–6832.
(71) Deng, H.; Bannister, T. D.; Jin, L.; Babine, R. E.; Quinn, J.; Nagafuji, P.; Celatka, C. A.; Lin, J.; Lazarova, T. I.; Rynkiewicz, M. J.; Bibbins, F.; Pandey, P.; Gorga, J.; Meyers, H. V.; Abdel-Meguid, S. S.; Strickler, J. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3049–3054.
(72) Desai, B.; Dallinger, D.; Kappe, C. O. *Tetrahedron* **2006**, *62*, 4651–4664.
(73) DiMaure, E. F.; Newcomb, J.; Nunes, J. L.; Bemis, J. E.; Boucher, C.; Buchanan, J. L.; Buckner, W. H.; Cee, V. J.; Chai, L.; Deak, H. L.; Epstein, L. F.; Faust, T.; Gallant, P.; Geuns-Myer, S. D.; Gore, A.; Gu, Y.; Henkle, B.; Hodous, B. L.; Hsieh, F.; Hunag, X.; Kim, J. L.; Lee, J. H.; Martin, M. W.; Masse, C. E.; McGowan, D. C.; Metz, D.; Mohn, D.; Morgenstern, K. A.; Oliveira-dos-Santos, A.; Patel, V. E.; Powers, D.; Rose, P. E.; Schneider, S.; Tomlinson, S. A.; Tudor, Y.-Y.; Turci, S. M.; Wlecher, A. A.; White, R. D.; Zhao, H.; Zhu, L.; Zhu, X. *J. Med. Chem.* **2006**, *49*, 5671–5686.
(74) Diness, F.; Beyer, J.; Meldal, M. *Chem.—Eur. J.* **2006**, *12*, 8056–8066.
(75) Ding, Y.; Girardet, J.-L.; Smith, K. L.; Larson, G.; Prigaro, B.; Wu, J. Z.; Yao, N. *Bioorg. Chem.* **2006**, *34*, 26–38.
(76) Dixon, S.; Ziebart, K. T.; He, Z.; Jeddeloh, M.; Yoo, C. L.; Wang, X.; Lehman, A.; Lam, K. S.; Toney, M. D.; Kurth, M. J. *J. Med. Chem.* **2006**, *49*, 7413–7426.
(77) Dixon, S. M.; Li, P.; Liu, R.; Wolosker, H.; Lam, K. S.; Kurth, M. J.; Toney, M. D. *J. Med. Chem.* **2006**, *49*, 2388–2397.
(78) Domling, A.; Beck, B.; Fuchs, T.; Yazbak, A. *J. Comb. Chem.* **2006**, *8*, 872–880.
(79) Domling, A.; Beck, B.; Magnin-Lachaux, M. *Tetrahedron Lett.* **2006**, *47*, 4289–4291.
(80) Doherty, S.; Knight, J. G.; Betham, M. *Chem. Commun.* **2006**, 88–90.
(81) Doi, T.; Hoshina, Y.; Mogi, H.; Yamada, Y.; Takahashi, T. *J. Comb. Chem.* **2006**, *8*, 571–582.
(82) Donelson, J. L.; Hodges, H. B.; MacDougall, D. D.; Henriksen, B. S.; Hrycyna, C. A.; Gibbs, R. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4420–4423.
(83) Dorbec, M.; Florent, J.-C.; Monneret, C.; Rager, M.-N.; Bertounesque, E. *Tetrahedron* **2006**, *62*, 11766–11781.
(84) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077–3079.
(85) El Kaim, L.; Grimaud, L.; Miranda, L. D.; Vieu, E. *Tetrahedron Lett.* **2006**, *47*, 8259–8261.
(86) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019–4021.
(87) El Kaim, L.; Grimaud, L.; Hadrot, S. *Tetrahedron Lett.* **2006**, *47*, 3945–3947.
(88) Eriksson, J.; Olsson, T.; Kann, N.; Graden, H. *Tetrahedron Lett.* **2006**, *47*, 635–638.
(89) Erlandsson, M.; Unden, A. *Tetrahedron Lett.* **2006**, *47*, 5829–5832.
(90) Ermolat′ev, D. S.; Gimenez, V. N.; Babaev, E. V.; Van der Eycken, E. *J. Comb. Chem.* **2006**, *8*, 659–663.
(91) Evans, K. A.; Chai, D.; Graybill, T. L.; Burton, G.; Sarisky, R. T.; Lin-Goerke, J.; Johnston, V. K.; Rivero, R. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2205–2208.
(92) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802–1808.
(93) Extance, A. R.; Benzies, D. W. M.; Morrish, J. J. *QSAR Comb. Sci.* **2006**, *25*, 484–490.
(94) Fernandez, J.-C.; Sole-Feu, L.; Fernandez-Forner, D.; de la Figuera, N.; Forns, P.; Albericio, F. *QSAR Comb. Sci.* **2006**, *25*, 961–965.
(95) Forrat, V. J.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2054–2058.
(96) Franckevicius, V.; Longbottom, D. A.; Turner, R. M.; Ley, S. V. *Synthesis* **2006**, 3215–3223.
(97) Fuchter, M. J.; Hoffman, B. M.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 724–729.
(98) Fukui, Y.; Brueckner, A. M.; Shin, Y.; Balachandran, R.; Day, B. W.; Curran, D. P. *Org. Lett.* **2006**, *8*, 301–304.
(99) Fustero, S.; Catalan, S.; Flores, S.; Jimenez, D.; del Pozo, C.; Acena, J. L.; Sanz-Cervera, J. F.; Merida, S. *QSAR Comb. Sci.* **2006**, *25*, 753–760.
(100) Fustero, S.; Garcia Sancho, A.; Chiva, G.; Sanz-Cervera, J. F.; Del Pozo, C.; Acena, J. L. *J. Org. Chem.* **2006**, *71*, 3299–3302.
(101) Gao, Y.; Lam, Y. *Org. Lett.* **2006**, *8*, 3283–3285.
(102) Gavrilyuk, J. I.; Evindar, G.; Batey, R. A. *J. Comb. Chem.* **2006**, *8*, 237–246.
(103) Gebinoga, M.; Gross, G. A.; Albrecht, A.; Luebeck, T.; Henkel, T.; Hoffmann, P.; Klemm, U.; Schlingloff, G.; Frank, T.; Schober, A. *QSAR Comb. Sci.* **2006**, *25*, 1063–1068.
(104) Gelens, E.; De Kanter, F. J. J.; Schmitz, R. F.; Sliedregt, L. A. J. M.; Van Steen, B. J.; Kruse, C. G.; Leurs, R.; Groen, M. B.; Orru, R. V. A. *Mol. Diversity* **2006**, *10*, 17–22.
(105) Gerard, B.; Ryan, J.; Beeler, A. B.; Porco, J. A., Jr. *Tetrahedron* **2006**, *62*, 6405–6411.
(106) Gheorghe, A.; Cuevas-Yanez, E.; Horn, J.; Bannwarth, W.; Narsaiah, B.; Reiser, O. *Synlett* **2006**, 2767–2770.
(107) Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Noto, R. *Tetrahedron Lett.* **2006**, *48*, 255–259.
(108) Gilleron, P.; Millet, R.; Houssin, R.; Wlodarczyk, N.; Farce, A.; Lemoine, A.; Goossens, J. F.; Chavatte, P.; Pommery, N.; Henichart, J. P. *Eur. J. Med. Chem.* **2006**, *41*, 745–755.
(109) Giovenzana, G. B.; Tron, G. C.; Di Paola, S.; Menegotto, I. G.; Pirali, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1099–1102.
(110) Girard, C.; Oenen, E.; Aufort, M.; Beauviere, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689–1692.
(111) Goess, B. C.; Hannoush, R. N.; Chan, L. K.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 5391–5403.
(112) Golub, A. G.; Yakovenko, O. Y.; Bdzhola, V. G.; Sapelkin, V. M.; Zien, P.; Yarmoluk, S. M. *J. Med. Chem.* **2006**, *49*, 6443–6450.
(113) Gong, X.; Yang, X. X.; Wang, D. X. *Chin. Chem. Lett.* **2006**, *17*, 469–472.
(114) Goodell, J. R.; Puig-Basagoiti, F.; Forshey, B. M.; Shi, P.-Y.; Ferguson, D. M. *J. Med. Chem.* **2006**, *49*, 2127–2137.
(115) Gopi, H. N.; Tirupula, K. C.; Baxter, S.; Ajith, S.; Chaiken, I. M. *ChemMedChem* **2006**, *1*, 54–57.
(116) Devel, L.; Rogakos, V.; David, A.; Makaritis, A.; Beau, F.; Cuniasse, P.; Yiotakis, A.; Dive, V. *J. Biol. Chem.* **2006**, *281*, 11152–11160.
(117) Goto, Y.; Arai-Otsuki, S.; Tachibana, Y.; Ichikawa, D.; Ozaki, S.; Takahashi, H.; Iwasawa, Y.; Okamoto, O.; Okuda, S.; Ohta, H.; Sagara, T. *J. Med. Chem.* **2006**, *49*, 847–849.
(118) Grigg, R.; Cook, A. *Tetrahedron* **2006**, *62*, 12172–12181.
