The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures

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I. Introduction

The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry. These structures represent a class of molecules capable of binding to multiple receptors with high affinity.[1,2] The exploitation of these molecules should allow the medicinal chemist to rapidly discover biologically active compounds across a broad range of therapeutic areas on a reasonable time scale.

The term privileged structure was first coined by Evans et al. in 1988 and was defined as "a single molecular framework able to provide ligands for diverse receptors". This group noted the ability of 1,4-benzodiazepin-2-ones to bind to cholecystokinin (CCK) (such as **1**), gastrin, and central benzodiazepine receptors (such as **2**) (Figure 1).[1] In addition to these, the benzodiazepine scaffold is also found as neurokinin-1 antagonists (**3**), as enzyme inhibitors such as κ-secretase inhibitors (**4**) and farnesyl:protein transferase inhibitors (**5**), and as ion channel ligands such as the delayed rectifier K^+ current modulator **6**.[3,4]

Prior to the seminal paper of Evans et al. coining the privileged structure term, the notion of these types of structures had been emerging for some time. Early on various groups had recognized the presence of recurring structural units in many receptor ligands. For example, Ariëns et al. noted the presence of hydrophobic double-ring systems in many biogenic amine antagonists, which they suggested must interact with accessory hydrophobic binding sites. They also observed multiple actions of some molecules and suggested this was related to conformational flexibility.[5] Subsequently, Andrews and Lloyd described a number of common topological arrangements for biogenic amine antagonists.[6] They concluded that a common pharmacophore existed throughout diverse drug classes, and that specificity resulted from secondary binding groups attached to the basic pharmacophore.[6]

Since the privileged structure term was introduced, it has appeared in the literature many times.[2,3,7−30] For example, organic scaffolds such as 1,4-benzodiazepin-2-one,[1] biphenyl,[3,8] 1,4-dihydropyridine,[9] benzopyran,[2,15−17] pyranocoumarin,[2,15−17] 2,6-dichloro-9-thiabicyclo[3.3.1]nonane,[7] isoxazole,[18] 3,5-linked pyrrolin-4-ones,[21] dihydro-β-agarofuran sesquiterpenes,[23] spiroindoline sulfonamide,[3,27] spiroindanyl piperidine,[27] β-glucose and monosaccharides in general,[24−26]

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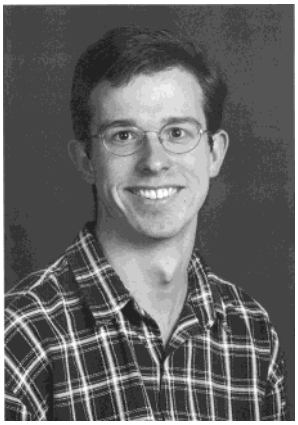
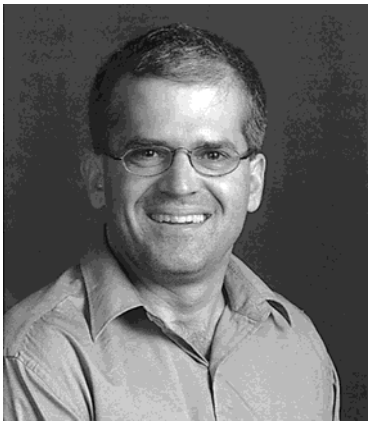


Douglas Horton completed a Bachelor of Applied Science in Drug Design and Development with Honors at the University of Queensland (UQ) in 2000, specializing in chemistry. He has received numerous awards and accolades for his graduate studies, which culminated in the University Medal. He was awarded first class Honors for his study into the synthesis of compounds to derive a novel pharmacophore for the nicotinic acetylcholine receptor. He is currently undertaking his doctoral research at the Institute for Molecular Bioscience at UQ under the supervision of Associate Professor Mark Smythe. His research project is focused on the discovery and synthesis of novel macrocyclic and heterocyclic privileged structures.

Greg Bourne has a Bachelor of Science with Honors from the University of Queensland and a PhD from Cambridge University (U.K.). His PhD was sponsored by Parke-Davis, a division of the Warner Lambert Pharmaceutical Company under the supervision of Dr. David C. Horwell of Parke-Davis and Prof. Laurie Hall, (Herchel Smith Laboratory for Medicinal Chemistry) Cambridge University. Greg undertook postdoctoral studies at the Cancer Research Institute, Arizona State University, under the supervision of Professor George R. Pettit. In 1994 he returned to Australia to a Research Officer position at the Centre for Drug Design and Development, University of Queensland. He is currently Senior Research Officer employed under the supervision of Associate Professor Mark L. Smythe, who heads the combinatorial chemistry laboratory at the Institute of Molecular Bioscience, University of Queensland. His current work involves the development of new technology to synthesize conformational constrained peptide libraries.

benzazepinone,[3] diphenylmethane,[3,12] biphenyltetrazole,[3,12] spiropiperidine,[3,12,28] 4-substituted piperidine,[31] indole,[3,12,29] and benzylpiperidine[3,12] have all been described as privileged structures. In addition to this, cyclic peptides have also been labeled privileged structures, from cyclic dodecapeptides and larger to cyclic dipeptides (diketopiperazines or piperazin-2,5-diones).[30]

To medicinal chemists, the true utility of privileged structures is the ability to synthesize one library based upon one core scaffold and screen it against a



Mark Smythe undertook graduate studies at James Cook University in Townsville and began his research career with Dr George Meehan on the synthesis of marine natural products. Mark obtained a PhD in Medicinal Chemistry at Melbourne University in 1992 under the supervision of Professor Mark von Itzstein and Professor Peter Andrews. He was awarded a Biota postgraduate fellowship to undertake his PhD studies and was a member of a team that designed and synthesized Relenza, an anti-influenza drug. Mark undertook postdoctoral studies with Professor Garland Marshall at Washington University, St Louis. In 1995 Mark returned to Australia to head the combinatorial chemistry and molecular modeling laboratory at the Centre for Drug Design and Development, The University of Queensland. He is currently principal investigator of combinatorial chemistry and molecular modeling at the Institute for Molecular Bioscience and founder and CEO of Protagonist Pty Ltd. Mark has a diverse group working the design and synthesis of compounds that modulate protein–protein interactions. In particular, this involves the discovery of biologically relevant chemotypes and the synthesis of arrays of such compounds.

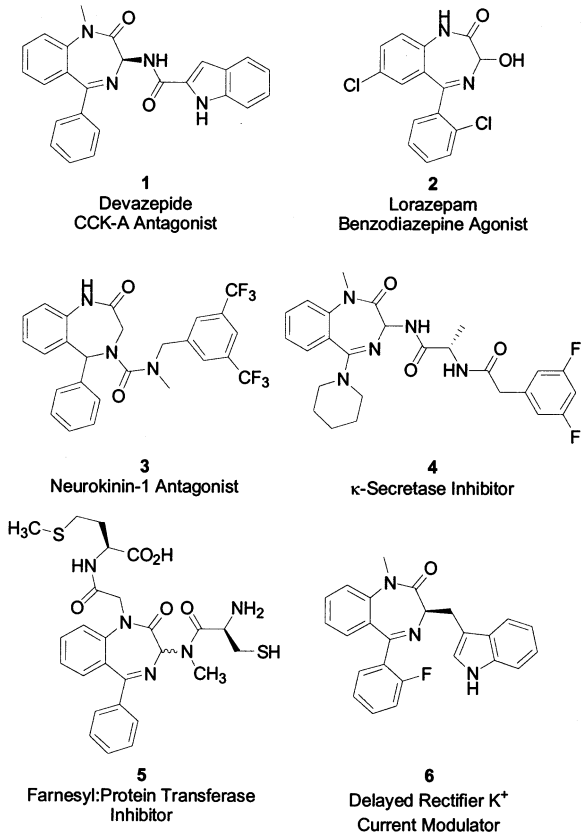


Figure 1. Representative biological activities of the benzodiazepine scaffold.[3,4]

variety of different receptors, yielding several active compounds. This was illustrated using the benzodiazepine scaffold (Figure 2). After developing the

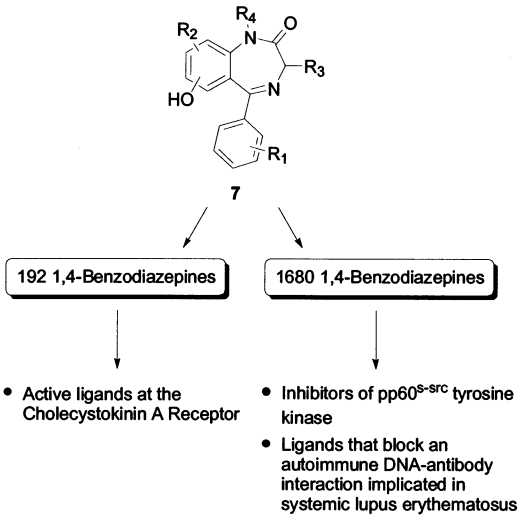


Figure 2. The utility of privileged substructures. One combinatorial library leads to active compounds at many receptors.[33]

synthetic route for the combinatorial synthesis of a series of 1,4-benzodiazepin-2-ones (**7**), Bunin et al. synthesized a small library of 192 molecules. Screening these compounds against the cholecystokinin A receptor yielded active compounds.[32] Subsequently, a larger library of 1680 1,4-benzodiazepines was synthesized and screened against a number of receptor and enzyme targets. Inhibitors of $pp60^{s-src}$ tyrosine kinase and ligands that block an autoimmune DNA−antibody interaction implicated in systemic lupus erythematosus were identified.[33]

The privileged structure term has gained prominence in the literature since it was first introduced some 15 years ago. However, by definition privileged structures are not structures in their own right, as they usually comprise only a subsection of any molecule. For clarification in this review, we have instead used the term privileged substructure, which is aligned with the common practice of describing a component of a molecule.

A. The Drug Discovery Process

A considerable amount of effort has been expended over the past few years to increase the success rate of the drug discovery process. Despite this, results have been limited. Today the situation grows worse, as an ever-increasing amount of money is required to bring a new drug to market. Further exacerbating this problem is the increasing demand which will be placed upon chemists to develop more compounds to access new targets identified through genomics initiatives. This is especially relevant when one realizes that currently marketed pharmaceuticals are directed at approximately 500 known biological targets,[34] while genomic research will identify thousands more.[35] Despite the successful introduction of protein therapeutics and the promise of gene therapy, major pharmaceutical companies are still focused on the discovery and manufacture of low molecular weight compounds (<500 Da) for clinical use. Thus, the pressure to accelerate the drug discovery process will increase substantially over the next few years.

Several techniques have been utilized in an effort to accelerate this process. One aspect was the introduction of combinatorial chemistry[36] and high-throughput screening. Despite some success with these techniques it rapidly became apparent that they did not produce their anticipated results.[35,37−39] This was believed to result from the immaturity of the technology, the inability to make the right types of molecules, and a lack of understanding of what types of molecules to make.[37]

Tools such as combinatorial chemistry and high-throughput screening are now relatively mature and have the capacity to be very powerful, once it is understood how to best utilize them. In the beginning, combinatorial chemistry was seen as a brute force method in which very large collections of compounds (>100 000) could be synthesized. It was more focused on using existing synthetic protocols rather than developing new synthetic processes. It became obvious that this approach did not yield the desired results. As a consequence, much more effort has gone into rational design of new molecules for combinatorial synthesis. This subsequently resulted in more extensive chemistry development,[40−46] which has been coupled with the development and implementation of computational concepts to aid in the design of smaller, more diverse libraries.[47,48] Retrospective analysis of collections of compounds suggested that they were not "drug-like".[47] This has resulted in the consideration of absorption, distribution, metabolism, excretion, and toxicity (ADMET) issues early in the discovery process.[49−52]

It seems clear that selecting the appropriate molecules to synthesize is one of the most troublesome questions. It has been estimated that the number of possible molecules with a molecular weight of less than 500 Da is 10^{200}, of which perhaps only 10^{60} may possess drug-like properties.[53] The proportion of these drug-like molecules synthesized to date has been estimated as one part in 10^{57}, or roughly the ratio of the mass of one proton to the mass of the sun.[54] The issue is therefore the selection of new molecules from this vast universe that have the potential to be biologically active.

In an effort to improve the hit rate in high-throughput screening, several groups have analyzed the relationship between drugs and their corresponding leads.[37,55,56] Oprea et al.[55,56] and Hann et al.[37] both concluded that lead compounds are "simpler" than their corresponding drugs in that they possess a lower molecular weight, are less complex and less hydrophobic. Oprea and co-workers suggested that the generation of libraries more consistent with lead-like characteristics would produce structurally simple leads with modest affinity, allowing further derivatization at a later stage to improve affinity and selectivity while retaining drug-like characteristics. Using a simple model, Hann and colleagues illustrated that as the molecular complexity increased, the chance of a molecule being a hit in an assay decreased. Thus, to date most combinatorial chemistry libraries have been too complex, and this may contribute to the low hit rates observed in high-throughput screening.

Privileged substructures represent an ideal source of lead compounds. As described previously in Figure 2, a single library based upon privileged substructures can lead to active compounds at a variety of receptors. Several groups have utilized these structures in this manner. For example, combinatorial libraries based upon privileged substructures have been synthesized by Nicolaou and colleagues, who utilized a benzopyran scaffold,[2,15,16] Schultz and co-workers, who made use of the purine scaffold,[57−60] and Hirschmann and Smith, who have worked with glycosides.[24−26] Patchett and co-workers utilized privileged substructures as "hydrophobic anchors" (harnessing their capabilities to bind to proteinaceous surfaces) to which they appended peptide functionality to gain specificity.[28,61,62] Hirschmann et al. also believed that the attachment of genetically encoded and uncoded amino acid side chains to privileged substructures are a promising means to produce diverse libraries of compounds.[24] While not every group intends to use these scaffolds in such a fashion, several groups have focused on privileged substructures to improve the efficiency of drug discovery. For example, Hirschmann, Smith, and colleagues have actively pursued the design and development of new privileged scaffolds[21] and have made hybrids of existing privileged substructures.[22] Privileged structures have also been the subject of several reviews in the literature.[3,30]

There has therefore been significant interest in the identification of new privileged substructures, and many groups have utilized computational procedures to aid this endeavor. For example, Nilson et al. explored databases of drugs to identify structural motifs that have broad biological activities and developed synthetic processes to prepare arrays of such compounds.[63] Another example is RECAP, a computational technique that has been developed to identify privileged substructures from biologically active molecules for use in library development.[10] Mason et al. has also developed a four-point pharmacophore method for the design of focused combinatorial libraries of molecules with privileged substructure characteristics.[12]

B. Characteristics of Privileged Substructures

Despite this interest in exploring privileged substructures, there is very little data shedding light on why certain molecules can bind widely to various receptors. Poulain et al. profiled a series of compounds against 70 receptors. Their investigation showed that judicious (and sometimes minor) changes in a privileged substructure can provide specific ligands for the opiate receptors.[64] Mason et al. suggested that specificity is attained by varying the substitution pattern on the scaffold of a privileged substructure.[12]

It would appear that some scaffolds have physicochemical characteristics that engender a capacity for promiscuous binding. There are many examples of proteins that have the ability to associate with multiple ligands using essentially the same binding determinants.[65,66] The available chemical diversity of protein surfaces is immense (as defined by the topographical arrangement of combinations of 20 different amino acids on the protein surface). Despite this, antibodies only use their complementarity determining regions when binding to antigens, while the rest of the protein surface is essentially inert.[67] In this instance the canonical loop conformations of antibodies provide a suitable "privileged" scaffold to bind to an infinite number of antigens.[68] The inherent specificity of antibodies is therefore a direct result of the amino acids that are attached to this scaffold.