(119) Gross, G. A.; Mayer, G.; Albert, J.; Riester, D.; Osterodt, J.; Wurziger, H.; Schober, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 3102–3106.
(120) Gross, G. A.; Wurziger, H.; Schlingloff, G.; Schober, A. *QSAR Comb. Sci.* **2006**, *25*, 1055–1062.
(121) Gross, G. A.; Wurziger, H.; Schober, A. *J. Comb. Chem.* **2006**, *8*, 153–155.
(122) Guarise, C.; Prins, L. J.; Scrimin, P. *Tetrahedron* **2006**, *62*, 11670–11674.

(123) Gudipati, V.; Curran, D. P.; Wilcox, C. S. *J. Org. Chem.* **2006**, *71*, 3599–3607.
(124) Gupta, R. N.; Vaidya, V. A.; Bhatia, N. M.; Kokare, C. R.; Singhvi, I.; Bhatia, M. S. *Asian J. Chem.* **2006**, *18*, 937–941.
(125) Habashita, H.; Kokubo, M.; Hamano, S.-I.; Hamanaka, N.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *J. Med. Chem.* **2006**, *49*, 4140–4152.
(126) Hamada, Y.; Igawa, N.; Ikari, H.; Ziora, Z.; Nguyen, J.; Yamani, A.; Hidaka, K.; Kimura, T.; Saito, K.; Hayashi, Y.; Ebina, M.; Ishiura, S.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4354–4359.
(127) Hamilton, G. L.; Backes, B. J. *Tetrahedron Lett.* **2006**, *47*, 967–968.
(128) Hao, X.; Yoshida, A.; Nishikido, J. *J. Fluorine Chem.* **2006**, *127*, 193–199.
(129) Harju, K.; Kylaenlahti, I.; Paananen, T.; Polamo, M.; Nielsen, J.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2006**, *8*, 344–349.
(130) Harvey, A. J.; Baell, J. B.; Toovey, N.; Homerick, D.; Wulff, H. *J. Med. Chem.* **2006**, *49*, 1433–1441.
(131) Hatamjafari, F. *Syn. Commun.* **2006**, *36*, 3563–3570.
(132) He, R.; Ching, S. M.; Lam, Y. *J. Comb. Chem.* **2006**, *8*, 923–928.
(133) He, X.; Alian, A.; Stroud, R.; Ortiz de Montellano, P. R. *J. Med. Chem.* **2006**, *49*, 6308–6323.
(134) He, Y.; Wilkins, J. P.; Kiessling, L. L. *Org. Lett.* **2006**, *8*, 2483–2485.
(135) Henon, H.; Anizon, F.; Kucharczyk, N.; Loynel, A.; Casara, P.; Pfeiffer, B.; Prudhomme, M. *Synthesis* **2006**, 711–715.
(136) Hensler, M. E.; Bernstein, G.; Nizet, V.; Nefzi, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5073–5079.
(137) Hernan, A. G.; Horton, P. N.; Hursthouse, M. B.; Kilburn, J. D. *J. Organomet. Chem.* **2006**, *691*, 1466–1475.
(138) Herpel, R. H.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *Tetrahedron Lett.* **2006**, *47*, 6429–6432.
(139) Hershberger, J. C.; Zhang, L.; Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2006**, *71*, 231–235.
(140) Heynekamp, J. J.; Weber, W. M.; Hunsaker, L. A.; Gonzales, A. M.; Orlando, R. A.; Deck, L. M.; Jagt, D. L. V. *J. Med. Chem.* **2006**, *49*, 7182–7189.
(141) Hioki, H.; Matsushita, K.; Kubo, M.; Kodama, M. *J. Comb. Chem.* **2006**, *8*, 462–463.
(142) Hirsh, A. J.; Molino, B. F.; Zhang, J.; Astakhova, N.; Geiss, W. B.; Sargent, B. J.; Swenson, B. D.; Usyatinsky, A.; Wyle, M. J.; Boucher, R. C.; Smith, R. T.; Zamurs, A.; Johnson, M. R. *J. Med. Chem.* **2006**, *49*, 4098–4115.
(143) Hoenke, N.; Payne, L. J.; Parsons, P. J.; Hitchcock, P. B. *Synlett* **2006**, 654–656.
(144) Hoesl, C. E.; Ostresh, J. M.; Houghten, R. A.; Nefzi, A. *J. Comb. Chem.* **2006**, *8*, 127–131.
(145) Hok, S.; Schore, N. E. *J. Org. Chem.* **2006**, *71*, 1736–1738.
(146) Holbach, M.; Weck, M. *J. Org. Chem.* **2006**, *71*, 1825–1836.
(147) Holczknecht, O.; Pozzi, G.; Quici, S. *QSAR Comb. Sci.* **2006**, *25*, 736–741.
(148) Howard, N.; Abell, C.; Blakemore, W.; Chessari, G.; Congreve, M.; Howard, S.; Jhoti, H.; Murray, C. W.; Seavers, L. C. A.; Van Montfort, R. L. M. *J. Med. Chem.* **2006**, *49*, 1346–1355.
(149) Huang, B.; Sheng, S.-R.; Huang, Y.-X.; Xin, Q.; Song, L.-Y.; Luo, N.-H. *J. Chem. Res.* **2006**, 623–625.
(150) Huang, C.-Y.; Stauffer, T. M.; Strickland, C. L.; Reader, J. C.; Huang, H.; Li, G.; Cooper, A. B.; Doll, R. J.; Ganguly, A. K.; Baldwin, J. J.; Rokosz, L. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 507–511.
(151) Huang, Y.; Qing, F.-L. *QSAR Comb. Sci.* **2006**, *25*, 716–718.
(152) Huck, B. R.; Llamas, L.; Robarge, M. J.; Dent, T. C.; Song, J.; Hodnick, W. F.; Crumrine, C.; Stricker-Krongrad, A.; Harrington, J.; Brunden, K. R.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4130–4134.
(153) Hunter, R. A.; Macfarlane, D. P. S.; Whitby, R. J. *Synlett* **2006**, 3314–3318.
(154) Hwang, J. Y.; Choi, H.-S.; Seo, J.-S.; La, H.-J.; Yoo, S.-E.; Gong, Y.-D. *J. Comb. Chem.* **2006**, *8*, 897–906.
(155) Zu, L.; Li, H.; Wang, J.; Yu, X.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 5131–5134.
(156) Hwang, J. Y.; Gong, Y.-D. *J. Comb. Chem.* **2006**, *8*, 297–303.
(157) Hwang, S. H.; Morisseau, C.; Do, Z.; Hammock, B. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5773–5777.
(158) Ilyin, A.; Kobak, V.; Dmitrieva, I.; Peregudova, Y.; Kustova, V.; Mishunina, Y.; Tkachenko, S.; Ivachtchenko, A. *Syn. Commun.* **2006**, *36*, 903–910.
(159) Ilyin, A.; Kysil, V.; Krasavin, M.; Kurashvili, I.; Ivachtchenko, A. V. *J. Org. Chem.* **2006**, *71*, 9544–9547.
(160) Ilyin, A. P.; Parchinski, V. Z.; Peregudova, J. N.; Trifilenkov, A. S.; Poutsykina, E. B.; Tkachenko, S. E.; Kravchenko, D. V.; Ivachtchenko, A. V. *Tetrahedron Lett.* **2006**, *47*, 2649–2653.
(161) Ilyn, A. P.; Loseva, M. V.; Vvedensky, V. Y.; Putsykina, E. B.; Tkachenko, S. E.; Kravchenko, D. V.; Khvat, A. V.; Krasavin, M. Y.; Ivachtchenko, A. V. *J. Org. Chem.* **2006**, *71*, 2811–2819.
(162) Ilyin, A. P.; Trifilenkov, A. S.; Kovrigin, D. I.; Yudin, M. V.; Ivachtchenko, A. V. *Heterocycl. Commun.* **2006**, *12*, 107–110.
(163) Ivanova, N. V.; Sviridov, S. I.; Stepanov, A. E. *Tetrahedron Lett.* **2006**, *47*, 8025–8027.
(164) Jang, M.-Y.; De Jonghe, S.; Gao, L.-J.; Rozenski, J.; Herdewijn, P. *Eur. J. Med. Chem.* **2006**, 4257–4269.
(165) Jayashankaran, J.; Manian, R. D. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *47*, 2265–2270.
(166) Jeon, H. S.; Kim, J. N.; Kim, T. H. *J. Comb. Chem.* **2006**, *8*, 799–801.
(167) Jeon, H. S.; Yoo, J. H.; Kim, J. N.; Kim, T. H. *Tetrahedron Lett.* **2006**, *48*, 439–441.
(168) Jessing, M.; Brandt, M.; Jensen, K. J.; Christensen, J. B.; Boas, U. *J. Org. Chem.* **2006**, *71*, 6734–6741.
(169) Jhala, Y. S.; Gahlot, U. S.; Dulawat, S. S.; Verma, B. L. *Heterocycl. Commun.* **2006**, *12*, 253–258.
(170) Ji, H.; Gomez-Vidal, J. A.; Martasek, P.; Roman, L. J.; Silverman, R. B. *J. Med. Chem.* **2006**, *49*, 6254–6263.