Similarly, the FC fragment of immunoglobulin G binds to numerous proteins, including protein A,[69] protein G,[70] rheumatoid factor,[71] and the neonatal receptor.[72] These interactions occur using essentially the same binding determinants.[69,70,72] Wells and colleagues used phage display to isolate peptides that bound the FC fragment without selecting for biological function.[73] The peptide that exhibited the strongest binding to the FC fragment did so at the functional binding site (the hinge region), suggesting that the physicochemical features of this site allow it to bind to multiple ligands.

Small molecules are also capable of binding to multiple receptors. Hajduk et al. performed a statistical analysis of NMR-derived binding data on 11 protein targets in an effort to identify molecular motifs that are preferred for protein binding.[8] They observed that the biphenyl framework, a well-known privileged substructure, bound to multiple proteins. In addition, it appeared this framework bound at the functional protein-binding site, even though no functional selection was carried out. Similarly, NMR[74] and X-ray crystal structure[75,76] investigations of proteins in organic solvents revealed that bound organic solvents cluster into protein binding sites. Once again, this suggests that certain characteristics of functional binding surfaces allow them to preferentially bind to ligands, which is one of the underlying principles behind the site-directed ligand discovery approach adopted by Wells and colleagues.[77] In this instance, libraries of appropriately functionalized small ligands were screened against receptors with engineered cysteines in or around the active site. Small ligands were captured that bind in proximity to the engineered cysteine.

As shown above, both proteins and small molecules have the capacity to bind promiscuously.This could result from either the physicochemical properties of the protein or the small molecule, or most likely, both. Hirschmann, Smith, and colleagues have suggested that the side-chain projections of privileged scaffolds are recognized by structural motifs in G-protein coupled receptors, therefore suggesting that the receptor active site geometry is complementary to the privileged scaffold architecture.[22,25]

A molecular recognition event is dependent on the electrostatic and steric surface complementarity of ligand and receptor. Hann and colleagues imply that keeping the ligand surface simple may result in broad binding activities.[37] To some degree, it would appear that the binding surface of the molecule is dependent on both the geometry in which the scaffold can project its substituents and the functionality of the substituents thus employed. However, in most cases scaf-

folds that are capable of doing this will account for a fair proportion of the total molecular weight before any substituents are appended, especially if the molecular weight is to stay below 500 Da. As a result, the scaffold will ideally be "functional" and form favorable interactions with the receptor. The crystal structure of aldose reductase with the quinazolindione, zenarestat, one of its most potent inhibitors, displayed the ability of a privileged substructure to actively bind to the enzyme in concert with its substituents.[78] It is possible to speculate that privileged substructures form favorable noncovalent interactions with proteinaceous receptors which give rise to their broad binding capacities. This is certainly validated by the NMR investigations of Hajduk et al.[8]

As stated above, privileged substructures may derive much of their binding characteristics through the presentation of appended functionality in biologically relevant topographical shapes. It is tempting to suggest that some of these shapes may also be displayed by common secondary structure elements such as β- and γ-turns, which have long been identified as important topographical recognition elements of peptides and proteins.[79−82] Medicinal chemists have spent a great deal of effort on clustering these motifs[83−92] and on the development of synthetic methods to generate organic equivalents.[79,93−102] Benzodiazepines, a prototypical privileged substructure, have been described to be β-turn mimetics.[50,103] Ripka et al. compared the conformation of many types of β-turns to the benzodiazepine scaffold, and it was observed that they matched very closely.[103] A different study by Poulain and colleagues reached a more general conclusion based upon the pharmacological profiles of a series of compounds: that special structural features underlie the ability of compounds to bind to multiple receptors.[64] It is therefore possible to speculate that characteristics of some privileged substructures are due to topological features of the scaffold, which subsequently influences the presentation of attached side chains. However, this role is obviously much less important in flexible molecules, such as as those produced by Patchett and Hirschmann,[24,28,61,62] who successfully generated molecules through capping peptides with privileged substructures. Nevertheless, the privileged substructure concept suggests that while chemical diversity is almost infinite, biological activity in that space is clustered around substructure elements.[104]

Through inspection, privileged substructures would appear to be dominated by natural products or natural product derivatives. For example, the benzodiazepine framework, discussed above, is found in the natural product Asperlicin.[105] The observed characteristics of these molecules may be a reflection of relentless evolutionary pressure that has resulted in the selection of scaffolds that bind to proteinaceous receptors. It is also possible that the ability of privileged substructures to bind to proteins may result from the biosynthetic processes used in their preparation. The biosynthesis of natural products would involve intermediates binding to proteins to catalyze their assembly, therefore preferentially selecting for physicochemical features that favor protein binding. Alternatively, it could also be argued that all chemistry is biologically relevant; we just have not screened compounds against the required receptors. Indeed, conclusions being drawn in this review are heavily biased toward historical medicinal chemistry efforts. It must be remembered that many privileged substructures and other active natural products have only been identified due to extensive research in natural product chemistry, which has historically been driven by bioassay-guided fractionation.

Critics of the privileged substructure concept may well argue that many of these structures have limited utility due to their promiscuous nature. There are certain molecules that show broad binding activities and have proven very difficult to optimize.[106] In these cases, it has been suggested that the promiscuous nature of these molecules is due to aggregation (micelle or vesicle formation), and as a result, identification of these molecules could avoid false positives in biological screening.[106] Although it is certainly worthwhile stating that the compounds reviewed here may bind to multiple receptors through aggregation phenomena, the effectiveness of the privileged substructure concept may amply be illustrated by the biphenyl framework. It has been described as a preferred substructure for protein binding and appears in 4.3% of all known drugs.[8] This may indicate that although privileged substructures have the capacity to bind nonspecifically to a number of receptors, the substituents attached to the scaffold may be responsible for its receptor specificity, while the scaffold itself provides a number of features conducive to binding. Judicious selection and placement of the substituents off the scaffold would therefore be paramount.

C. Scope of the Review

Privileged substructures must display key physicochemical characteristics that facilitate their ability to bind to multiple receptors, but the nature of these characteristics is not well understood. Hirschmann and colleagues have stressed that "no unifying three-dimensional structural feature for privileged substructures has been identified".[22,25] However, observations in biology and chemistry have suggested that molecules do display such characteristics. In this review, we have focused on the strategies used for the combinatorial synthesis of molecules that display an ability to bind to multiple receptors.

In selecting the compounds to be reviewed, we focused on the identification of scaffolds of low molecular weight that would be of interest in a drug-discovery program. It was also concluded that cyclic structures are ideal scaffolds for drug development. This is because they provide molecular rigidity, allowing less entropic energy to be lost upon binding, and also provide better bioavailability. Studies have shown that a major contributor to good oral bioavailability is the number of rotatable bonds.[107] Bicyclic and tricyclic scaffolds are therefore an ideal size for library synthesis. They have a small enough molecular weight to provide scope for improved specificity and affinity through the attachment of suitable

substituents (which will consequently increase molecular weight, yet retain drug-like character) in a wide variety of topologies.

The size of the privileged substructure relative to the entire molecule is an important factor. For example, the indole ring may be considered to be a privileged substructure; yet it cannot be argued that every protein with a tryptophan residue owes its binding properties to the indole ring in only one of its residues (despite the importance of tryptophan in protein complexes). The critical element is the size of the privileged substructure relative to the overall molecule; the structure must be a central or crucial component. Functional groups such as amides and carboxylic acids are too small and too ubiquitous to be classified as privileged substructures. Small monocycles such as benzene, furan or thiophene are also clearly capable of being privileged substructures, but when they form part of structures with a molecular weight of around 500 Da, the nature and extent of their contribution to the overall molecule is uncertain. However, larger structures such as immunoglobulins clearly display all of the characteristics of a privileged substructure, if on a macromolecular scale. Hence, a privileged substructure should constitute a significant portion of the total mass of the molecule, and represent its core element.

Bicyclic and tricyclic compounds are capable of fulfilling these requirements. However, it was noted that many privileged substructures larger than bicycles were merely combinations or hybrids of two or more bicyclic privileged substructures. Hence, bicyclic privileged substructures may represent the core elements of an entire suite of privileged substructures. We therefore focused primarily on "bicyclic" structures (either with two rings joined by a single bond, or in a fused ring), which are capable of binding to multiple receptors.

We have paid no attention to reviewing the physicochemical characteristics of molecules derived from these scaffolds, primarily because this is not the focus of this review and some libraries are as large as 10 000 molecules. Since such physicochemical characteristics are a function of the entire molecule, it is possible to enumerate "in silico" large libraries of compounds based on the scaffolds reported in this review. Using the medicinal chemists favourite suite of descriptors, be it rotatable bonds,[107] polar surface area,[108] Lipinsky's drug-like characteristics,[47] or Oprea's lead-like characteristics,[55,56] libraries based upon these scaffolds can be appropriately tailored. However, and as described previously, the selection of scaffolds was biased to be of low molecular weight, allowing a large variety of appropriate functionality to be added as desired to retain drug-like character.

Every effort has been made to comprehensively review the literature within the framework outlined above, but due to the sheer size and scope of this work it is impractical to cover every detail. It should be noted here that the material surveyed does not encompass patent literature. Privileged substructures that have not been included in this review include, but are not limited to, biphenyltetrazoles,[3,12] spiropiperidines,[3,12,28] steroids,[109] prostanoids,[109] β-carbolines,[110] isoquinolines,[111] purines,[57,58] saccharides,[24−26] and macrocycles.[30] There are also many other preceding reviews on solid-phase organic and heterocyclic chemistry[112−115] and small molecule combinatorial chemistry,[33,109,116−119] many of which discuss some of the scaffolds in this review.

II. Phenyl-Substituted Monocycles

Phenyl-substituted monocycles have been utilized frequently in medicinal chemistry. This basic framework is commonly observed in many different scaffolds, from biphenyls to arylpiperazines. Unsurprisingly, many of these frameworks have been observed to be a core element of molecules that bind to multiple, unrelated classes of receptor with high affinity. Due to the frequency to which many of these structures appear in the literature, it is especially difficult, and often impractical, to find every example of a combinatorial library of privileged substructures utilizing these scaffolds.

A. Biphenyls

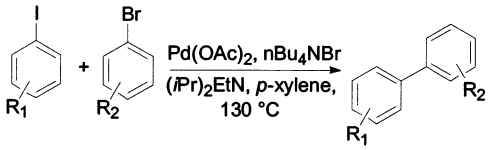
The biphenyl framework is without doubt a privileged substructure. The Comprehensive Medicinal Chemistry Database listed the following distinct therapeutic classes for molecules containing this framework in 1996: antiamebic, antifungal, antiinfective, antihypercholesteremic, antihyperlipoproteinemic, fasciolicide, antirheumatic, analgesic, antiinflammatory, antithrombotic, uricosuric, and antiarrhythmic.[120] In addition to this, the biphenyl substructure is found in 4.3% of all known drugs.[8] Biphenyls are also known to have potential as antitumor,[121,122] antihypertensive,[123] and antiatherosclerotic agents.[124] This diversity in receptor selectivity is not overly surprising when one considers that aromatic moieties have long been considered as major players in molecular recognition. When drugs containing aromatic substituents bind to proteins, aromatic and hydrophobic interactions dominate.[8,125] Aromatics have also been shown to form favorable interactions with polar substituents and even positively charged groups.[8] With this degree of versatility in binding interactions, it is not surprising that the biphenyl framework is so common in pharmaceuticals.

Several known reactions exist for the synthesis of biphenyls, including the Ullmann synthesis[126] for the creation of symmetrical biaryls and the Stille,[127−131] Suzuki,[132−135] and Negishi[136] reactions and the use of organosilicates[137,138] for the creation of unsymmetrical biaryls. The Grignard reaction has also been utilized for the creation of unsymmetrical biaryls,[139] but there are few, if any, examples of the use of this reaction to create a combinatorial library of biphenyls. All of these reactions proceed with an arylorganometallic reagent and a phenyl group with an appropriate leaving group, with the aid of a palladium or nickel catalyst. Numerous combinatorial syntheses of the biphenyl framework have been achieved, most of them occurring in the last nine years.

The Ullmann synthesis was reported at the turn of last century and consists of the condensation of

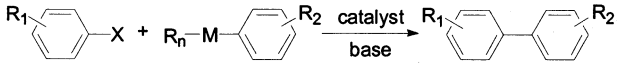
two molecules of aryl halides in the presence of copper. Unfortunately, this method requires stoichiometric amounts of copper and a high reaction temperature.[126,140,141] Nevertheless, this reaction has been used to generate a core symmetrical biphenyl which was subsequently derivatized into a combinatorial library.[142] However, the synthesis of unsymmetrical biphenyls is also possible using a modification of this reaction. Hassan et al. reported such a synthesis in which the selectivity for cross-coupling versus homocoupling was driven by the electronegativities of the substituents on the benzene rings, and as a result, cross-coupled products could be obtained in quantitative yield (Scheme 1).[141] A modified Ullmann reaction has also been utilized in solution-phase combinatorial libraries for homo-[143] and heterocoupling[144] of arylhalides.

Scheme 1. Unsymmetrical Biphenyl Synthesis by Hassan et al.[141]



The most versatile procedures for the synthesis of biphenyl systems are the Stille[127−131] and Suzuki[132−135] reactions (Scheme 2). These reactions are stereospecific and regioselective and proceed with high yields of products. Both of these reactions have been adapted to solid-phase numerous times.[145,146]

Scheme 2. General Formulas for the Stille,[127−131] Suzuki[132−135] and Negishi Reactions[136] for the Synthesis of Biphenyls



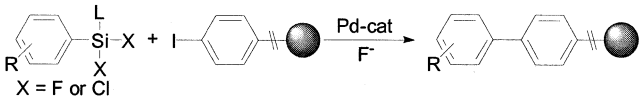
Stille Reaction: M = Sn; catalyst = PdL_n
Suzuki Reaction: M=B; catalyst = PdL_n
Negishi Reaction: M=Zn, Al, Zr; catalyst=$Ni(PPh_3)_4$, $PdCl_2(PPh_3)_2$

The majority of biphenyl combinatorial libraries have been synthesized using either the Suzuki or the Stille reaction. Solid-phase libraries of biphenyls synthesized via the Suzuki reaction first appeared in 1994[147,148] and have since appeared many times on both solid[149−162] and solution phases.[121,122,163−167] The reaction has even been used to generate combinatorial libraries on the solid phase using microwave radiation.[168] Resin-to-resin Suzuki coupling has also been reported.[169] The Stille reaction has also been used many times in the synthesis of combinatorial libraries, first appearing in solid-phase combinatorial library synthesis in 1995.[170] Since then, there has been many examples of the Stille reaction in combinatorial synthesis on the solid[171,172] and solution phases.[122,172−175]

Negishi has also presented a series of papers on cross-coupling reactions.[136,176−182] Organoaluminum, zinc, and zirconium reagents have been used interchangeably to couple two unsaturated groups (this includes aryls, alkenes and alkynes in varying combinations) in either a palladium or nickel catalyzed reaction.[136,176−182] This process has also been utilized in the creation of biphenyls, in which organozinc compounds were used with either a nickel or palladium catalyst as shown in Scheme 2.[136] The reaction provides high chemo- and regioselectivity as well as high cross-coupling versus homocoupling ratios. Although the Suzuki or the Stille reactions are far more common, the technique described by Negishi has been frequently applied to solid-phase combinatorial chemistry.[183,184]

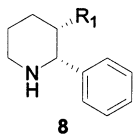
Another strategy by Homsi et al. reported the use of organosilicates in a palladium-catalyzed reaction for the synthesis of biphenyls.[137,138] Eight aryl(cyclohexyl)(difluoro)silanes were treated with Wang resin-tethered 4-iodobenzoic acid to generate a small library of biphenyls with high efficiency (>94% in nearly all cases) on the solid-phase (Scheme 3).[137]

Scheme 3. Unsymmetrical Biaryl Synthesis by Homsi et al.[137]



B. Arylpiperidines

The arylpiperidine scaffold is a key element involved in binding to a wide variety of receptors. Many molecules based on this scaffold target neurokinin receptors. For example, the *cis*-(2*S*,3*S*)-piperidine framework (**8**) has been reported to be a basic framework for high-affinity neurokinin-1 receptor (NK_1) antagonists (Figure 3).[185] Neurokinin antagonists are implicated in a variety of disease states, including migraine, emesis, pain, arthritis, asthma, depression, and anxiety.[185−188] Many neurokinin-1 receptor antagonists have been reported in the literature based on the arylpiperidine scaffold.[185,187,189] Less effort has been applied to the discovery of nonpeptide antagonists of the neurokinin-2 and -3 receptors.[186] Possible applications of drugs specific for these receptors include the treatment of asthma, as well as psychosis and anxiety.[186,190] It should be noted that the endogenous ligands of the neurokinin-1, -2, and -3 receptors (substance P, neurokinin A, and neurokinin B, respectively) have the highest affinity for their native receptor subtypes, but all three peptides have a relatively high affinity for, and are able to act as full agonists for all three receptor subtypes.[186]



8

Figure 3. The *cis*-(2*S*,3*S*)-piperidine framework is a basic framework for high-affinity neurokinin-1 receptor (NK_1) antagonists.[185]

The arylpiperidine moiety is also found in antagonists for other neuroreceptors. This framework has been used as a scaffold for inhibitors of neuropeptide Y (possible application for obesity),[191] the dopamine transporter (cocaine antagonist),[192] somatostatin (inhibition of tumor cell growth),[193,194] the CCR2B receptor (antifungal properties),[195] the opioid κ recep-

tor (substance abuse, analgesic),[196] the serotonin receptor, and serotonin reuptake inhibitor (antidepressant)[197] and as a reversible inhibitor of monoamine oxidase A (antidepressant).[197]

In contrast to many other privileged substructures described in this section, there appears to be no named reactions for the synthesis of arylpiperidines. The strategies chosen to synthesize these compounds vary widely and can be loosely grouped into three types: synthesis in which the piperidine ring is attached to the aryl group through the ring nitrogen, carbon−carbon bond formation between the two cyclic structures, and synthesis in which the piperidine ring is formed during the synthesis.

Probably the most common arylpiperidine structure chosen for combinatorial synthesis contains the nitrogen of the piperidine ring bonded directly to the aromatic group (**9**) (Figure 4). This of course alleviates the need to form a carbon−carbon bond between the two ring systems (as opposed to arylpiperidines such as **10**) and allows the chemist to join two cyclic structures directly together, reducing the number of synthetic steps. Arylpiperidines of this type are easily synthesized from arylhalides and substituted piperidines in the presence of either a base[191,198] or a palladium catalyst (Scheme 4).[199] This has been accomplished on both the solid[198,199] and solution phases.[191]

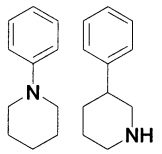
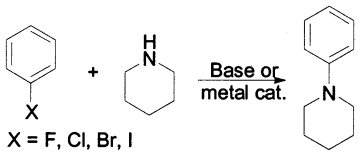


Figure 4. Arylpiperidines.

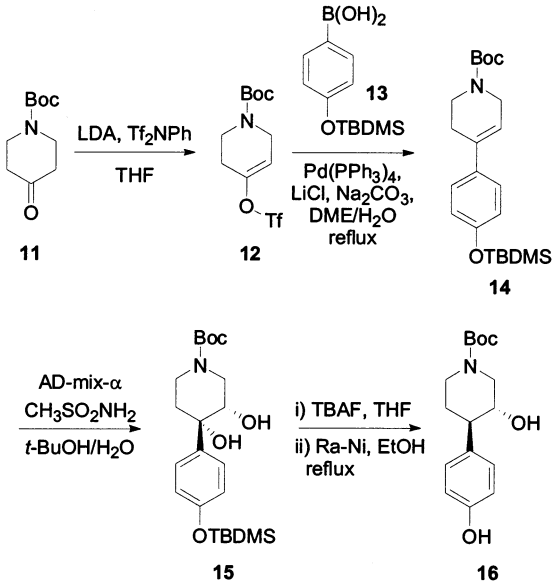
Scheme 4. Synthesis of Arylpiperidines of Type 9[191,198,199]



Arylpiperidines such as **10** may also be formed through carbon−carbon bond formation between two preformed ring systems. This strategy is well illustrated by Bursavich et al. (Scheme 5).[200,201] *tert*-Butoxycarbonylpiperid-4-one (**11**) was converted to the triflate (**12**) using LDA and *N*-phenyltrifluoromethanesulfonamide. Suzuki-type coupling with the arylboronic acid (**13**) then produced the aryltetrahydropyridine (**14**) in moderate yield. Sharpless asymmetric dihydroxylation (AD) then converted this product to the corresponding diol (**15**), which then could be stereoselectively reduced to **16**, which was the arylpipidine scaffold used for solid-phase library synthesis.[200]

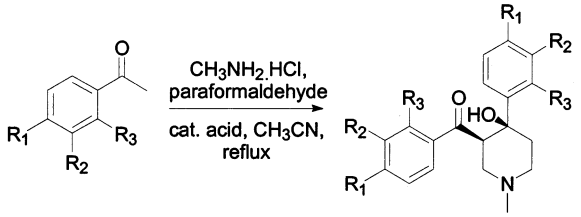
The third strategy for arylpiperidine synthesis involves the formation of the piperidine ring during the synthesis. Wang et al. reported a condensation-cyclization reaction to provide the arylpiperidine in moderate to good yield (50−71%) (Scheme 6).[192] The arylpiperidine compounds were then able to be

Scheme 5. Arylpiperidine Scaffold Synthesis for Combinatorial Library Generation by Bursavich and Rich[200,201]

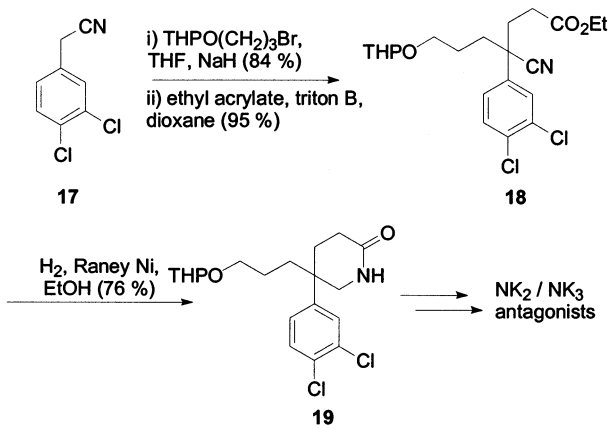


further derivatized, generating a small library in solution phase. A different approach was used by Harrison et al. (Scheme 7).[186] The authors started with the benzyl nitrile derivative (**17**) and took advantage of the resonance stabilized negative charge α to the nitrile to afford **18**. Following this, treatment with Raney Nickel produced the cyclized lactam (**19**). This lactam was then further derivatized to make two small solution-phase libraries, one based on the lactam ring (affording selective NK_2 receptor antagonists) and the other based upon an arylpiperidine structure (providing selective NK_3 receptor antagonists).

Scheme 6. Synthesis of an Arylpiperidine Combinatorial Library by Wang et al.[192]



Scheme 7. Synthesis of an Arylpiperidine Combinatorial Library by Harrison et al.[186]



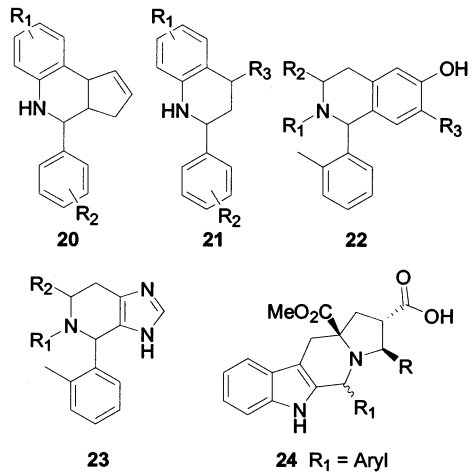


Figure 5. Combinatorial libraries of larger heterocycles based on an arylpiperidine framework.[111,202−204]

Other strategies are applicable if the piperidine ring is fused to other heterocycles. A three component reaction was utilized by Kiselyov et al. to synthesize tetrahydroquinolines such as **20** and **21** on the solid phase (Figure 5).[202,203] Another example was reported by Hutchins et al. who synthesized a small library of tetrahydroisoquinolines and tetrahydroimidazopyridines such as **22** and **23** on the solid phase.[111] Dondas and co-workers have also reported the synthesis of **24** through sequential 1,3-dipolar cycloaddition-Pictet−Spengler reactions.[204] Additional arylpiperidine libraries have been synthesized using solution-phase methods, although the initial construction of the arylpiperidine moiety was either not reported or was commercially available.[185,196,205]

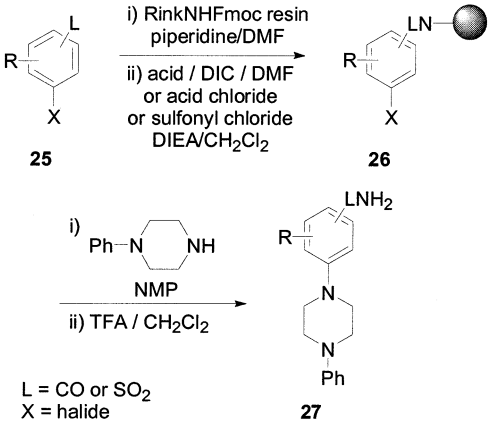
C. Arylpiperazines

The arylpiperazine framework is observed in a large number of compounds of pharmaceutical interest. In 2001 the MDDR (MDL Drug Data Report) listed 2271 phenylpiperazines which totaled 65 structures in phase II clinical trials or higher across 23 therapeutic areas.[63] This total includes antibacterials, α_1-adrenergic blockers, α_2-adrenergic agonists, antidepressants,[197] serotonin receptor (5-HT_{2A}) antagonists, phosphodiesterase III inhibitors, antitussives, antifungals, antivirals, anxiolytics, antipsychotics, antimycobacterials, antidepressants, lipooxygenase inhibitors, analgesics, antiaggregants, endothelin antagonists, hypolipidemic compounds, and also molecules that treat cognition disorders.[63] In addition to this, the arylpiperazine scaffold is active against most subtypes of the serotonin receptor, including the 5-HT_{1A}[206] and 5-HT_{1D} receptors,[207] 5-HT_{2B} and 5-HT_{2C} receptors,[208] and the 5-HT_6 receptor.[209,210] The scaffold also shows some application as dihydrofolate reductase inhibitors[211] and as human rhinovirus 3C protease inhibitors.[212]

The arylpiperazine scaffold has been used frequently in combinatorial libraries. The most common utilization of this scaffold in combinatorial synthesis is as a substituent of another small molecule scaffold.[211−227] Nevertheless, arylpiperazines have also been used frequently as the core component of combinatorial syntheses. Classically, arylpiperazines were synthesized through ring closure of appropriately substituted anilines and bis(2-chloroethyl)amine hydrochloride in the presence of base.[228,229] This procedure has been utilized to synthesize arylpiperazine precursors for combinatorial libraries.[230]

More recently, several other methods have been developed that are considerably more versatile. In 1995 Dankwardt et al. published a novel route for arylpiperazine synthesis through nucleophilic aromatic substitution (Scheme 8).[231] The synthesis begins with the attachment of variously substituted aryl halides (**25**) to Rink amide resin with diisopropylcarbodiimide (DIC) in *N*-methylpyrrolidinone (NMP) or diisopropylethylamine (DIEA) in dichloromethane. The resultant polymer supported aryl halides (**26**) were then treated with excess phenylpiperazine in NMP at room temperature for 48 h before cleavage from resin to afford the benzamide or benzthiamide (**27**). This procedure was used to synthesize a 190-membered library through the split and mix technique. Unfortunately, this method requires a nitro group in the ortho or para position for a complete reaction.[199]