(171) Jian, S.-Z.; Yuan, Q.; Wang, Y.-G. *Synthesis* **2006**, 1829–1835.
(172) Joossens, J.; Van der Veken, P.; Surpateanu, G.; Lambeir, A.-M.; El-Sayed, I.; Ali, O. M.; Augustyns, K.; Haemers, A. *J. Med. Chem.* **2006**, *49*, 5785–5793.
(173) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661–662.
(174) Zhu, T.; Yan, Z.; Chucholowski, A.; Webb, T. R.; Li, R. *J. Comb. Chem.* **2006**, *8*, 401–409.
(175) Kaleta, Z.; Makowski, B. T.; Soos, T.; Dembinski, R. *Org. Lett.* **2006**, *8*, 1625–1628.
(176) Kaleta, Z.; Tarkanyi, G.; Goemoery, A.; Kalman, F.; Nagy, T.; Soos, T. *Org. Lett.* **2006**, *8*, 1093–1095.
(177) Kalinski, C.; Umkehrer, M.; Gonnard, S.; Jaeger, N.; Ross, G.; Hiller, W. *Tetrahedron Lett.* **2006**, *47*, 2041–2044.
(178) Kalinski, C.; Umkehrer, M.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W. *Tetrahedron Lett.* **2006**, *47*, 3423–3426.
(179) Kalinski, C.; Umkehrer, M.; Schmidt, J.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W.; Hoffmann, S. D. *Tetrahedron Lett.* **2006**, *47*, 4683–4686.
(180) Kamal, A.; Devaiah, V.; Shankaraiah, N.; Reddy, K. L. *Synlett* **2006**, 2609–2612.
(181) Kamal, A.; Shankaraiah, N.; Devaiah, V.; Reddy, K. L. *Tetrahedron Lett.* **2006**, *47*, 9025–9028.
(182) Kamal, A.; Shankaraiah, N.; Reddy, K. L.; Devaiah, V. *Tetrahedron Lett.* **2006**, *47*, 4253–4257.
(183) Kanizsai, I.; Szakonyi, Z.; Sillanpaeae, R.; Fueloep, F. *Tetrahedron Lett.* **2006**, *47*, 9113–9116.
(184) Karskela, T.; Loennberg, H. *Org. Biomol. Screening* **2006**, *4*, 4506–4513.
(185) Kasahara, T.; Kondo, Y. *Chem. Commun.* **2006**, 891–893.
(186) Kasahara, T.; Kondo, Y. *Heterocycles* **2006**, *67*, 95–100.
(187) Kavitha, C. V.; Basappa; Swamy, S. N.; Mantelingu, K.; Doreswamy, S.; Sridhar, M. A.; Shashidhara Prasad, J.; Rangappa Kanchugarakoppal, S. *Bioorg. Med. Chem.* **2006**, *14*, 2290–2299.

(188) Khan, K. M.; Ullah, Z.; Lodhi, M. A.; Ali, M.; Choudhary, M. I.; ur Rahman, A.; ul Haq, Z. *Mol. Diversity* **2006**, *10*, 223–231.
(189) Kahnberg, P.; Lucke, A. J.; Glenn, M. P.; Boyle, G. M.; Tyndall, J. D. A.; Parsons, P. G.; Fairlie, D. P. *J. Med. Chem.* **2006**, *49*, 7611–7622.
(190) Kikuchi, S.; Hashimoto, Y. *Heterocycles* **2006**, *68*, 453–457.
(191) Kim, J.-W.; Cho, J.-H.; Han, T.; Lee, J.; Oh, C.-H. *Bull. Korean Chem. Soc.* **2006**, *27*, 484–488.
(192) Kim, P.; Zhang, Y.-M.; Shenoy, G.; Nguyen, Q.-A.; Boshoff, H. I.; Manjunatha, U. H.; Goodwin, M. B.; Lonsdale, J.; Price, A. C.; Miller, D. J.; Duncan, K.; White, S. W.; Rock, C. O.; Barry, C. E., III; Dowd, C. S. *J. Med. Chem.* **2006**, *49*, 159–171.
(193) Ko, S. K.; Jang, H. J.; Kim, E.; Park, S. B. *Chem. Commun.* **2006**, 2962–2964.
(194) Kojima, M.; Nakamura, Y.; Ishikawa, T.; Takeuchi, S. *Tetrahedron Lett.* **2006**, *47*, 6309–6314.
(195) Kormann, C.; Heinemann, F. W.; Gmeiner, P. *Tetrahedron* **2006**, *62*, 6899–6908.
(196) Kou, B.-B.; Zhang, F.; Yang, T.-M.; Liu, G. *J. Comb. Chem.* **2006**, *8*, 841–847.
(197) Kowalski, J. A.; Leonard, S. F.; Lee, G. E., Jr. *J. Comb. Chem.* **2006**, *8*, 774–779.
(198) (a) Kravchenko, D. V.; Ivanenkov, Y. A.; Balakin, K. V.; Kisil, V. M.; Tkachenko, S. E.; Okun, I. M.; Ivashchenko, A. V. *Pharm. Chem. J.* **2006**, *40*, 127–131. (b) Okun, I.; Malarchuk, S.; Dubrovskaya, E.; Khvat, A.; Tkachenko, S.; Kysil, V.; Ilyin, A.; Kravchenko, D.; Prossnitz, E. R.; Sklar, L.; Ivachtchenko, A. *J. Biomol. Screening* **2006**, *11*, 277–285.
(199) Ku, I. W.; Cho, S.; Doddareddy, M. R.; Jang, M. S.; Keum, G.; Lee, J.-H.; Chung, B. Y.; Kim, Y.; Rhim, H.; Kang, S. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5244–5248.
(200) Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635–3638.
(201) Kumar, A.; Koul, S.; Razdan, T. K.; Kapoor, K. K. *Tetrahedron Lett.* **2006**, *47*, 837–842.
(202) Kumar, A.; Ye, G.; Ahmadibeni, Y.; Parang, K. *J. Org. Chem.* **2006**, *71*, 7915–7918.
(203) Kurosu, M. *Tetrahedron Lett.* **2006**, *47*, 3395–3399.
(204) Kurosu, M.; Dey, S. S.; Crick, D. C. *Tetrahedron Lett.* **2006**, *47*, 4871–4875.
(205) Kuster, G. J. T.; van Berkom, L. W. A.; Kalmoua, M.; Van Loevezijn, A.; Sliedregt, L. A. J. M.; Van Steen, B. J.; Kruse, C. G.; Rutjes, F. P. J. T.; Scheeren, H. W. *J. Comb. Chem.* **2006**, *8*, 85–94.
(206) Ladziata, U.; Willging, J.; Zhdankin, V. V. *Org. Lett.* **2006**, *8*, 167–170.
(207) Lagerlund, O.; Larhed, M. *J. Comb. Chem.* **2006**, *8*, 4–6.
(208) Larbig, G.; Schmidt, B. *J. Comb. Chem.* **2006**, *8*, 480–490.
(209) Lattmann, E.; Merino, I.; Dunn, S.; Parveen, B.; Lattmann, P.; Billington, D. C.; Bunprakob, Y.; Sattayasai, J. *Lett. Drug Des. Discovery* **2006**, *3*, 49–54.
(210) Lattmann, E.; Sattayasai, N.; Schwalbe, C. S.; Niamsanit, S.; Billington, D. C.; Lattmann, P.; Langley, C. A.; Singh, H.; Dunn, S. *Curr. Drug Discovery Technol.* **2006**, *3*, 125–134.
(211) Lau, J. F.; Jeppesen, C. B.; Rimvall, K.; Hohlweg, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5303–5308.
(212) Le Lamer, A.-C.; Gouault, N.; David, M.; Boustie, J.; Uriac, P. *J. Comb. Chem.* **2006**, *8*, 643–645.
(213) Lee, K.; Moon, S.-J.; Ha, D.-C.; Lee, K.-I.; Gong, Y.-D.; Lee, J.-C. *Bull. Korean Chem. Soc.* **2006**, *27*, 974–975.
(214) Lee, S.; Sivakumar, K.; Shin, W.; Xie, F.; Wang, Q. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4596–4599.
(215) Lee, S.-C.; Choi, S. Y.; Chung, Y. K.; Park, S. B. *Tetrahedron Lett.* **2006**, *47*, 6843–6847.
(216) Lee, S.-C.; Park, S. B. *J. Comb. Chem.* **2006**, *8*, 50–57.
(217) Lee, T.-K.; Ryoo, S.-J.; Lee, Y.-S. *Tetrahedron Lett.* **2006**, *48*, 389–391.
(218) Lei, M.; Tao, X.-L.; Wang, Y.-G. *Helv. Chim. Acta* **2006**, *89*, 532–536.
(219) Lesma, G.; Danieli, B.; Lodroni, F.; Passarella, D.; Sacchetti, A.; Silvani, A. *Comb. Chem. High Throughput Screening* **2006**, *9*, 691–701.
(220) Li, G.; Zhao, G. *Org. Lett.* **2006**, *8*, 633–636.
(221) Li, J.; Zhang, J.; Chen, J.; Luo, X.; Zhu, W.; Shen, J.; Liu, H.; Shen, X.; Jiang, H. *J. Comb. Chem.* **2006**, *8*, 326–337.