Scheme 8. Arylpiperazine Library Synthesis by Dankwardt et al.[231]



Nucleophilic aromatic substitution reactions for aryl piperazine library synthesis has also been accomplished in the liquid phase under similar conditions,[198,229] or on solid phase with the aid of a palladium catalyst.[199,208,232] The limitations inherent in both reaction types lead to their tandem use in one solid-phase combinatorial library which utilized *ortho*-, *meta*-, and *para*-fluoro-nitrobenzene as the starting materials.[63] Libraries have also been constructed in which the starting material used are fully constructed arylpiperazine precursors.[207,209,210,233,234]

D. 1,4-Dihydropyridines

1,4-Dihydropyridines are very attractive targets for combinatorial library synthesis due to their wide range of biological activities. Perhaps the best known pharmacological class of 1,4-dihydropyridines known are the calcium channel blockers, such as nifedipine (**28**), which have been in clinical medicine since 1975 (Figure 6). These compounds are routinely used in the treatment of a variety of cardiovascular disorders, such as hypertension, cardiac arrhythmias or angina.[235,236] More recently, many second-generation

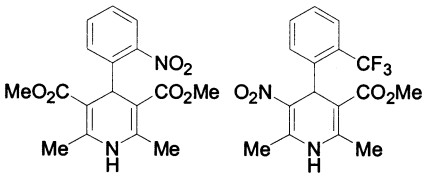
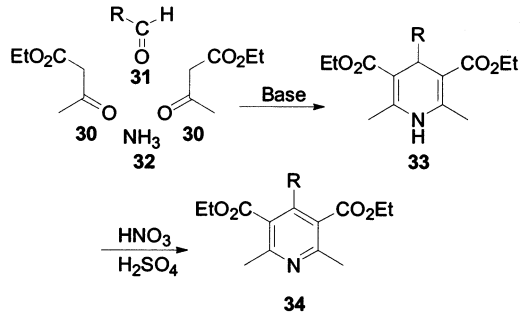


Figure 6. Nifedipine (**28**) and BAY K 8644 (**29**).

calcium antagonists have emerged with improved bioavailability and tissue selectivity/stability (such as Benidipine and Lacidipine),[237] and calcium agonists (such as BAY K 8644, **29**)[238] have been discovered. 1,4-Dihydropyridines have also been reported to be vasodilators, antihypertensives and bronchodilators and possess antiatherosclerotic, antioxidant, hepatoprotective, antitumor, antimutagenic, antidiabetic, geroprotective, herbicidal, and photosensitizing activities.[239−241] These molecules can also be utilized to promote drug transfer across the blood−brain barrier.[239] Other 1,4-dihydropyridines have been reported to be active at P2 receptors[9] and to inhibit platelet aggregation.[242] The 1,4-dihydropyridine Cerebrocrast has also recently been introduced as a neuroprotectant and cognition enhancer lacking neuronal-specific calcium antagonist properties.[240,241]

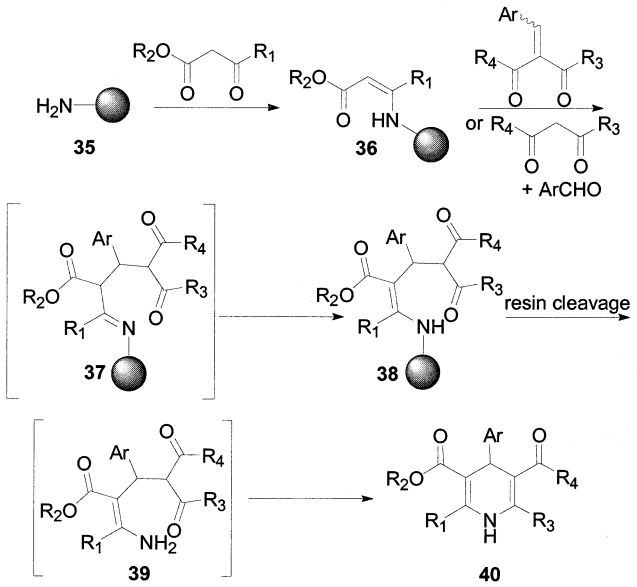
One of the most facile routes to 1,4-dihydropyridine synthesis is the Hantzsch condensation, which was first developed by Hantzsch in 1882,[243] and was originally designed for the synthesis of pyridines. A typical reaction begins with a β-keto ester (**30**), an aldehyde (**31**), and ammonia (**32**), which react under basic conditions to furnish the 1,4-dihydropyridine (**33**) in good yield (Scheme 9). **33** can then be oxidized under acidic conditions to yield the pyridine derivative (**34**).[244] As 1,4-dihydropyridines have become medicinally important compounds over the last century, variations of this method have been used to synthesize molecules such as **33**.[239]

Scheme 9. Hantzsch Pyridine Condensation[478]



Multicomponent condensations have proven to be very simple and effective methods for combinatorial synthesis. The Hantzsch condensation has been used to synthesize 1,4-dihydropyridines in both solution-[242] and solid-phase[245] combinatorial synthesis. In 1996, Gordeev and co-workers developed a solid-phase synthesis of 1,4-dihydropyridines (Scheme 10).[240,241] In this scheme, a β-dicarbonyl compound reacted with a polystyrene based acid-cleavable resin (**35**) to afford the enamine (**36**) on solid-support. Next, **36** was treated with either a preformed α-arylmethylene-β-dicarbonyl compound or was treated directly

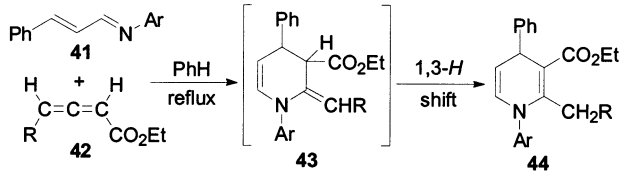
Scheme 10. Solid-Phase Split and Mix Combinatorial 1,4-Dihydropyridine Synthesis by Gordeev et al.[240,241]



with an aromatic or heteroaromatic aldehyde and a β-dicarbonyl compound to afford **37**, which underwent imine−enamine tautomerisation to produce **38**. Acidic cleavage from resin produced **39**, which then completed the cyclo-condensation, yielding the 1,4-dihydropyridine (**40**).

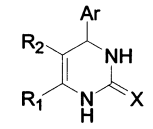
Other strategies for 1,4-dihydropyridine combinatorial synthesis have been reported. A novel approach for their synthesis was reported by Ishar et al. (Scheme 11).[246] Heating an azadiene (**41**) and an allenic ester (**42**) in dry refluxing benzene led to the formation of 2-alkyl-1-aryl-3-ethoxycarbonyl-4-phenyl-1,4-dihydropyridine (**43**), which rearranged to the 1,4-dihydropyridine (**44**) in high yield. It appears that 1,4-dihydropyridines produced by this route are formed through a (4 + 2) cycloaddition followed by a 1,3-hydrogen shift.

Scheme 11. 1,4-Dihydropyridine Synthesis by Ishar et al.[246]



E. Dihydropyrimidones

4-Aryl-3,4-dihydropyrimidin-2(1*H*)-ones (**45**) have been reported in the literature since the nineteenth century (Figure 7). In 1893, Pietro Biginelli devised a multicomponent reaction that produced multifunctionalized dihydropyrimidones in a one pot process.[247] Since then, interest waned until the early 1980s, when the apparent structural similarity of dihydropyrimidones to the well-known calcium channel modulators of the Hantzsch type (such as nifedipine, **28**, Figure 6) was recognized.[235,248]



45

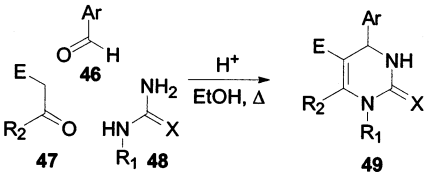
R_1, R_2 = alkyl groups
X = O, S
Ar = subsituted aryl

Figure 7. 4-Aryl-3,4-dihydropyrimidin-2(1*H*)-one (**45**).

More recently, the Biginelli reaction has proven to be very applicable to combinatorial chemistry, and many diverse dihydropyrimidone compound libraries have been synthesized for high-throughput screening. Compounds with the dihydropyrimidone core scaffold are reported to be antihypertensives (calcium channel modulators) and anticancer leads (mitotic kinesin Eg5 motor protein inhibitors and blood platelet aggregation inhibitors). This class of compounds also exhibits antiviral activity and antiinflammatory activity and is also used to treat benign prostatic hyperplasia (α_{1a}-adrenergic receptor antagonists).[235,248]

The basic form of the Biginelli reaction is illustrated in Scheme 12.[235] A three-component acid-catalyzed cyclo-condensation protocol is used to produce the dihydropyrimidone (**49**). The three components are an aromatic aldehyde (**46**), a 1,3-dicarbonyl component (**47**), and a urea or thiourea derivative (**48**). If the urea or thiourea is monosubstituted, then the substituted nitrogen regiospecifically forms *N*1-substituted dihydropyrimidones (Scheme 12). The multicomponent one-pot strategy is a very attractive synthetic route for chemists, but the method has its downfalls. A major drawback of the original Biginelli protocols (using ethanol and hydrochloric acid as the reaction medium) are the low yields that are encountered when using sterically demanding thioureas or ureas. Several recent modifications have largely overcome this problem.[248]

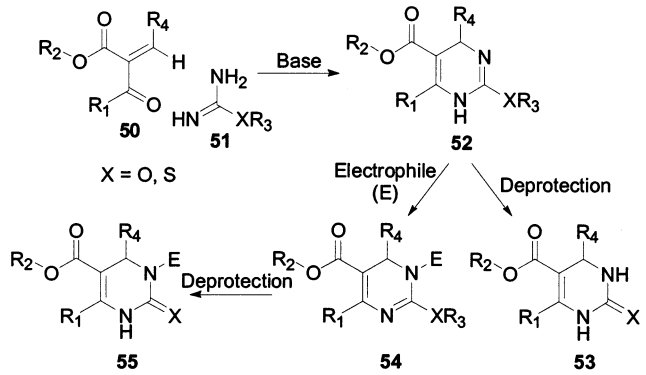
Scheme 12. The Biginelli Reaction for Dihydropyrimidone Synthesis[235]



X = O, S
E = ester, amide, acyl group
Ar = substituted aryl group

A second improved procedure which has frequently been used for the synthesis of dihydropyrimidones is the "Atwal modification" of the Biginelli reaction (Scheme 13).[249−251] This procedure is similar to the method described above, except that the enone **50** is preformed prior to further reaction, and the urea or thiourea (**51**) are *O* or *S* protected. Cyclo-condensation of **50** with **51** under mild conditions then produces the 1,4-dihydropyrimidine (**52**). At this point, *N*3 can be regiospecifically acylated prior to deprotection (**54**), or left underivatized. The protecting group (R_3) is then removed to yield **55** or the underivatized dihydropyrimidone (**53**), respectively.

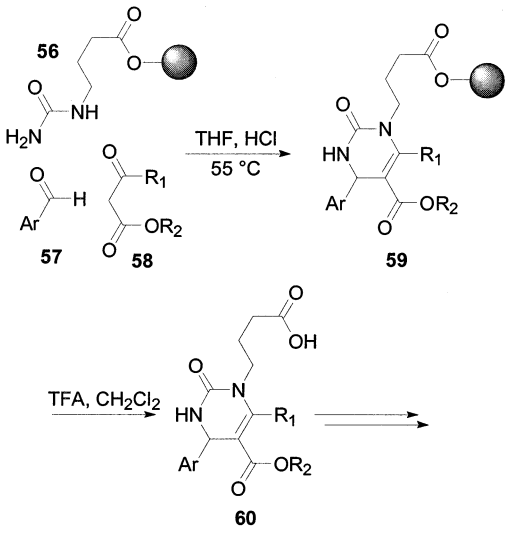
Scheme 13. Atwal Modification of the Biginelli Reaction[249−251]



This method is very reliable and allows the synthesis of many pharmacologically active dihydropyrimidones.[248] Both of these reactions have been utilized in combinatorial synthesis.

One of the first solid-phase modifications of the Biginelli reaction was reported in 1995 by Wipf and Cunningham (Scheme 14).[252] The synthesis requires the attachment of an γ-aminobutyric acid-derived urea to Wang resin, providing **56**. Following this, the acid-catalyzed Biginelli reaction was performed, in which 4 equivalents of β-ketoester **58** and aryl aldehyde **57** was used. After cleavage of the resultant dihydropyrimidone (**59**) from the resin with trifluoroacetic acid, further derivatization of the resulting acid (**60**) was possible.

Scheme 14. Solid-Phase Synthesis of Dihydropyrimidones by Wipf and Cunningham[252]



Ar = substituted aryl group

In recent years, there have been numerous combinatorial syntheses of dihydropyrimidones. Libraries of dihydropyrimidones have been prepared via the Biginelli reaction in solution phase to generate *C*-glycosylated dihydropyrimidones,[253] on fluorous phase (through attachment to the urea),[254,255] and have been synthesized for use in chiral HPLC (preparation in solution phase).[256,257] Combinatorial libraries have also been synthesized on solid phase, attaching the dihydropyrimidone through different substituents on the heterocyclic ring to afford scaffolds that are unsubstituted at *N*1.[258,259]

III. Fused [7–6] Ring Systems

Benzodiazepines are the prototypical privileged substructure. It was this class of compounds to which the term "privileged structure" was first applied by Evans et al. in 1988 in reference to the ability of 1,4-benzodiazepin-2-ones (**61**) to bind to cholecystokinin (CCK), gastrin and central benzodiazepine receptors.[1] Since then, many different types of benzodiazepines have been synthesized and their pharmacology reported. Presently, there are numerous types of benzodiazepines (Figure 8), including 1,4-benzodiazepin-2-ones (**61**), 1,5-benzodiazepin-2-ones (**62**), 1,4-benzodiazepin-2,5-diones (**63**), 1,4-benzothiazepin-5-ones (**64**), pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones (**65**), and 5,11-dihydro-benzo[*e*]pyrido[3,2-*b*][1,4]diazepin-6-ones (**66**), all of which have been synthesized combinatorially. These compounds may be substituted almost anywhere on either ring to produce a variety of biological effects, although commonly these molecules are substituted at *C*3. Not surprisingly, a variety of synthetic methods must be used to access these molecules as no single strategy is sufficiently generic.