(222) Li, J.-H.; Hu, X.-C.; Xie, Y.-X. *Tetrahedron Lett.* **2006**, *47*, 9239–9243.
(223) Li, R.; Xue, L.; Zhu, T.; Jiang, Q.; Cui, X.; Yan, Z.; McGee, D.; Wang, J.; Gantla, V. R.; Pickens, J. C.; McGrath, D.; Chucholowski, A.; Morris, S. W.; Webb, T. R. *J. Med. Chem.* **2006**, *49*, 1006–1015.
(224) Li, Y. H.; Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Patel, M.; Gale, J.; Li, H.; Tavares, F.; Thomson, S. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5892–5896.
(225) Liang, F.-S.; Brik, A.; Lin, Y.-C.; Elder, J. H.; Wong, C.-H. *Bioorg. Med. Chem.* **2006**, *14*, 1058–1062.
(226) Liley, M. J.; Johnson, T.; Gibson, S. E. *J. Org. Chem.* **2006**, *71*, 1322–1329.
(227) Limbeck, M.; Wamhoff, H.; Roelle, T.; Griebenow, N. *Tetrahedron Lett.* **2006**, *47*, 2945–2948.
(228) Lin, J.; Deng, H.; Jin, L.; Pandey, P.; Quinn, J.; Cantin, S.; Rynkiewicz, M. J.; Gorga, J. C.; Bibbins, F.; Celatka, C. A.; Nagafuji, P.; Bannister, T. D.; Meyers, H. V.; Babine, R. E.; Hayward, N. J.; Weaver, D.; Benjamin, H.; Stassen, F.; Abdel-Meguid, S. S.; Strickler, J. E. *J. Med. Chem.* **2006**, *49*, 7781–7791.
(229) Lin, M.-J.; Sun, C.-M. *J. Comb. Chem.* **2006**, *8*, 455–458.
(230) Lin, Q.; Blackwell, H. E. *Chem. Commun.* **2006**, 2884–2886.
(231) Lin, S.-Y.; Isome, Y.; Stewart, E.; Liu, J.-F.; Yohannes, D.; Yu, L. *Tetrahedron Lett.* **2006**, *47*, 2883–2886.
(232) Lindquist, C.; Ersoy, O.; Somfai, P. *Tetrahedron* **2006**, *62*, 3439–3445.
(233) Lingaiah, B. V.; Ezikiel, G.; Yakaiah, T.; Reddy, G. V.; Rao, P. S. *Synlett* **2006**, 2507–2509.
(234) Liu, J.; Dang, Q.; Wei, Z.; Shi, F.; Bai, X. *J. Comb. Chem.* **2006**, *8*, 410–416.
(235) Liu, J.-F.; Kaselj, M.; Isome, Y.; Ye, P.; Sargent, K.; Sprague, K.; Cherrak, D.; Wilson, C. J.; Si, Y.; Yohannes, D.; Ng, S.-C. *J. Comb. Chem.* **2006**, *8*, 7–10.
(236) Liu, X.-L.; Sheng, S.-R.; Wang, Q.-Y.; Sun, W.-K.; Xin, Q.; Ao, H.-Y. *J. Chem. Res.* **2006**, 118–120.
(237) Liu, Y.; Mills, A. D.; Kurth, M. J. *Tetrahedron Lett.* **2006**, *47*, 1985–1988.
(238) Liu, Z.; Zhao, J.; Huang, X. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1828–1830.
(239) Loaiza, P. R.; Lober, S.; Hubner, H.; Gmeiner, P. *J. Comb. Chem.* **2006**, *8*, 252–261.
(240) Looper, R. E.; Pizzirani, D.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 2063–2066.
(241) Lu, F.; Chi, S.-W.; Kim, D.-H.; Han, K.-H.; Kuntz, I. D.; Guy, R. K. *J. Comb. Chem.* **2006**, *8*, 315–325.
(242) Lu, K.; Huang, M.; Xiang, Z.; Liu, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2006**, *8*, 1193–1196.
(243) Lu, Y.; Zhang, W. *QSAR Comb. Sci.* **2006**, *25*, 728–731.
(244) Lucke, A. J.; Boyle, G. M.; Parsons, P. G.; Fairlie, D. P. *Med. Chem.* **2006**, *2*, 123–132.
(245) Lundquist, J. T.; Satterfield, A. D.; Pelletier, J. C. *Org. Lett.* **2006**, *8*, 3915–3918.
(246) Lysek, R.; Schuetz, C.; Favre, S.; O'Sullivan, A. C.; Pillonel, C.; Kruelle, T.; Jung, P. M. J.; Clotet-Codina, I.; Este, J. A.; Vogel, P. *Bioorg. Med. Chem.* **2006**, *14*, 6255–6282.
(247) Ma, L.; Williard, P. G. *Tetrahedron: Asymmetry* **2006**, *17*, 3021–3029.
(248) Ma, V.; Bannon, A. W.; Baumgartner, J.; Hale, C.; Hsieh, F.; Hulme, C.; Rorrer, K.; Salon, J.; van Staden, C.; Tempest, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5066–5072.
(249) Ma, Z.; Xiang, Z.; Luo, T.; Lu, K.; Xu, Z.; Chen, J.; Yang, Z. *J. Comb. Chem.* **2006**, *8*, 696–704.
(250) Macleod, C.; Martinez-Teipel, B. I.; Barker, W. M.; Dolle, R. E. *J. Comb. Chem.* **2006**, *8*, 132–140.
(251) Madrid, P. B.; Liou, A. P.; DeRisi, J. L.; Guy, R. K. *J. Med. Chem.* **2006**, *49*, 4535–4543.

(252) Magnier-Bouvier, C.; Blazejewski, J.-C.; Larpent, C.; Magnier, E. *Tetrahedron Lett.* **2006**, *47*, 9121–9124.
(253) Mahajan, S. S.; Hou, L.; Doneanu, C.; Paranji, R.; Maeda, D.; Zebala, J.; Atkins, W. M. *J. Am. Chem. Soc.* **2006**, *128*, 8615–8625.
(254) Mai, W.; Gao, L. *Synlett* **2006**, 2553–2558.
(255) Mamidyala, S. K.; Firestine, S. M. *Tetrahedron Lett.* **2006**, *47*, 7431–7434.
(256) Mang, C.; Jakupovic, S.; Schunk, S.; Ambrosi, H.-D.; Schwarz, O.; Jakupovic, J. *J. Comb. Chem.* **2006**, *8*, 268–274.
(257) Manzoni, L.; Castelli, R. *Org. Lett.* **2006**, *8*, 955–957.
(258) Marsault, E.; Hoveyda, H. R.; Peterson, M. L.; Saint-Louis, C.; Landry, A.; Vezina, M.; Ouellet, L.; Wang, Z.; Ramaseshan, M.; Beaubien, S.; Benakli, K.; Beauchemin, S.; Deziel, R.; Peeters, T.; Fraser, G. L. *J. Med. Chem.* **2006**, *49*, 7190–7197.
(259) Mas, V.; Falco, A.; Brocal, I.; Perez, L.; Coll, J. M.; Estepa, A. *Antiviral Res.* **2006**, *72*, 107–115.
(260) Masaki, Y.; Yamada, T.; Kawai, H.; Itoh, A.; Arai, Y.; Furukawa, H. *Synlett* **2006**, 288–290.
(261) Masquelin, T.; Bui, H.; Brickley, B.; Stephenson, G.; Schwerkoske, J.; Hulme, C. *Tetrahedron Lett.* **2006**, *47*, 2989–2991.
(262) Masse, C. E.; Ng, P. Y.; Fukase, Y.; Sanchez-Rosello, M.; Shaw, J. T. *J. Comb. Chem.* **2006**, *8*, 293–296.
(263) Matsugi, M.; Yamanaka, K.; Inomata, I.; Takekoshi, N.; Hasegawa, M.; Curran, D. P. *QSAR Comb. Sci.* **2006**, *25*, 713–715.
(264) McAllister, L. A.; Turner, K. L.; Brand, S.; Stefaniak, M.; Procter, D. J. *J. Org. Chem.* **2006**, *71*, 6497–6507.
(265) McClure, K.; Hack, M.; Huang, L.; Sehon, C.; Morton, M.; Li, L.; Barrett, T. D.; Shankley, N.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 72–76.
(266) Stroke, I. L.; Cole, A. G.; Simhadri, S.; Brescia, M.-R.; Desai, M.; Zhang, J. J.; Merritt, J. R.; Appell, K. C.; Henderson, I.; Webb, M. L. *Biochem. Biophys. Res. Commun.* **2006**, *349*, 221–228.
(267) McCormick, R. A.; James, K. M.; Willetts, N.; Procter, D. J. *QSAR Comb. Sci.* **2006**, *25*, 709–712.
(268) McKay, G. A.; Reddy, R.; Arhin, F.; Belley, A.; Lehoux, D.; Moeck, G.; Sarmiento, I.; Parr, T. R.; Gros, P.; Pelletier, J.; Far, A. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1286–1290.
(269) Metzger, A.; Diller, D. J.; Lin Tsung, H.; Henderson, I.; Webb, M. L. *Comb. Chem. High Throughput Screening* **2006**, *9*, 351–358.