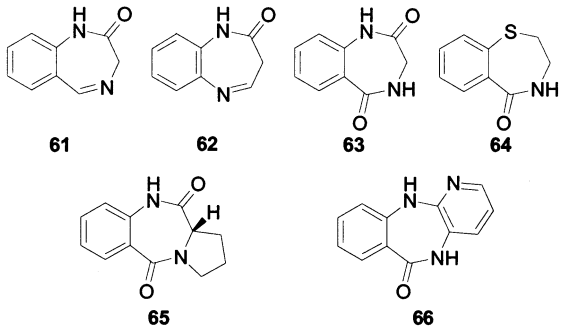


Figure 8. Fused [7−6] ring systems based on the benzodiazepine framework.

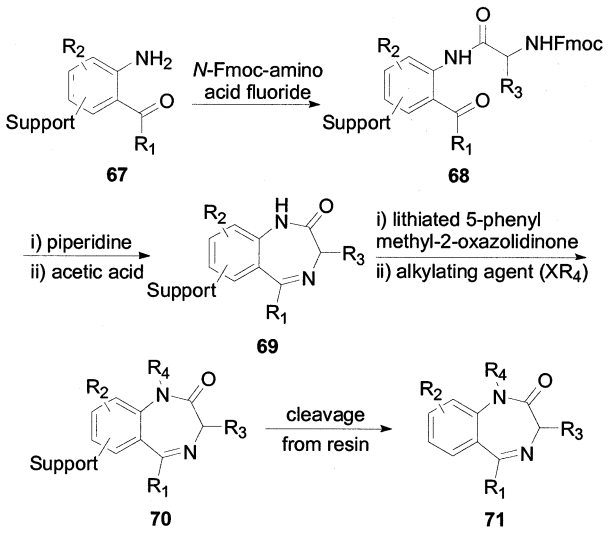
A. 1,4-Benzodiazepin-2-ones

In general terms, much of the biological activity of the 1,4-benzodiazepin-2-ones (**61**) can be predominately ascribed to their action in the central nervous system. This includes sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity. Nevertheless, they are also active in peripheral tissues: coronary vasodilation is seen after intravenous administration of therapeutic doses of certain benzodiazepines, and neuromuscular blockade which is seen only with very high doses.[260] To be more specific, these molecules are neurokinin antagonists, opioid receptor agonists, cholecystokinin receptor (CCK) A and B antagonists, oxytocin antagonists, HIV transactivator Tat antagonists, HIV reverse transcriptase inhibitors, ras farnesyl transferase inhibitors, potassium channel blockers, phosphodiesterase IV inhibitors, platelet activating factor antagonists, Src protein tyrosine kinase inhibitors, gastrin inhibitors, central benzodiazepine receptor inhibitors and have potential in the treatment of systemic lupus erythematosus.[1,3,261−267]

As would be expected, many combinatorial syntheses based on this scaffold have been reported in the literature. One of the most obvious synthetic precursors to 1,4-benzodiazepin-2-ones is amino acids and an aryl moiety. Amino acids are an excellent choice due to the number of natural and unnatural amino acids available commercially. Only one of the synthetic strategies discussed here does not begin from these precursors. Synthetic strategies include ring closure between *N*4 and *C*5, amide bond formation between *N*1 and *C*2, and cyclization between *C*3 and *N*4.

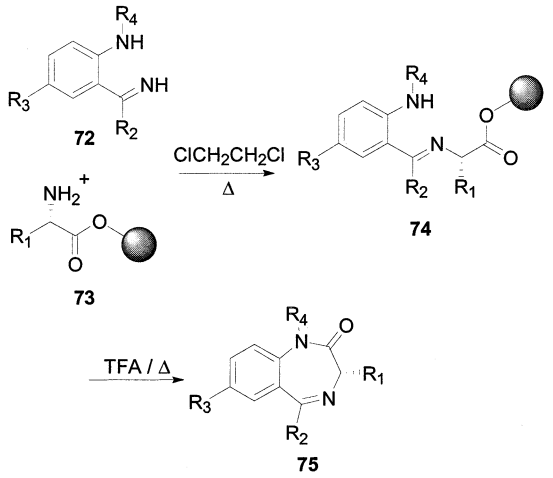
The first strategy to be discussed is ring closure between *N*4 and *C*5. Combinatorial libraries synthesized by Ellman et al. (solid phase)[32,262−264,268−272] and by Evans et al. (solution phase)[1] utilized this strategy. An example of this type of synthesis by Ellman et al. is displayed below in Scheme 15.[32,262,271] A substituted 2-amino-benzyl ketone (**67**) is treated with an Fmoc-protected amino acid fluoride to yield **68**. After removal of the Fmoc-group, the compound is treated with 5% acetic acid to affect ring closure via a condensation reaction yielding **69**. Following treatment with lithiated 5-phenylmethyl-2-oxazolidinone, the alkylating agent was added, allowing substitution at *N*1 (**70**). Cleavage from resin then yielded the benzodiazepine with four points of diversity (**71**). Selnick et al. synthesized a library from similar precursors in solution phase, except bromoacetyl bromide was used instead of an amino acid. Substituents at *C*3 were later added through use of potassium *tert*-butoxide and trisyl azide and subsequent reduction to the amine.[273]

Scheme 15. 1,4-Benzodiazepin-2-one Combinatorial Library Synthesis by Ellman et al.[32,262,271]



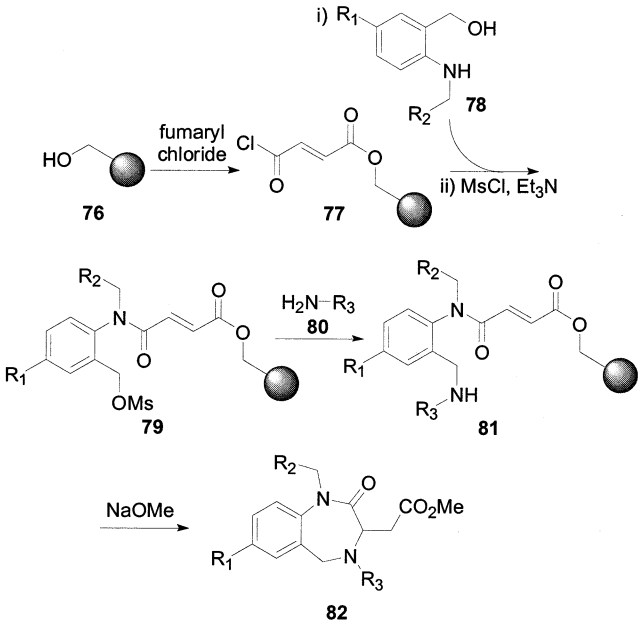
Ring closure via amide bond formation between *N*1 and *C*2 has also been reported and solid-phase libraries have been made on this theme.[274,275] This strategy was amply illustrated by DeWitt et al. in 1993 (Scheme 16),[275] in which 40 discrete benzodiazepines were synthesized. The scheme begins with the treatment of five different amino acid resins (**73**) with each of eight 2-amino benzophenone imines (**72**) to produce **74**. Cyclization and cleavage then occurred through treatment with TFA at 60 °C for 20 h, producing the 1,4-benzodiazepin-2-one scaffold (**75**).

Scheme 16. 1,4-Benzodiazepin-2-one Combinatorial Library Synthesis by DeWitt et al.[275]



1,4-Benzodiazepin-2-one synthesis has also been reported in which the final ring closure is achieved through *C*3 and *N*4. Bhalay et al. synthesized 120 tetrahydro-1,4-benzodiazepin-2-ones on the solid phase (Scheme 17).[265] Wang resin (**76**) was treated with fumaryl chloride to yield the acid chloride **77**. Following this, **77** was treated with the preformed amino alcohol **78** and mesylated to produce **79**. Following treatment with amine **80**, the resin was treated with sodium methoxide to form **82** in a single cyclization/cleavage step via a 7-*exo*-*trig* cyclization.

Scheme 17. Tetrahydro-1,4-benzodiazepin-2-one Combinatorial Library Synthesis by Bhalay et al.[265]



A differential release combinatorial chemistry library of 1296 discrete 1,4-benzodiazepin-2-ones was also reported by Evans et al.[266] In this strategy, chemical encoding of each monomer on resin was combined with two orthogonally cleavable linkers. This method proved to be an effective strategy for the biological screening of these libraries, first as pooled mixtures, then as discrete compounds. Using this strategy, the authors were able to identify a potent and selective oxytocin antagonist. Wyatt et al. then attempted to optimize this lead compound through the synthesis of several libraries of 1,4-benzodiazepin-2-ones.[267]

B. 1,5-Benzodiazepin-2-ones

Significantly less research has been undertaken on the 1,5-benzodiazepin-2-ones (**62**), compared to the 1,4-benzodiazepin-2-ones. Molecules with the 1,5-benzodiazepin-2-one scaffold are privileged substructures exhibiting a range of biological activities including interleukin-1β converting enzyme (ICE) inhibitors, such as **83**, and delayed rectifier potassium current blockers, (I_K) such as **84** (Figure 9).[276]

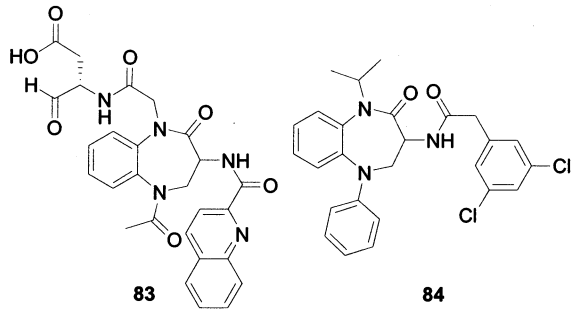
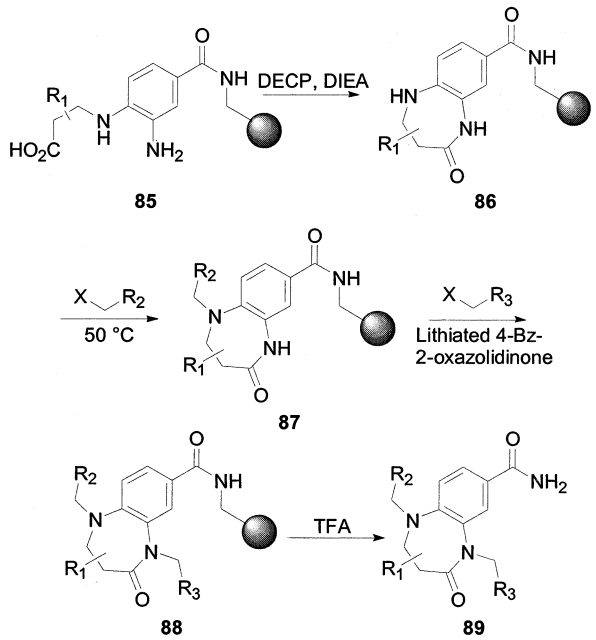


Figure 9. Examples of biologically active 1,5-benzodiazepin-2-ones.[276]

Although few combinatorial syntheses of these molecules have been reported, combinatorial libraries have been constructed which either employ *N*1/*C*2 ring closure,[277,278] or begin with a pre-assembled 1,5-benzodiazepin-2-one scaffold.[276] The former strategy is well illustrated by the synthesis reported by Schwarz et al. (Scheme 18).[277] After assembling **85**,

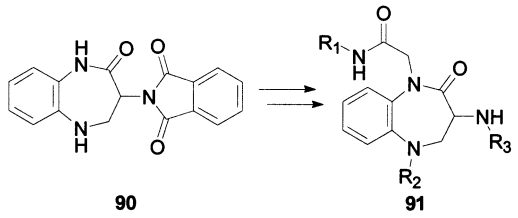
Scheme 18. 1,5-Benzodiazepin-2-one Combinatorial Library Synthesis by Schwarz et al.[277]



treatment with diethyl cyanophosphonate (DECP) and diisopropylethylamine (DIEA) afforded the cyclic product **86**. Regioselective *N*5 alkylation by alkylhalides produced **87** in >85% purity. A final alkylation was then accomplished at *N*1 using lithiated 4-benzyl-2-oxazolidinone as a base, yielding **88** with no evidence of *C*- and/or *O*-alkylation. Finally, **88** was treated with trifluoroacetic acid (TFA) to cleave the 1,5-benzodiazepin-2-one (**89**) from the resin.

A different strategy was used by Herpin et al. to synthesize a 10 000-member 1,5-benzodiazepin-2-one combinatorial library.[276] In this synthesis, preassembled 3-phthalyl-1,5-benzodiazepin-2-one (**90**) was attached to resin through the amide nitrogen. Following this, the scaffold was derivatized and then cleaved from resin, yielding **91** (Scheme 19).

Scheme 19. 1,5-Benzodiazepin-2-one Combinatorial Library by Herpin et al.[276]



90 **91**

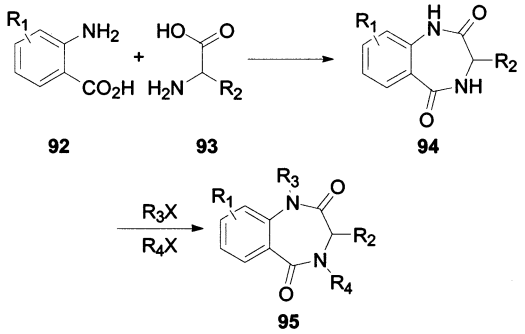
C. 1,4-Benzodiazepin-2,5-diones and Pyrrolo-[2,1-*c*][1,4]benzodiazepin-5,11-diones

1,4-Benzodiazepin-2,5-diones (**63**) are perhaps the next most studied benzodiazepine framework after the 1,4-benzodiazepin-2-ones (**61**). 1,4-Benzodiazepin-2,5-diones have been reported to possess anticonvulsant, anxiolytic, and antitumor properties, as well as being cholecystokinin receptor (CCK), opiate receptor and platelet glycoprotein IIb−IIIa antagonists.[279−281] These compounds have also been reported to possess herbicidal properties.[282] Pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones (**65**) are merely the proline substituted 1,4-benzodiazepin-2,5-dione scaffold. These molecules possess similar biological activities to their parent compound, which includes anxiolytic, sedative, psychomotor depressant, analgesic, antitumor, antiphage, and antiinflammatory activities as well as some herbicidal properties.[283,284]

There are two major combinatorial strategies for the synthesis of these compounds: the first is based on the use of amino acid derivatives,[281−287] the second is a four component Ugi reaction.[279,280,288,289] The former strategy normally relies upon the condensation of anthranilic acid or an anthranilic acid derivative (often *N* protected or masked as a nitro or azido group) (**92**) and an amino acid or derivative (**93**) to form the 1,4-benzodiazepin-2,5-dione ring (**94**) (Scheme 20). This allows for subsequent treatment with an alkylating agent to afford **95**. In most cases, a *C*-terminal protected amino acid is used, so *N*1/*C*2 amide bond formation is the cyclization step.