(270) Milanesi, L.; Hunter, C. A.; Sedelnikova, S. E.; Waltho, J. P. *Chem. Eur. J.* **2006**, *12*, 1081–1087.
(271) Mitchell, J. M.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1722–1726.
(272) Monroc, S.; Feliu, L.; Planas, M.; Bardaji, E. *Synlett* **2006**, 1311–1314.
(273) Moro, S.; Bacilieri, M.; Cacciari, B.; Bolcato, C.; Cusan, C.; Pastorin, G.; Klotz, K.-N.; Spalluto, G. *Bioorg. Med. Chem.* **2006**, *14*, 4923–4932.
(274) Morwick, T. M. *J. Comb. Chem.* **2006**, *8*, 649–651.
(275) Moulin, E.; Barluenga, S.; Totzke, F.; Winssinger, N. *Chem.–Eur. J.* **2006**, *12*, 8819–8834.
(276) Muller, P.; Lena, G.; Boilard, E.; Bezzine, S.; Lambeau, G.; Guichard, G.; Rognan, D. *J. Med. Chem.* **2006**, *49*, 6768–6778.
(277) Murata, A.; Wada, T. *Tetrahedron Lett.* **2006**, *47*, 2147–2150.
(278) Musonda, C. C.; Gut, J.; Rosenthal, P. J.; Yardley, V.; Carvalho de Souza, R. C.; Chibale, K. *Bioorg. Med. Chem.* **2006**, *14*, 5605–5615.
(279) Nad, S.; Roller, S.; Haag, R.; Breinbauer, R. *Org. Lett.* **2006**, *8*, 403–406.
(280) Ng, P. Y.; Masse, C. E.; Shaw, J. T. *Org. Lett.* **2006**, *8*, 3999–4002.
(281) Nagai, K.; Doi, T.; Sekiguchi, T.; Namatame, I.; Sunazuka, T.; Tomoda, H.; Omura, S.; Takahashi, T. *J. Comb. Chem.* **2006**, *8*, 103–109.
(282) Nakamura, Y.; Takeuchi, S. *QSAR Comb. Sci.* **2006**, *25*, 703–708.
(283) Nefzi, A.; Ostresh, J. M.; Appel, J. R.; Bidlack, J.; Dooley, C. T.; Houghten, R. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4331–4338.
(284) Nefzi, A.; Santos, R. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3358–3361.
(285) Nefzi, A.; Santos, R. T. *Tetrahedron Lett.* **2006**, *47*, 3819–3822.
(286) Nenajdenko, V. G.; Gulevich, A. V.; Balenkova, E. S. *Tetrahedron* **2006**, *62*, 5922–5930.
(287) Niculescu-Duvaz, I.; Roman, E.; Whittaker, S. R.; Friedlos, F.; Kirk, R.; Scanlon, I. J.; Davies, L. C.; Niculescu-Duvaz, D.; Marais, R.; Springer, C. J. *J. Med. Chem.* **2006**, *49*, 407–416.
(288) Nie, A.; Huang, Z. *J. Comb. Chem.* **2006**, *8*, 655–658.
(289) Nie, A.; Wang, J.; Huang, Z. *J. Comb. Chem.* **2006**, *8*, 646–648.
(290) Nishio, R.; Wessely, S.; Sugiura, M.; Kobayashi, S. *J. Comb. Chem.* **2006**, *8*, 459–461.
(291) Nnanabu, E.; Burgess, K. *Org. Lett.* **2006**, *8*, 1259–1262.
(292) Nolt, M. B.; Smiley, M. A.; Varga, S. L.; McClain, R. T.; Wolkenberg, S. E.; Lindsley, C. W. *Tetrahedron* **2006**, *62*, 4698–4704.
(293) Olsen, C. A.; Christensen, C.; Nielsen, B.; Mohamed, F. M.; Witt, M.; Clausen, R. P.; Kristensen, J. L.; Franzyk, H.; Jaroszewski, J. W. *Org. Lett.* **2006**, *8*, 3371–3374.
(294) Zhu, J.; Pottorf, R. S.; Player, M. R. *Tetrahedron Lett.* **2006**, *47*, 7267–7270.
(295) Omote, M.; Nishimura, Y.; Sato, K.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **2006**, *127*, 74–78.
(296) Omote, M.; Nishimura, Y.; Sato, K.; Ando, A.; Kumadaki, I. *Tetrahedron* **2006**, *62*, 1886–1894.
(297) Ortega, A.; Erra, M.; Navarro, E.; Roberts, R. S.; Fernandez-Forner, D. *QSAR Comb. Sci.* **2006**, *25*, 598–604.
(298) Pagliai, F.; Pirali, T.; Del Grosso, E.; Di Brisco, R.; Tron, G. C.; Sorba, G.; Genazzani, A. A. *J. Med. Chem.* **2006**, *49*, 467–470.
(299) Park, J. G.; Sill, P. C.; Makiyi, E. F.; Garcia-Sosa, A. T.; Millard, C. B.; Schmidt, J. J.; Pang, Y.-P. *Bioorg. Med. Chem.* **2006**, *14*, 395–408.
(300) Paulick, M. G.; Hart, K. M.; Brinner, K. M.; Tjandra, M.; Charych, D. H.; Zuckermann, R. N. *J. Comb. Chem.* **2006**, *8*, 417–426.
(301) Peng, W.; Blagg, B. S. J. *Org. Lett.* **2006**, *8*, 975–978.
(302) Peters, U.; Cherian, J.; Kim, J. H.; Kwok, B. H.; Kapoor, T. M. *Nature Chem. Biol.* **2006**, *2*, 618–626.
(303) Petros, A. M.; Dinges, J.; Augeri, D. J.; Baumeister, S. A.; Betebenner, D. A.; Bures, M. G.; Elmore, S. W.; Hajduk, P. J.; Joseph, M. K.; Landis, S. K.; Nettesheim, D. G.; Rosenberg, S. H.; Wang, S.; Thomas, S.; Wang, X.; Zanze, I.; Zhang, H.; Fesik, S. W. *J. Med. Chem.* **2006**, *49*, 656–663.
(304) Pevarello, P.; Fancelli, D.; Vulpetti, A.; Amici, R.; Villa, M.; Pittala, V.; Vianello, P.; Cameron, A.; Ciomei, M.; Mercurio, C.; Bischoff, J. R.; Roletto, F.; Varasi, M.; Brasca, M. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1084–90.
(305) Pipalia, N. H.; Huang, A.; Ralph, H.; Rujoi, M.; Maxfield, F. R. *J. Lipid Res.* **2006**, *47*, 284–301.
(306) Polito, L.; Cravini, M.; Poletti, L.; Lay, L. *Syn. Commun.* **2006**, *36*, 2203–2209.
(307) Pomel, V.; Klicic, J.; Covini, D.; Church, D. D.; Shaw, J. P.; Roulin, K.; Burgat-Charvillon, F.; Valognes, D.; Camps, M.; Chabert, C.; Gillieron, C.; Francon, B.; Perrin, D.; Leroy, D.; Gretener, D.; Nichols, A.; Vitte, P. A.; Carboni, S.; Rommel, C.; Schwarz, M. K.; Rueckle, T. *J. Med. Chem.* **2006**, *49*, 3857–3871.
(308) Porcheddu, A.; Giacomelli, G. *J. Org. Chem.* **2006**, *71*, 7057–7059.
(309) Poulsen, S.-A. *J. Am. Soc. Mass. Spectrom.* **2006**, *17*, 1074–1080.
(310) Poulsen, S.-A.; Bornaghi, L. F. *Bioorg. Med. Chem.* **2006**, *14*, 3275–3284.
(311) Prakesch, M.; Sharma, U.; Sharma, M.; Khadem, S.; Leek, D. M.; Arya, P. *J. Comb. Chem.* **2006**, *8*, 715–734.

(312) Prakesch, M.; Srivastava, S.; Leek, D. M.; Arya, P. *J. Comb. Chem.* **2006**, *8*, 762–773.
(313) Probst, K. C.; Jung, G. *Amino acids* **2006**, *30*, 243–250.
(314) Pryde, D. C.; Maw, G. N.; Planken, S.; Platts, M. Y.; Sanderson, V.; Corless, M.; Stobie, A.; Barber, C. G.; Russell, R.; Foster, L.; Barker, L.; Wayman, C.; Van Der Graaf, P.; Stacey, P.; Morren, D.; Kohl, C.; Beaumont, K.; Coggon, S.; Tute, M. *J. Med. Chem.* **2006**, *49*, 4409–4424.
(315) Qian, H.; Huang, X. *Synlett* **2006**, 1547–1548.
(316) Qian, H.; Huang, X. *Synthesis* **2006**, 1934–1936.
(317) Rahman, M. T.; Fukuyama, T.; Ryu, I.; Suzuki, K.; Yonemura, K.; Hughes, P. F.; Nokihara, K. *Tetrahedron Lett.* **2006**, *47*, 2703–2706.
(318) Rao, H. S. P.; Sivakumar, S. *J. Org. Chem.* **2006**, *71*, 8715–8723.
(319) Rao, Z.; Peng, H.; Yang, G.; Chen, Z. *Comb. Chem. High Throughput Screening* **2006**, *9*, 743–746.
(320) Rasmussen, L. K.; Begtrup, M.; Ruhland, T. *J. Org. Chem.* **2006**, *71*, 1230–1232.
(321) Reddy, P. T.; Quevillon, S.; Gan, Z.; Forbes, N.; Leek, D. M.; Arya, P. *J. Comb. Chem.* **2006**, *8*, 856–871.
(322) Reddy, S. M.; Srinivasulu, M.; Reddy, Y. V.; Narasimhulu, M.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 5285–5288.
(323) Reddy, T. R. K.; Mutter, R.; Heal, W.; Guo, K.; Gillet, V. J.; Pratt, S.; Chen, B. *J. Med. Chem.* **2006**, *49*, 607–615.
(324) Robins, L. I.; Dixon, S. M.; Wilson, D. K.; Kurth, M. J. *Bioorg. Med. Chem.* **2006**, *14*, 7728–7735.
(325) Rodenko, B.; Detz, R. J.; Pinas, V. A.; Lambertucci, C.; Brun, R.; Wanner, M. J.; Koomen, G.-J. *Bioorg. Med. Chem.* **2006**, *14*, 1618–1629.
(326) Rodriguez, H.; Martin, O.; Ochoa, E.; Suarez, M.; Reyes, O.; Garay, H.; Albericio, F.; Martin, N. *QSAR Comb. Sci.* **2006**, *25*, 921–927.
(327) Roettger, S.; Waldmann, H. *Eur. J. Med. Chem.* **2006**, 2093–2099.
(328) Rokosz, L. L.; Huang, C.-Y.; Reader, J. C.; Stauffer, T. M.; Southwick, E. C.; Li, G.; Chelsky, D.; Baldwin, J. J. *Comb. Chem. High Throughput Screening* **2006**, *9*, 545–558.
(329) da Costa, R. C.; Gladysz, J. A. *Chem. Commun.* **2006**, 2619–2621.
(330) Ruan, Z.; Lawrence, R. M.; Cooper, C. B. *Tetrahedron Lett.* **2006**, *47*, 7649–7651.
(331) Rydzewski, R. M.; Burrill, L.; Mendonca, R.; Palmer, J. T.; Rice, M.; Tahilramani, R.; Bass, K. E.; Leung, L.; Gjerstad, E.; Janc, J. W.; Pan, L. *J. Med. Chem.* **2006**, *49*, 2953–2968.
(332) Sadaghiani, A. M.; Verhelst, S. H. L.; Bogyo, M. *J. Comb. Chem.* **2006**, *8*, 802–804.
(333) Sagara, Y.; Sagara, T.; Uchiyama, M.; Otsuki, S.; Kimura, T.; Fujikawa, T.; Noguchi, K.; Ohtake, N. *J. Med. Chem.* **2006**, *49*, 5653–5663.
(334) Schmid, S.; Schuehle, D.; Austel, V. *Synthesis* **2006**, 2031–2038.
(335) Schuster, C.; Knollmueller, M.; Gaertner, P. *Tetrahedron: Asymmetry* **2006**, *17*, 2430–2441.
(336) Sehon, C.; McClure, K.; Hack, M.; Morton, M.; Gomez, L.; Li, L.; Barrett, T. D.; Shankley, N.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 77–80.
(337) Senaiar, R. S.; Young, D. D.; Deiters, A. *Chem. Commun.* **2006**, 1313–1315.
(338) Seo, J.-S.; Joo, Y.-H.; Yi, J. B.; Lee, E. J.; Lee, N.; Cho, Y.-B.; Kwak, W. J.; Hwang, J. Y.; Jeon, Y. S.; Jeon, H. S.; Yoo, S.-E.; Yoon, C. M.; Dong, M.-S.; Gong, Y.-D. *Bull. Korean Chem. Soc.* **2006**, *27*, 909–917.
(339) Shaabani, A.; Farhangi, E.; Rahmati, A. *Comb. Chem. High Throughput Screening* **2006**, *9*, 771–776.
(340) Shao, W.-Y.; Cao, Y.-N.; Yu, Z.-W.; Pan, W.-J.; Qiu, X.; Bu, X.-Z.; An, L.-K.; Huang, Z.-S.; Gu, L.-Q.; Chan, A. S. C. *Tetrahedron Lett.* **2006**, *47*, 4085–4089.
(341) Sharma, U.; Srivastava, S.; Prakesch, M.; Sharma, M.; Leek, D. M.; Arya, P. *J. Comb. Chem.* **2006**, *8*, 735–761.
(342) Shearer, A. S.; de Miguel, Y. R. *Tetrahedron Lett.* **2006**, *47*, 447–450.
(343) Sheng, S.-R.; Luo, Q.-Y.; Huang, P.-G.; Guo, L.; Wang, Q.-Y.; Pei, X.-L. *J. Chem. Res.* **2006**, 24–26.
(344) Sheng, S.-R.; Wang, Q.; Wang, Q.-Y.; Guo, L.; Liu, X.-L.; Huang, X. *Synlett* **2006**, 1887–1890.
(345) Sheng, S.-R.; Wang, Q.-Y.; Huang, Y.-X.; Xin, Q.; Liu, X.-L. *Syn. Commun.* **2006**, *36*, 429–434.
(346) Sheng, S.-R.; Xin, Q.; Liu, X.-L.; Sun, W.-K.; Guo, R.; Huang, X. *Synthesis* **2006**, 2293–2296.
(347) Sheng, S.-R.; Xu, L.; Zhang, X.-L.; Liu, X.-L.; Wei, M.-H. *J. Comb. Chem.* **2006**, *8*, 805–807.
(348) Shi, B.; Stevenson, R.; Campopiano, D. J.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 8459–8467.
(349) Shokouhimehr, M.; Kim, J.-H.; Lee, Y.-S. *Synlett* **2006**, 618–620.
(350) Simoneau, C. A.; George, E. A.; Ganem, B. *Tetrahedron Lett.* **2006**, *47*, 1205–1207.
(351) Sluis-Cremer, N.; Hamamouch, N.; San, F. A.; Velazquez, S.; Balzarini, J.; Camarasa, M.-J. *J. Med. Chem.* **2006**, *49*, 4834–4841.
(352) Soh, C. H.; Chui, W. K.; Lam, Y. *J. Comb. Chem.* **2006**, *8*, 464–468.
(353) Solodenko, W.; Broeker, P.; Messinger, J.; Schoen, U.; Kirschning, A. *Synthesis* **2006**, 461–466.
(354) Song, A.; Wu, L.; Ho, L.; Lam, K. S. *Tetrahedron* **2006**, *62*, 4393–4399.
(355) Spiegel, D. A.; Schroeder, F. C.; Duvall, J. R.; Schreiber, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 14766–14767.
(356) Sreejalekshmi, K. G.; Devi, S. K. C.; Rajasekharan, K. N. *Tetrahedron Lett.* **2006**, *47*, 6179–6182.
(357) Srinivasan, R.; Uttamchandani, M.; Yao, S. Q. *Org. Lett.* **2006**, *8*, 713–716.
(358) Stanger, K. J.; Krchnak, V. *J. Comb. Chem.* **2006**, *8*, 435–439.
(359) Stanger, K. J.; Krchnak, V. *J. Comb. Chem.* **2006**, *8*, 652–654.
(360) Stern, E.; Muccioli, G. G.; Millet, R.; Goossens, J.-F.; Farce, A.; Chavatte, P.; Poupaert, J. H.; Lambert, D. M.; Depreux, P.; Henichart, J.-P. *J. Med. Chem.* **2006**, *49*, 70–79.
(361) Su, J.; Tang, H.; McKittrick, B. A.; Burnett, D. A.; Zhang, H.; Smith-Torhan, A.; Fawzi, A.; Lachowicz, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4548–4553.
(362) Sun, Q.; Law, A.; Crowder, M. W.; Geysen, H. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5169–5175.
(363) Sung, K.; Chen, F.-L.; Huang, P.-C. *Synlett* **2006**, 2667–2669.
(364) (a) Swain, C. J.; Teran, A.; Maroto, M.; Cabello, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6058–6062. (b) SMARTS (smiles arbitrary target specification) is a language used for describing molecular patterns and properties: *SMARTS*; Daylight Chemical Information Systems Inc.: Suite 550, Aliso Viejo, CA 92656; see http://www.daylight.com.
(365) Tesevic, V.; Gladysz, J. A. *J. Org. Chem.* **2006**, *71*, 7433–7440.
(366) Testero, S. A.; Mata, E. G. *Org. Lett.* **2006**, *8*, 4783–4786.
(367) Thiot, C.; Schmutz, M.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2868–2871.
(368) Thompson, L. A.; Liauw, A. Y.; Ramanjulu, M. M.; Kasireddy-Polam, P.; Mercer, S. E.; Maduskuie, T. P.; Glicksman, M.; Roach, A. H.; Meredith, J. E.; Liu, R.-Q.; Combs, A. P.; Higaki, J. N.; Cordell, B.; Seiffert, D.; Zaczek, R. C.; Robertson, D. W.; Olson, R. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2357–2363.
(369) Tomasi, S.; Picard, S.; Laine, C.; Babonneau, V.; Goujeon, A.; Boustie, J.; Uriac, P. *J. Comb. Chem.* **2006**, *8*, 11–14.