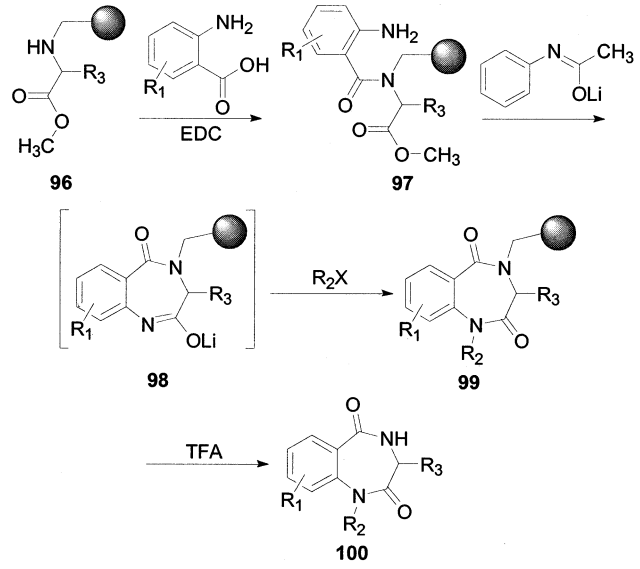
Amide bond formation may be acid[287] or base[281,282,285] catalyzed, and there are reports of both in the synthesis of combinatorial libraries of these structures. An example of a base-catalyzed cyclization is displayed in Scheme 21.[282,285] After addition of an acid labile linker to Merrifield resin ((chloromethyl)-polystyrene resin) and subsequent derivatization, **96** was acylated with variously substituted anthranilic acids and EDC (1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide·hydrochloride) to provide the resin-bound tertiary amide **97**. Treatment with the lithium salt of acetanilide then afforded a base-catalyzed cyclization to produce **98**, which was subsequently alkylated to afford **99** in a single step. Treatment with trifluoroacetic acid (TFA) cleaved the backbone amide linker, yielding the 1,4-benzodiazepin-2,5-dione (**100**). Pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones (**65**) have also been synthesized combinatorially by this route.[283,284] The main drawback of this strategy is the difficult alkylation of the amide bond nitrogen (this can be circumvented through the use of *N*-alkylamino acids, but additional synthetic effort is required to produce these compounds).[279]

Scheme 20. General Strategy for 1,4-benzodiazepin-2,5-dione Synthesis via Amide Bond Formation[281−287]



92 **93** **94** **95**

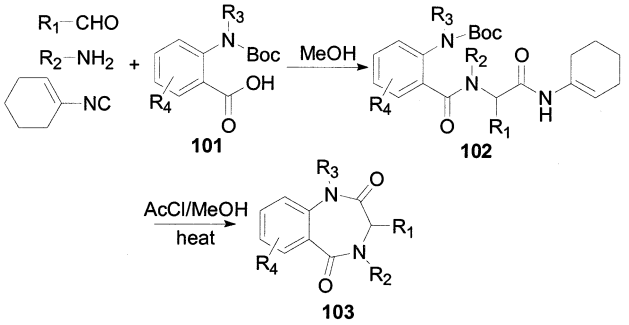
Scheme 21. 1,4-Benzodiazepin-2,5-dione Combinatorial Synthesis by Boojamra et al.[282,285]



96 **97** **98** **99** **100**

Use of the Ugi reaction to produce 1,4-benzodiazepin-2,5-diones is potentially more versatile than the methods described above, accomplishing the entire synthesis in fewer steps and circumventing many drawbacks. An example strategy is displayed in Scheme 22.[280] A substituted *N*-protected anthranilic

Scheme 22. 1,4-Benzodiazepin-2,5-dione Combinatorial Synthesis via the Ugi Reaction by Hulme et al.[280]



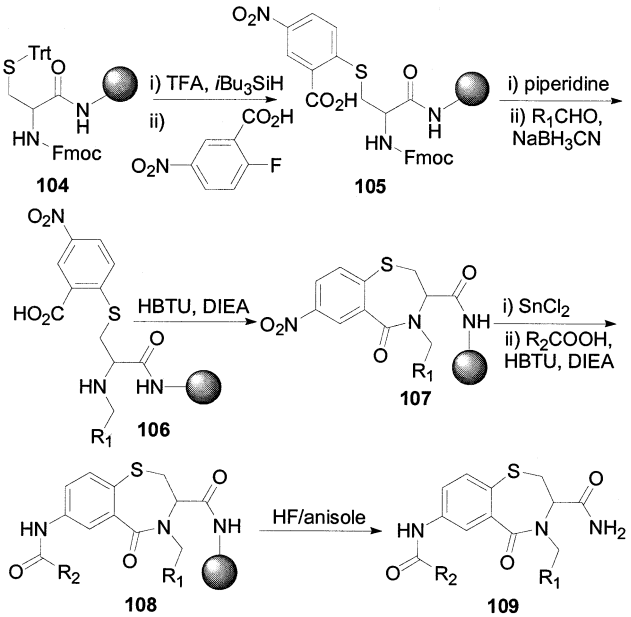
acid (**101**) was treated with an aldehyde, an amine, and an isonitrile in order of its participation in the Ugi reaction to yield **102**. After removing the solvent, **102** could be treated with either acetyl chloride in methanol, or trifluoroacetic acid in dichloroethane, to affect cyclization/deprotection and yield **103**. This procedure has also been accomplished in a one-step process, although it was not effective in all cases.[279] Combinatorial synthesis of these molecules utilizing this reaction has been reported on both solid-[88,290] and solution phases.[279,280,289]

D. 1,4-Benzothiazepin-5-ones

Molecules containing the 1,4-benzothiazepin-5-one scaffold (**64**) display a variety of interesting biological activities. This includes angiotensin converting enzyme inhibitors, endogenous natriuretic factors, and calcium channel blockers.[291] A number of these compounds also display some promise as anticancer agents.[291] Despite these interesting biological activities, few combinatorial syntheses of these molecules have been reported.

Perhaps the only combinatorial synthesis to date has been reported by Nefzi et al. (Scheme 23).[291] After coupling *N*-α-Fmoc-S-trityl-L-cysteine to *para*-methylbenzhydrylamine (MBHA) resin (**104**), the trityl group was cleaved and 2-fluoro-5-nitrobenzoic acid was coupled to the sulfur yielding **105**. Removal of the Fmoc group, and subsequent alkylation via a reductive amination reaction produced **106**, which was treated with HBTU (*O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) and DIEA (diisopropylethylamine) to afford formation of the amide bond and intramolecular cyclization, producing the 1,4-benzothiazepin-5-one scaffold (**107**). Reduction of the nitro group with $SnCl_2$, followed by *N*-acylation, produced **108**, which was then cleaved from the resin to afford **109** in good purity (>87%).

Scheme 23. 1,4-Benzothiazepin-5-one Combinatorial Synthesis by Nefzi et al.[291]



E. 5,11-Dihydro-benzo[*e*]pyrido[3,2-*b*][1,4]-diazepin-6-ones

5,11-Dihydro-benzo[*e*]pyrido[3,2-*b*][1,4]diazepin-6-ones (**66**) possess diverse therapeutic activities and are very similar structurally to many of the compounds discussed previously in this section. Essentially, **66** is merely a 1,4-benzodiazepin-5-one scaffold to which a pyridine ring has been fused. This scaffold has diverse therapeutic activities which include inhibition of HIV-1 reverse transcriptase[292] and muscarinic receptor inhibition (including the prototypical M_1-selective muscarinic receptor inhibitor, pirenzipine (**110**, Figure 10), which is used for ulcer treatment).[293−296]

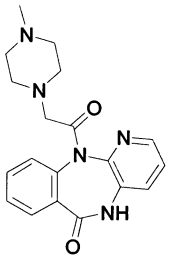
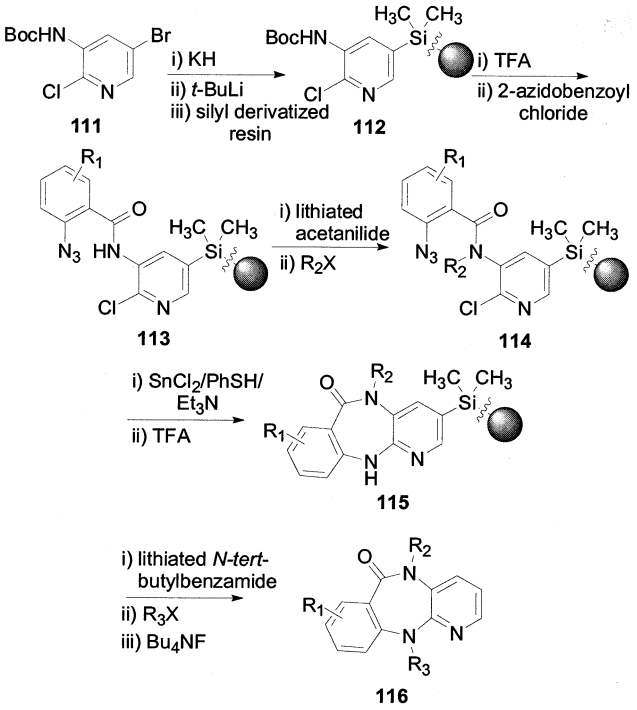


Figure 10. Pirenzipine.[293−296]

Unsurprisingly, combinatorial syntheses of these molecules usually employ a similar strategy to that of the 1,4-benzodiazepines. Ring closure is usually affected via amide bond formation between *N*4 and *C*5. A good example of this was reported by Woolard et al. (Scheme 24), who utilized a traceless silicon linker.[297] After synthesis of a specially derivatized silicon linker and attachment to resin, *N*-Boc-3-amino-5-bromo-2-chloropyridine (**111**) was added to the linker through treatment with potassium hydride followed by halogen metal exchange to produce **112**. Following this, deprotection of the Boc group and subsequent coupling with 2-azidobenzoyl chloride in the presence of pyridine produced **113**, which was readily alkylated through treatment with a base and an alkyl halide, yielding **114**. The azide was then converted to the amine through treatment with $SnCl_2$, thiophenol, and triethylamine, producing an intermediate which on treatment with acid yielded the desired scaffold (**115**). A second base-mediated alkylation followed, which upon cleavage produced **116**. Other combinatorial libraries of these molecules have also been reported using a similar strategy for solution-phase synthesis.[293,294] Combinatorial librar-

Scheme 24. 5,11-Dihydro-benzo[*e*]pyrido[3,2-*b*][1,4]-diazepin-6-one Combinatorial Synthesis by Woolard et al.[297]



ies have also been formed from a preformed 5,11-dihydro-benzo[*e*]pyrido[3,2-*b*][1,4]diazepin-6-one scaffold in solution phase.[295,296]

IV. Fused [6–6] Ring Systems

A. Benzopyrans, Chromones, Coumarins, and Pyranocoumarins

Benzopyran (**117**), chromone (**118**), and coumarin (**119**) all possess a similar core structure (Figure 11).

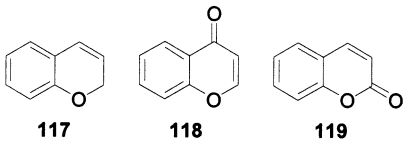


Figure 11. Benzopyran (**117**), chromone (**118**) and coumarin (**119**).

They are all seen frequently in a broad range of natural products, and each displays a wide diversity in the types of receptors to which they bind. Whether the privileged nature of these molecules arises out of a common structural element or is due to independent molecular characteristics is open to debate. Pyranocoumarins are a related scaffold which is also discussed in this section due to its structural similarity to the benzopyran and coumarin scaffolds. Due to their similarity, all of these structures will be discussed in this section, but due to the wealth of chemical and biological information available on each substructure, they will be treated separately.

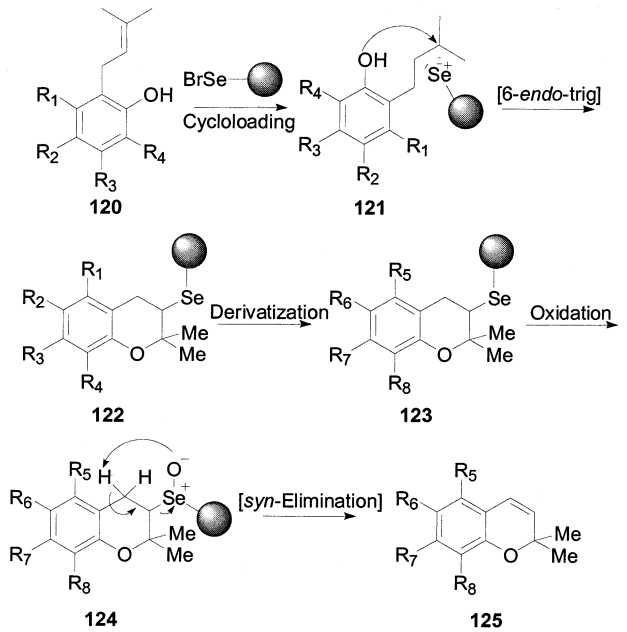
1. Benzopyrans

The benzopyran structural framework appears in a plethora of natural products and in a variety of known inhibitors for a broad range of receptors. The occurrence of this framework in so many natural products may be at least in part attributed to the numerous prenylation and cyclization reactions in many polyketide biosynthesis pathways.[2] Structures with a benzopyran framework (excluding larger substituted frameworks such as coumarins, chromones, etc) have antitumor, antibacterial, and antiinflammatory activity and inhibit HIV-1 reverse transcriptase, interleukin-1 production, protein kinases, electron transport acting at NADH:ubiquinone oxidoreductase, arachidonate 5-lipoxygenase, interferon-γ-induced nitric oxide generation, tyrosinase, endothelin converting enzyme, phorbol ester-induced ornithine decarboxylase, and cyclo-oxygenase and can cleave DNA.[2,17,298−300] They are also known serotonin (5-HT_3) receptor antagonists, inhibit aldosterone biosynthesis and phosphodiesterase IV, activate potassium channels, and have bradycardia activity.[2]

Despite this wealth of activity, few combinatorial libraries containing this core structure have been synthesized. Far more effort has been expended in the synthesis of combinatorial libraries of benzopyran derivatives, such as coumarins and chromones. One of the most thorough examples of a combinatorial synthesis of a benzopyran library that has been reported is by Nicolaou et al.[2,15,16] This group synthesized a 10 000-member benzopyran library with the aid of the IRORI NanoKan optical encoding system for the high-throughput nonchemical tagging and sorting of library members during split-and-pool synthesis.