(370) Trifilenkov, A. S.; Kobak, V. V.; Salina, M. A.; Kusovkova, J. A.; Ilyin, A. P.; Khvat, A. V.; Tkachenko, S. E.; Ivachtchenko, A. V. *J. Comb. Chem.* **2006**, *8*, 469–479.
(371) Tripathy, R.; Reiboldt, A.; Messina, P. A.; Iqbal, M.; Singh, J.; Bacon, E. R.; Angeles, T. S.; Yang, S. X.; Albom, M. S.; Robinson, C.; Chang, H.; Ruggeri, B. A.; Mallamo, J. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2158–2162.
(372) Tsukamoto, H.; Suzuki, R.; Kondo, Y. *J. Comb. Chem.* **2006**, *8*, 289–292.
(373) Tullberg, M.; Luthman, K.; Grotli, M. *J. Comb. Chem.* **2006**, *8*, 915–922.

(374) Turner, K. L.; Baker, T. M.; Islam, S.; Procter, D. J.; Stefaniak, M. *Org. Lett.* **2006**, *8*, 329–332.
(375) Uozumi, Y.; Suzuka, T. *J. Org. Chem.* **2006**, *71*, 8644–8646.
(376) Uozumi, Y.; Suzuka, T.; Kawade, R.; Takenaka, H. *Synlett* **2006**, 2109–2113.
(377) Varga, L.; Nagy, T.; Dorman, G.; Kalman, F.; Uerge, L.; Darvas, F. *J. Comb. Chem.* **2006**, *8*, 338–343.
(378) Vazquez, J.; Albericio, F. *Tetrahedron Lett.* **2006**, *47*, 1657–1661.
(379) Wan, D.-B.; Chen, J.-M. *J. Chem. Res.* **2006**, 32–33.
(380) Wang, G.; Ella-Menye, J.-R.; Sharma, V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2177–2181.
(381) Wang, Y.; Sarris, K.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 4823–4826.
(382) Weber, C.; Demeter, A.; Greiner, I. *Tetrahedron* **2006**, *62*, 2304–2312.
(383) Weide, T.; Arve, L.; Prinz, H.; Waldmann, H.; Kessler, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 59–63.
(384) Wendt, M. D.; Wang, S.; Kunzer, A.; McClellan, W. J.; Bruncko, M.; Oost, T. K.; Ding, H.; Joseph, M. K.; Zhang, H.; Nimmer, P. M.; Ng, S.-C.; Shoemaker, A. R.; Petros, A. M.; Oleksijew, A.; Marsh, K.; Bauch, J.; Oltersdorf, T.; Belli, B. A.; Martineau, D.; Fesik, S. W.; Rosenberg, S. H.; Elmore, S. W. *J. Med. Chem.* **2006**, *49*, 1165–1181.
(385) Werner, S.; Iyer, P. S.; Fodor, M. D.; Coleman, C. M.; Twining, L. A.; Mitasev, B.; Brummond, K. M. *J. Comb. Chem.* **2006**, *8*, 368–380.
(386) Werner, S.; Turner, D. M.; Lyon, M. A.; Huryn, D. M.; Wipf, P. *Synlett* **2006**, 2334–2338.
(387) Whiting, M.; Tripp, J. C.; Lin, Y.-C.; Lindstrom, W.; Olson, A. J.; Elder, J. H.; Sharpless, K. B.; Fokin, V. V. *J. Med. Chem.* **2006**, *49*, 7697–710.
(388) Wiles, C.; Watts, P.; Haswell, S. J. *Tetrahedron Lett.* **2006**, *47*, 5261–5264.
(389) Wishka, D. G.; Walker, D. P.; Yates, K. M.; Reitz, S. C.; Jia, S.; Myers, J. K.; Olson, K. L.; Jacobsen, E. J.; Wolfe, M. L.; Groppi, V. E.; Hanchar, A. J.; Thornburgh, B. A.; Cortes-Burgos, L. A.; Wong, E. H. F.; Staton, B. A.; Raub, T. J.; Higdon, N. R.; Wall, T. M.; Hurst, R. S.; Walters, R. R.; Hoffmann, W. E.; Hajos, M.; Franklin, S.; Carey, G.; Gold, L. H.; Cook, K. K.; Sands, S. B.; Zhao, S. X.; Soglia, J. R.; Kalgutkar, A. S.; Arneric, S. P.; Rogers, B. N. *J. Med. Chem.* **2006**, *49*, 4425–4436.
(390) Wone, D. W. G.; Rowley, J. A.; Garofalo, A. W.; Berkman, C. E. *Bioorg. Med. Chem.* **2006**, *14*, 67–76.
(391) Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. *Chem. Commun.* **2006**, 3296–3298.
(392) Loughlin, W. A.; Henderson, L. C.; Elson, K. E.; Murphy, M. E. *Synthesis* **2006**, 1975–1980.
(393) Xiang, J. S.; Hu, Y.; Rush, T. S.; Thomason, J. R.; Ipek, M.; Sum, P.-E.; Abrous, L.; Sabatini, J. J.; Georgiadis, K.; Reifenberg, E.; Majumdar, M.; Morris, E. A.; Tam, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 311–316.
(394) Xiao, K.; Li, X.; Li, J.; Ma, L.; Hu, B.; Yu, H.; Fu, Y.; Wang, R.; Ma, Z.; Qiu, B.; Li, J.; Hu, D.; Wang, X.; Shen, J. *Bioorg. Med. Chem.* **2006**, *14*, 4535–4551.
(395) Xie, F.; Cheng, G.; Hu, Y. *J. Comb. Chem.* **2006**, *8*, 286–288.
(396) Xie, Y.; Deng, S.; Chen, Z.; Yan, S.; Landry, D. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4657–4660.
(397) Xing, X.; Wu, J.; Feng, G.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 6774–6781.
(398) Xing, X.; Wu, J.; Luo, J.; Dai, W.-M. *Synlett* **2006**, 2099–2103.
(399) Xu, C.; Yang, L.; Bhandari, A.; Holmes, C. P. *Tetrahedron Lett.* **2006**, *47*, 4885–4888.
(400) Xu, W. M.; Wu, L. L.; Huang, X. *Chin. Chem. Lett.* **2006**, *17*, 603–605.
(401) Xu, X.-J.; Zong, Y.-X. *Tetrahedron Lett.* **2006**, *48*, 129–132.
(402) Xu, Y.; Lu, H.; Kennedy, J. P.; Yan, X.; McAllister, L. A.; Yamamoto, N.; Moss, J. A.; Boldt, G. E.; Jiang, S.; Janda, K. D. *J. Comb. Chem.* **2006**, *8*, 531–539.
(403) Xu, Y.; Sculimbrene, B. R.; Miller, S. J. *J. Org. Chem.* **2006**, *71*, 4919–4928.
(404) Xu, Y.; Shi, J.; Yamamoto, N.; Moss, J. A.; Vogt, P. K.; Janda, K. D. *Bioorg. Med. Chem.* **2006**, *14*, 2660–2673.
(405) Yan, C.; Zeng, X.; Zhang, W.; Luo, M. *J. Organomet. Chem.* **2006**, *691*, 3391–3396.
(406) Yang, F.; Curran, D. P. *J. Am. Chem. Soc.* **2006**, *128*, 14200–14205.
(407) Yang, Y.-H.; Liu, Y.-H.; Shi, M. *Org. Biomol. Screening* **2006**, *4*, 4131–4134.
(408) Yeager, A. R.; Min, G. K.; Porco, J. A., Jr.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 5065–5068.
(409) Yi, W.; Cai, C. *J. Fluorine Chem.* **2006**, *127*, 1515–1521.
(410) Yin, Z.; Patel, S. J.; Wang, W.-L.; Chan, W.-L.; Ranga Rao, K. R.; Wang, G.; Ngew, X.; Patel, V.; Beer, D.; Knox, J. E.; Ma, N. L.; Ehrhardt, C.; Lim, S. P.; Vasudevan, S. G.; Keller, T. H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 40–43.
(411) Yingyongnarongkul, B.-E.; Apiratikul, N.; Aroonrerk, N.; Suksamrarn, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5870–5873.
(412) Young, D. D.; Senaiar, R. S.; Deiters, A. *Chem.—Eur. J.* **2006**, *12*, 5563–5568.
(413) Yu, C.-Y.; Yang, P.-H.; Zhao, M.-X.; Huang, Z.-T. *Synlett* **2006**, 1835–1840.
(414) Yue, G.; Chen, Z.; Yang, G. *J. Heterocycl. Chem.* **2006**, *43*, 781–786.
(415) Zajdel, P.; Subra, G.; Bojarski, A. J.; Duszynska, B.; Pawlowski, M.; Martinez, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3406–3410.
(416) Zhang, L.; Zhang, J. Y. *J. Comb. Chem.* **2006**, *8*, 361–367.
(417) Zhang, S.; Zeng, X.; Wei, Z.; Zhao, D.; Kang, T.; Zhang, W.; Yan, M.; Luo, M. *Synlett* **2006**, 1891–1894.
(418) Zhang, W.; Lu, Y. *J. Comb. Chem.* **2006**, *8*, 890–896.