The synthetic strategy utilized by Nicolaou et al. is displayed in Scheme 25.[2,15,16,301,302] It begins with the attachment of an *ortho*-prenylated phenol (**120**) to resin via a traceless selenium linker. The resultant compound (**121**) then undergoes a 6-*endo*-trig cyclization to furnish resin bound benzopyrans (**122**), which may then be derivatized via condensation, annulation, glycosidation, aryl/vinyl couplings, or organo-

Scheme 25. Benzopyran Combinatorial Library Synthesis by Nicolaou et al.[2,15,16,301,302]

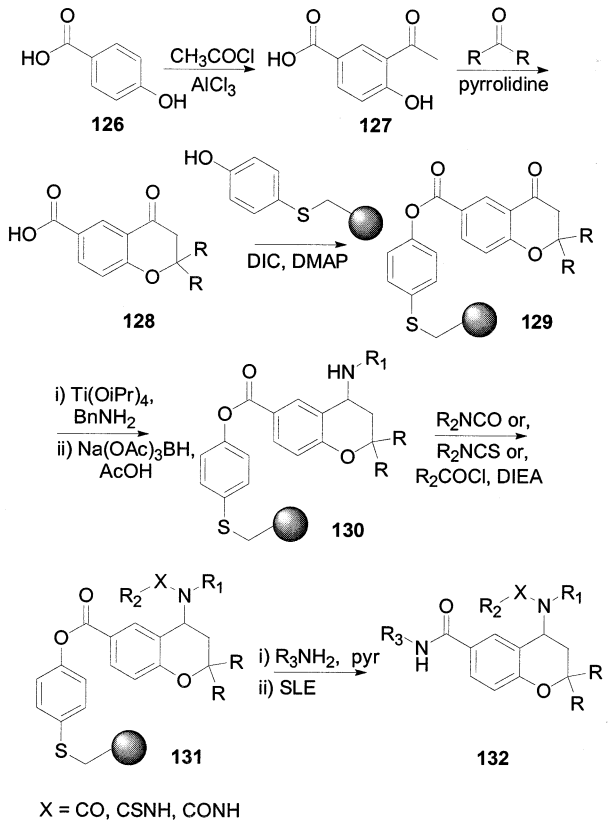


metallic addition reactions (among others) to provide **123**. Upon oxidation of the selenium to the selenoxide (**124**), spontaneous syn elimination occurs at room temperature to provide the benzopyran (**125**). The linkage through the pyran ring allows diversity elements to be added at all four sites of the benzene ring, in contrast to more traditional linking strategies.

Nicolaou et al. also reported the synthesis of a second combinatorial library of benzopyrans.[17] The second library was synthesized differently to the first. The core benzopyran framework was assembled in solution phase through coupling 2-methyl-3-butyn-2-ol to a variety of phenols. A similar ring-forming step was also utilized by Xie et al. to assemble the pyran component of a pyranocoumarin library (see Scheme 33).[303]

Breitenbucher and Hui have also reported a solid-phase combinatorial synthesis of dihydrobenzopyrans.[304] The core dihydrobenzopyranone scaffold was synthesized in solution, via acylation of *para*-hydroxybenzoic acid (**126**) to form **127**, then subsequent condensation with a ketone or an aldehyde to form the dihydrobenzopyranone (**128**) (Scheme 26). This molecule was then attached to resin via an acylation reaction to produce **129**. Derivatization at the carbonyl of the dihydrobenzopyranone ring through treatment of **129** with Ti(O*i*Pr)$_4$ and benzylamine and subsequent reduction produced **130**. Further derivatization at the amine then afforded a variety of compounds (**131**), which could be cleaved from resin through treatment with an amine in pyridine. Supported liquid extraction (SLE) then removed the excess amine used for cleavage from the desired products (**132**). This library produced 8 448 substituted dihydrobenzopyrans.

Scheme 26. Synthesis of Dihydrobenzopyrans by Breitenbucher and Hui[304]

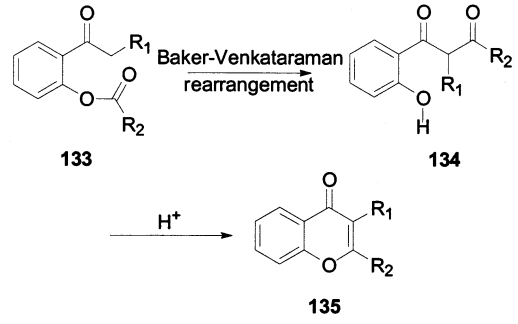


2. Chromones

Chromones (**118**) are a group of naturally occurring compounds that are widely distributed in nature, especially in the plant kingdom. Molecules containing the chromone or benzopyranone ring have a wide range of biological activities.[305,306] They have been shown to be tyrosine and protein kinase C inhibitors, as well as antifungal, antiviral, antitubulin, and antihypertensive agents.[307] Chromone derivatives are also active at benzodiazepine receptors[308] and on lipoxygenase and cyclooxygenase.[309] In addition to this, they have been shown to be anticancer agents,[310] possessing antimutagenic properties[311] as well as the ability to inhibit electron transport through inhibition at NADH:ubiquinone oxidoreductase and phorbol ester-induced ornithine decarboxylase.[299,300] Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis transmembrane conductance regulator.[312] These compounds also possess low mammalian toxicity and are present in large amounts in the diet of humans due to their origin in plants.[309]

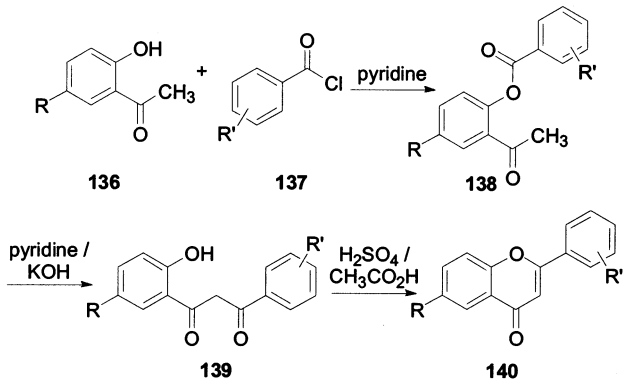
Chromones may be synthesized under either acidic or basic conditions. The classical 2,3-disubstituted benzopyranone (**135**) synthesis utilizes acidic conditions and is by far the most common method.[313] It proceeds through an intramolecular condensation of molecules such as **134**, which are usually obtained through a Baker-Venkataraman rearrangement of compound **133**, or via a Claisen ester condensation (Scheme 27). Most syntheses require harsh acidic conditions as the final step. On the other hand, syntheses utilizing basic conditions typically consist of piperidine in refluxing pyridine for several hours to affect ring closure. This is far less common.[313] Microwave heating has also been employed to affect ring cyclization.[306]

Scheme 27. Classical Synthesis of the Benzopyranone Ring[313]



There are many examples of combinatorial syntheses of benzopyranone libraries. Marder et al.[308] utilize a method similar to that displayed in Scheme 27 (Scheme 28). This synthesis produced 36 compounds which were tested for biological activity against the benzodiazepine receptor. A set of four 2-hydroxyacetophenones (**136**) were treated with a set of nine benzoyl chlorides (**137**) in pyridine to

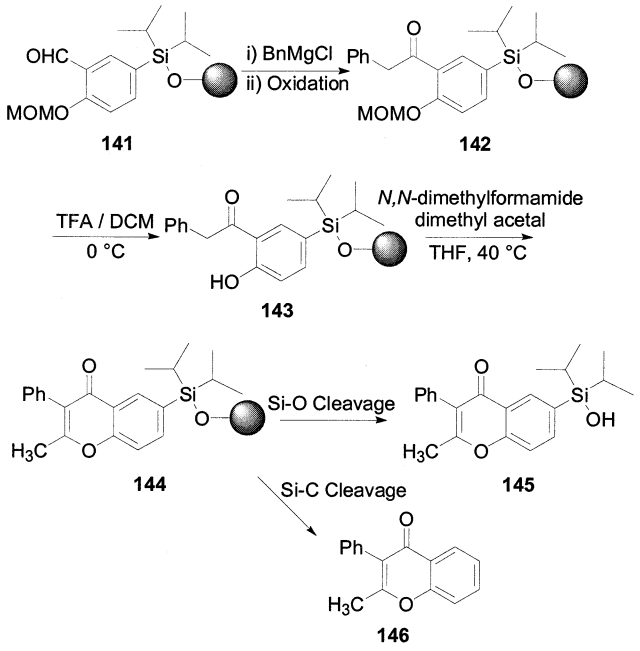
Scheme 28. Combinatorial Synthesis of Benzopyranones by Marder et al.[308]



produce **138**. This compound then underwent the Baker−Venkataraman rearrangement to **139**, which then condensed under acidic conditions to form **140**. A similar synthesis was achieved by Galietta et al., yielding a library of chromones.[312]

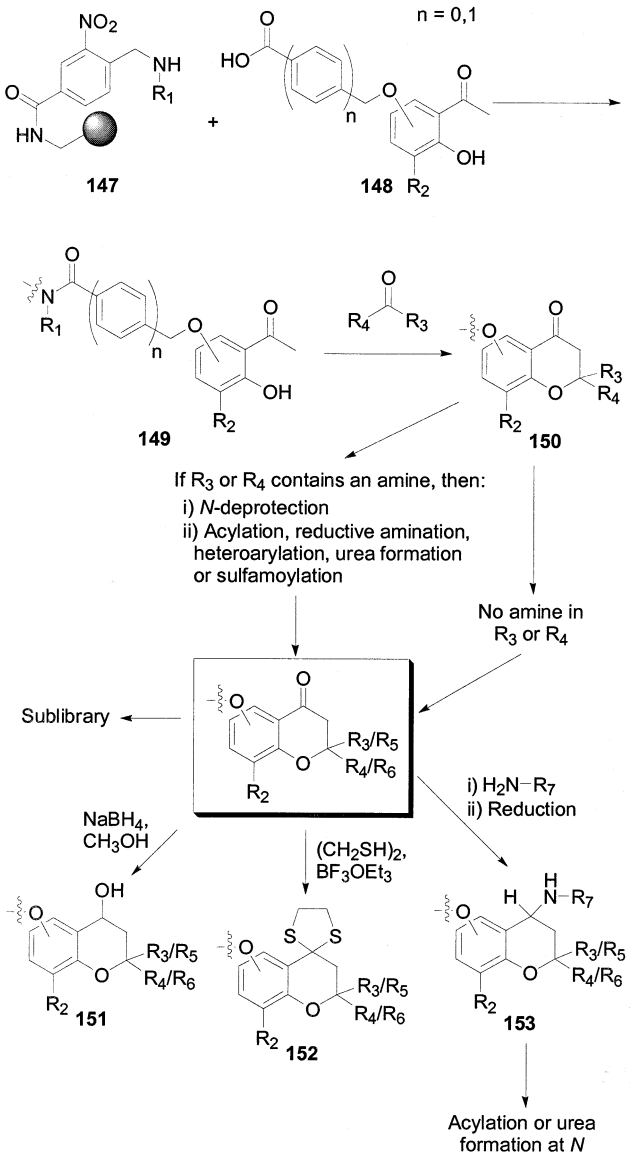
An example of a combinatorial synthesis utilizing a basic route to benzopyranones was reported by Harikrishnan and Showalter.[313] Once attached to resin, the aldehyde **141** was treated with benzylmagnesium chloride via a Grignard reaction to yield **142** following oxidation (Scheme 29). Deprotection of the methoxymethyl (MOM) group (**143**) followed by condensation with *N*,*N*-dimethylformamide dimethyl acetal provided the resin bound chromone **144**. This molecule could then be cleaved from the resin, either through silicon−oxygen bond cleavage to yield the silanol **145** or through silicon−carbon bond cleavage, to yield the benzopyranone **146**.

Scheme 29. Combinatorial Synthesis of Benzopyranones by Harikrishnan and Showalter[313]

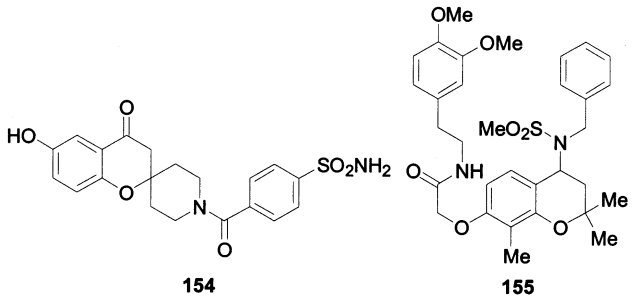


Baldwin reported a different strategy for dihydrobenzopyranone library synthesis.[314] An encoded 1263 member dihydrobenzopyranone library was produced

Scheme 30. Combinatorial Synthesis of Dihydrobenzopyranones by Baldwin[314]



which was expandable to over 85 000 members (Scheme 30). In this synthesis, *N*-Boc-protected **147** was prepared through attachment of seven different amines (R_1) to the photolabile *ortho*-nitro-α-bromo-*para*-toluic acid and coupling to lysine-modified TentaGel resin. Deprotection of the amine to produce **147** and subsequent acylation with **148** (six different agents) produced **149**, which was then treated with a variety of different ketones, forming **150**. If the ketones contained an amine group, they were then deprotected and further derivatized through acylation, reductive amination, heteroarylation, urea formation, or sulfamoylation. These derivatized products were then separated, and one portion was held as a sublibrary. The remainder were reduced to the 4-hydroxy derivative (**151**), converted to the dithiolane (**152**), or reductively aminated (**153**). The attraction of this synthetic scheme was that molecules such as **154** and **155** could be synthesized, which would be difficult to access by the route displayed in Scheme 27 (Figure 12).



154 155

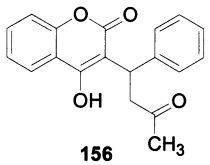
Figure 12. Molecules that could be accessed via Scheme 30 that would be difficult to obtain via Scheme 27.