(419) Zhang, W.; Lu, Y.; Chen, C. H.-T.; Curran, D. P.; Geib, S. *Eur. J. Org. Chem.* **2006**, 2055–2059.
(420) Zhang, W.; Lu, Y.; Chen, C. H.-T.; Zeng, L.; Kassel, D. B. *J. Comb. Chem.* **2006**, *8*, 687–695.
(421) Zhang, W.; Nagashima, T. *J. Fluorine Chem.* **2006**, *127*, 588–591.
(422) Zhao, H.; Serby, M. D.; Xin, Z.; Szczepankiewicz, B. G.; Liu, M.; Kosogof, C.; Liu, B.; Nelson, L. T. J.; Johnson, E. F.; Wang, S.; Pederson, T.; Gum, R. J.; Clampit, J. E.; Haasch, D. L.; Abad-Zapatero, C.; Fry, E. H.; Rondinone, C.; Trevillyan, J. M.; Sham, H. L.; Liu, G. *J. Med. Chem.* **2006**, *49*, 4455–4458.
(423) Zhao, L.; Huang, W.; Liu, H.; Wang, L.; Zhong, W.; Xiao, J.; Hu, Y.; Li, S. *J. Med. Chem.* **2006**, *49*, 4059–4071.
(424) Zhang, W.; Lu, Y. *QSAR Comb. Sci.* **2006**, *25*, 724–727.
(425) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 1626–1632.
(426) Zhang, Y. M.; Pan, Y. J.; Gueritte, F.; Wu, X. M.; Bai, H.; Stockigt, J. *J. Nat. Prod.* **2006**, *69*, 1145–1152.
(427) Zheng, L.; Xiang, J.; Dang, Q.; Guo, S.; Bai, X. *J. Comb. Chem.* **2006**, *8*, 381–7.
(428) Zheng, Y.; Stevens, P. D.; Gao, Y. *J. Org. Chem.* **2006**, *71*, 537–542.
(429) Zhou, Z.-Z.; Yang, G.-F. *Bioorg. Med. Chem.* **2006**, *14*, 8666–8674.
(430) Roller, S.; Tuerk, H.; Stumbe, J.-F.; Rapp, W.; Haag, R. *J. Comb. Chem.* **2006**, *8*, 350–354.
(431) Engstroem, J. U. A.; Helgee, B. *J. Comb. Chem.* **2006**, *8*, 355–360.
(432) Kim, D.-H.; Lee, H. Y.; Kim, H.; Kim, H.; Lee, Y.-S.; Park, S. B. *J. Comb. Chem.* **2006**, *8*, 280–285.
(433) Boughtflower, B.; Lane, S.; Mutton, I.; Stasica, P. *J. Comb. Chem.* **2006**, *8*, 441–454.
(434) El Bakkari, M.; Vincent, J.-M. *QSAR Comb. Sci.* **2006**, *25*, 689–696.
(435) Mercier, K. A.; Germer, K.; Powers, R. *Comb. Chem. High Throughput Screening* **2006**, *9*, 515–534.
(436) Bittermann, H.; Boeckler, F.; Einsiedel, J.; Gmeiner, P. *Chem.—Eur. J.* **2006**, *12*, 6315–6322.
(437) Schnur, D. M.; Hermsmeier, M. A.; Tebben, A. J. *J. Med. Chem.* **2006**, *49*, 2000–2009.

(438) Ertl, P.; Jelfs, S.; Muehlbacher, J.; Schuffenhauer, A.; Selzer, P. *J. Med. Chem.* **2006**, *49*, 4568–4573.
(439) Zhang, W. *QSAR Comb. Sci.* **2006**, *25*, 679.
(440) Curran, D. P. *Aldrichmica* **2006**, *39*, 3–9.
(441) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837–11865.
(442) Dandapani, S. *QSAR Comb. Sci.* **2006**, *25*, 681–688.
(443) Zhang, W. *Microwave Methods in Organic Synthesis*; Topics in Current Chemistry; Larhed, M., Olofsson, K., Eds.; Springer: New York, 2006; Vol. 266, pp 145–166.
(444) Zhang, W. *New Synthetic Directions, Technologies, Materials and Biological Applications*; ACS Symposium Series: Current Fluoroorganic Chemistry; Soloshonok, V. A., Mikami, K. Yamazaki, T., Welch, J. T., Honek, J., Eds.; Oxford University Press: New York, 2006; pp 207–220.
(445) Yoder, N. C.; Yuksel, D.; Dafik1, L.; Kumar, K. *Curr. Opin. Chem. Bio.* **2006**, *10*, 1–8.
(446) Ubeda, M. A.; Dembinski, R. *J. Chem. Educ.* **2006**, *83*, 84–92.
(447) Domling, A. *Chem. Rev.* **2006**, *106*, 17–89.
(448) Gerencser, J.; Dorman, G.; Darvas, F. *QSAR Comb. Sci.* **2006**, *25*, 439–448.
(449) Lessmann, T.; Waldmann, H. *Chem. Commun.* **2006**, 3380–3389.
(450) Jung, N.; Encinas, A.; Braese, S. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 713–728.
(451) Erlanson, D. A. *Curr. Opin. Biotechnol.* **2006**, *17*, 643–652.
(452) Dumelin, C. E.; Scheuermann, J.; Melkko, S.; Neri, D. *QSAR Comb. Sci.* **2006**, *25*, 1081–1087.
(453) Scheuermann, J.; Dumelin, C. E.; Melkko, S.; Neri, D. *J. Biotechnol.* **2006**, *126*, 568–581.
(454) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711.
(455) Sharpless, K. B.; Manetsch, R. *Expert Opin. Drug Discovery* **2006**, *1*, 525–538.
(456) (a) Boldt, G. E.; Dickerson, T. J.; Janda, K. D. *Drug Discovery Today* **2006**, *11*, 143–148. (b) Balakin, K. V.; Tkachenko, S. E.; Kiselyov, A. S.; Savchuk, N. P. *Drug Discovery Today: Technol.* **2006**, *3*, 397–403. (c) Itami, K.; Yoshida, J. *Chem.—Eur. J.* **2006**, *12*, 3966–3974. (d) Scott, P. J. H.; Steel, P. G. *Eur. J. Org. Chem.* **2006**, 2251–2268. (e) Reyes, S. J.; Bergess, K. *Chem. Soc. Rev.* **2006**, *35*, 416–423.
(457) Gorse, A.-D. *Curr. Top. Med. Chem.* **2006**, *6*, 3–18.
(458) Walsh, D. P.; Chang, Y.-T. *Chem. Rev.* **2006**, *106*, 2476–2530.
(459) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 700–712.
(460) (a) Orry, A. J. W.; Abagyan, R.A.; Cavasotto, C. N. *Drug Discovery Today* **2006**, *11*, 261–266. (b) Rupasinghe, C. N.; Spaller, M. R. *Curr. Opin. Chem. Biol.* **2006**, *10*, 188–193. (c) Huwe, C. M. *Drug Discovery Today* **2006**, *11*, 763–767.
(461) Blackwell, H. E. *Curr. Opin. Chem. Biol.* **2006**, *10*, 203–212.
(462) Chen, J.; Yang, G.; Zhang, H.; Chen, Z. *React. Funct. Polym.* **2006**, *66*, 1434–1451.
(463) (a) Edwards, P. J.; Allart, B.; Andrews, M.; Clase, J. A.; Menet, C. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 425–444. (b) Koppitz, M.; Eis, K. *Drug Discovery Today* **2006**, *11*, 561–568.
(464) Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1594–1596.
(465) Dolle, R. E.; Macleod, C.; Martinez-Teipel, B. I.; Barker, W. M.; Seida, P.; Herbetz, T *Angew. Chem., Int. Ed.* **2005**, *44*, 5830–5833.
(466) Harju, K.; Vahermo, M.; Mutikainen, I.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2003**, *5*, 826–833.
(467) Phoon, C. W.; Sim, M. M. *Synlett* **2001**, 697–699.
(468) Barlos, K.; Gatos, D.; Hondrelis, J.; Matsoukas, J.; Moore, G. J.; Schafer, W.; Sotiriou, P. *Liebigs Ann. Chem.* **1989**, 951–955.
(469) Ji, Y.-F.; Pan, X.-D.; Wei, X.-Y. *Synlett* **2004**, *9*, 1607–1609.
(470) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
(471) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, *3*, 312–318.
(472) Suga, H.; Ikai, K.; Ibata, T. *J. Org. Chem.* **1999**, *64*, 7040–7047.
(473) (a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799.
(474) (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834.
(475) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379–2380.
(476) Khand, I. U.; Knox, G. R.; Pauson, P. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977–981.
(477) Kim, Y.-K.; Arai, M. A.; Arai, T.; Lamenzo, J. O.; Dean, E. F.; Patterson, N.; Patterson, N.; Clemons, P. A.; Schreiber, S.L. *J. Am. Chem. Soc.* **2004**, *126*, 14740–14745.
(478) (a) Castagnoli, N., Jr.; Cushman, M. *J. Org. Chem.* **1971**, *36*, 3404–3406. (b) Cushman, M.; Madaj, E. J. *J. Org. Chem.* **1987**, *52*, 907–915.
(479) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231–234.

CC700111E