There are also a variety of other methods for the combinatorial synthesis of chromones. This includes an intramolecular cyclization of 1-(2-hydroxyphenyl)-propynone derivatives[307,315] and palladium-catalyzed carbonylative cyclization of *ortho*-iodophenol and acetylenes.[305]

3. Coumarins

Coumarins number among the most important classes of natural products. The first member of this class, coumarin (**119**), was discovered in 1820.[316] This scaffold is prolific in the plant kingdom but may also be found in fungi and bacteria, providing an enormous diversity in substitution patterns on the core scaffold.[316−321]

The therapeutic potential of these compounds is immense. Coumarin is the parent molecule of warfarin (**156**, Figure 13), which is used clinically as an



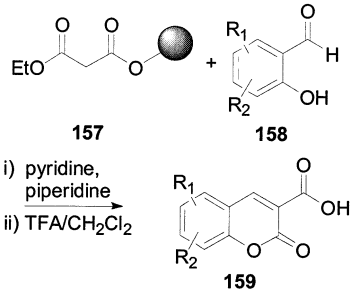
156

Figure 13. Warfarin.

anticoagulant and as a rodenticide. Coumarins have been reported to exhibit antibacterial and antifungal activity and to act as diuretics and analgesics.[322] There have also been reports that structures containing the coumarin ring reduce tissue swelling due to various kinds of trauma or disease, display hypolipidaemic, vasorelaxant, antiplatelet aggregation, antioxidant, antiinflammatory, and immunosuppressive activities, as well as exerting nonspecific antispasmolytic effects and decrease the occurrence and duration of reperfusion induced ventricular fibrillation.[323] This scaffold has also been reported to inhibit DNA gyrase and T-cell activation.[324] Coumarins also exhibit a variety of anticancer activities, displaying antimutagenic,[325] and antitumor properties.[324] Other biological activities of the coumarins include inhibitors of HIV-1 protease,[326] monoamine oxidase,[327] caspase-1 (interleukin-1β converting enzyme, antiinflammatory applications),[328,329] a variety of proteases (includes cathepsin B, elastase, Factor Xa, urokinase, thrombin),[330] reversible inhibitors of thyrotropin-releasing hormone degrading ectoenzyme (possible use in the treatment of brain and spinal injury and central nervous system disorders including spinocerebellar degeneration, cognitive deficits and spinal cord pain transmission),[331] and high-affinity Src homology 2 (SH2) domain targeted agents (a component of many signal transducing proteins).[332] Multicyclic molecules containing the coumarin scaffold include furanocoumarins, pyranocoumarins, and psoralens, which also have a range of biological activities. Coumarin-ring-containing compounds are present in large quantities in human diets, and as a result, they represent an attractive source of medicinally interesting compounds due to their low toxicity.[323]

A variety of combinatorial libraries containing the coumarin ring have appeared in the literature. A number of these libraries utilize this scaffold to cap the *N*-terminus[332] and/or *C*-terminus of peptide-based libraries.[328−331] In the latter case, the structure most commonly used is 7-amino-4-methylcoumarin. Far fewer groups have synthesized libraries in which the coumarin ring is the central scaffold. An example of a small library in which the coumarin ring was generated is displayed below (Scheme 31).[333] In this case, the strategy chosen is a method classically used to synthesize coumarins, the Knoevenagel condensation. Ethyl malonate attached to Wang resin (**157**) was suspended in pyridine, and treated with a substituted *ortho*-hydroxyarylaldehyde (**158**) and a catalytic amount of piperidine. Treatment with trifluoroacetic acid then cleaved the substituted coumarin-3-carboxylic acid (**159**) from the resin in high yields (80% to >98% yield).

Scheme 31. Combinatorial Synthesis of Coumarin Compounds by Watson and Christiansen[333]



Other combinatorial libraries have also been synthesized which involve the coumarin ring. Wu et al. synthesized a combinatorial library utilizing a substituted coumarin ring as the starting material, to which more diversity elements were subsequently added.[334] A report by Bussolari et al. also described a parallel synthesis of a small library in which a substituted coumarin ring was also the starting material. In the latter case, the coumarin ring was broken down to form a substituted benzene library.[335]

4. Pyranocoumarins

Pyranocoumarins are a naturally occurring framework that has been used for many centuries in medicine. Although the range of biological activities of these chemicals has only come to light relatively recently, they are an active chemical in many plants that have been used in traditional medicines. Examples of this include Bai-Hua Qian-Hu, which was used in traditional Chinese medicine for the treat-

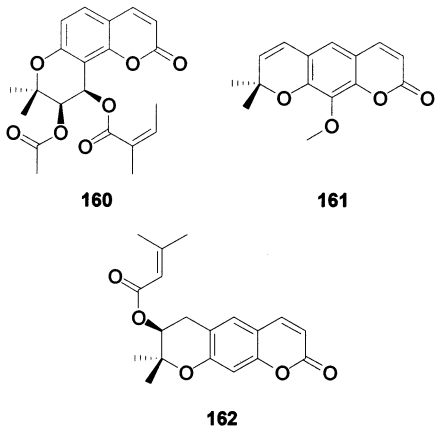


Figure 14. Pyranocoumarins from natural products: pteryxin (**160**),[336] luvangetin (**161**),[337] and decursin (**162**).[338]

ment of certain respiratory diseases and pulmonary hypertension,[336] *Aegle marmelos* Correa, an Indian medicinal plant that was used to treat various ailments,[337] and *Angelica gigas* Nakai (Umbelliferae), which was used not only to treat anemia, but also as a sedative, an anodyne, and a tonic agent in Korea.[338] Active pyranocoumarins in these plants include pteryxin (**160**), which has been shown to relax the smooth muscle of tracheas and pulmonary arteries, luvangetin (**161**), which displayed gastroprotective activity, and decursin (**162**), which was reported to have cyctotoxic activity and activate protein kinase C, respectively.

In pharmaceutical medicine, pyranocoumarins have been shown to exhibit a wide range of biological activities. They show great promise in cancer therapy, as they can inhibit NADH:ubiquinone oxidoreductase (also known as complex I—this enzyme has also been implicated in the pathogenesis of diseases such as Parkinson's, focal dystonia, and Leber's hereditary optic neuropathy (e.g., deguelin (**163**), Figure 15)),[298−300] inhibits phorbol ester-induced ornithine decarboxylase (this enzyme is responsible for the biosynthesis of polyamine growth factors required for normal cellular proliferation; possible use in cancer therapy),[299,300] shows some application in preventing benzo(*a*)pyrene and hydrogen peroxide induced mutagenesis,[325] and activates protein kinase C.[338] Another area in which

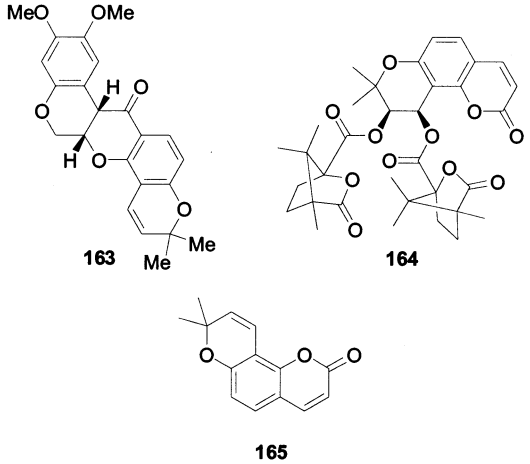
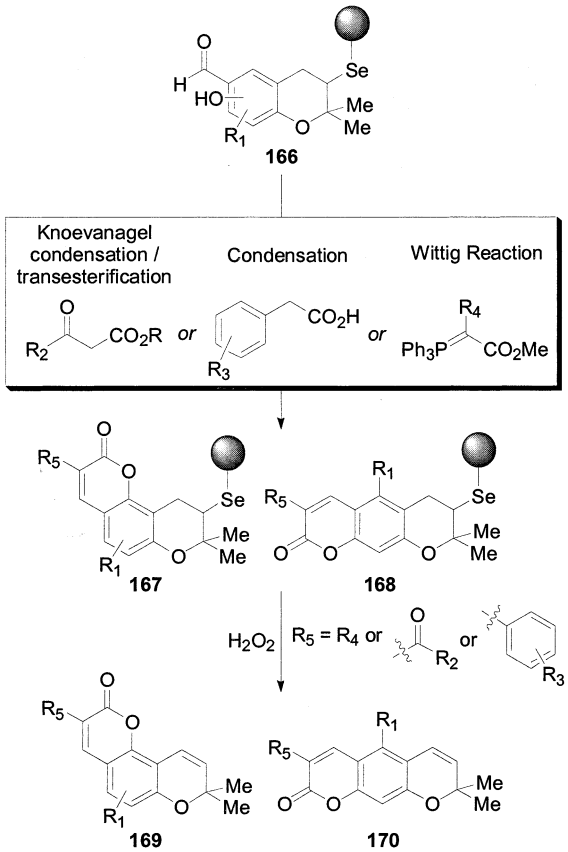


Figure 15. Deguelin (**163**),[299,300] DCK (**164**),[303] and seselin (**165**).[345]

these compounds display great potential is as anti-HIV drugs. DCK (**164**) has been reported to inhibit HIV-1 replication in H9 lymphocytes,[303] and other dipyranocoumarins from the *Calophyllum* genus exhibit HIV-1 specific reverse transcriptase inhibitor activity.[339] Pyranocoumarins also exhibit antimalarial activity,[340] antibacterial and antifungal activity,[341−343] and antiulcer activity,[337] are hemorrhagic toxins,[344] antiprotozoans,[344] and uterotonics,[344] and are used to promote smooth muscle relaxation (tracheal and pulmonary artery relaxation).[336] Other pyranocoumarins, such as seselin (**165**) are also clinically used as photoactive drugs in the photochemotherapy of the skin, to treat vitiligo and to prevent sun burning.[345] This class of scaffolds can also inhibit protein kinases, endothelin-converting enzyme, osteoclast-like cell line bone reabsorption, arachidonate 5-lipoxygenase, and interferon-γ-induced nitric oxide generation.[2]

Few combinatorial syntheses of pyranocoumarins have appeared in the literature. Nicolaou et al. have reported the synthesis of a 10 000-membered benzyopyran library, containing a sizable angular and linear pyranocoumarin library (Scheme 32).[2,15,16] The

Scheme 32. Pyranocoumarin Library Synthesis by Nicolaou et al.[2,15,16]

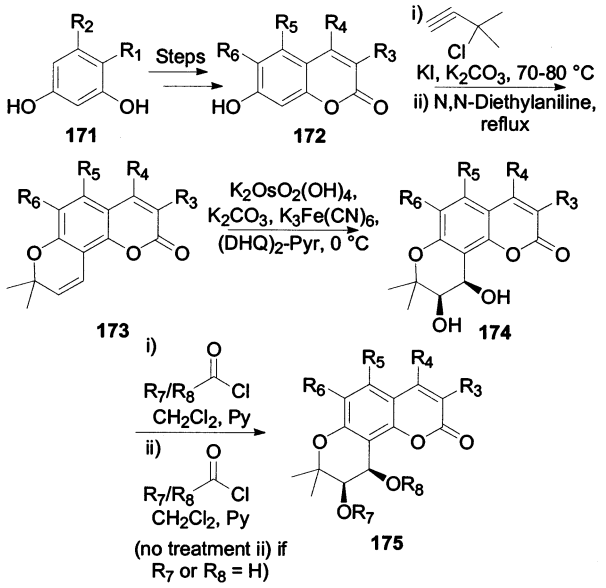


synthesis of either the angular (**169**) or linear (**170**) pyranocoumarin analogue was dependent on the position of the hydroxy group relative to the aldehyde in the starting benzopyran **166** (see Scheme 25 for synthesis). A Knoevanagel condensation, a condensation reaction, or a Wittig reaction was used to replace the aldehyde of **166** with a carbon−carbon double bond, while ester or acid functionality in the reagents

provided the means for lactone ring cyclization. The use of three different strategies to generate the pyranocoumarin ring system allows great diversity in functionality at R_5. Oxidation of the selenium atom in the pyranocoumarin analogues **167** and **168** resulted in spontaneous syn elimination of the selenium tether and the release of the angular (**169**) and linear (**170**) pyranocoumarin.

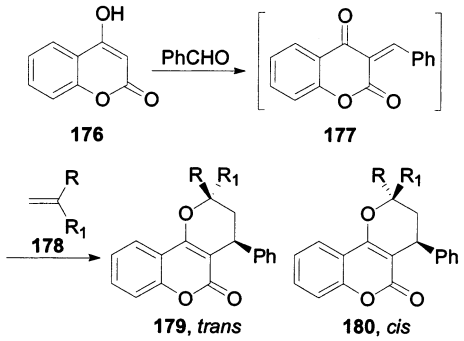
Xie et al. prepared a pyranocoumarin library via a different strategy in which twenty-four monosubstituted 3′,4′-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone (DCK, **164**) derivatives were prepared in solution phase in the search for new anti-HIV agents (Scheme 33).[303] Hydroxycoumarins (**172**) were prepared through a variety of different methods (depending on the substitution pattern) from variously substituted benzene-1,3-diols (**171**). **172** was then treated with 3-chloro-3-methyl-1-butyne in the presence of anhydrous potassium carbonate and potassium iodide to produce the corresponding α,α-dimethylpropargyl ethers, which under thermal rearrangement yielded pyranocoumarins **173**. Sharpless asymmetric dihydroxylation then yielded (+)-*cis*-khellactones **174**, which were treated with a variety of acid chlorides to yield DCK analogues **175**.

Scheme 33. Pyranocoumarin Library Synthesis by Xie et al.[303]



The final synthetic strategy to be discussed was reported by Cravotto et al. in 2001.[344] This library was prepared via a one-pot three-component hetero Diels−Alder reaction from 4-hydroxycoumarin (**176**) (Scheme 34). This was accomplished via inverse electron demand between **176**, aromatic aldehydes, and electron rich alkenes (**178**). An analysis of HOMO−LUMO interactions suggested that vinyl ethers or enamines were the best dienophiles for **178**. The scheme begins with the treatment of 4-hydroxycoumarin (**176**) with benzaldehyde to yield a chromanedione intermediate (**177**), which was then treated with the dienophile (**178**) to produce the trans (**179**) and cis (**180**) pyranocoumarin in high regioselectivity.

Scheme 34. Pyranocoumarin Library Synthesis by Cravotto et al.[344]



B. Quinoxalines/Quinazolines

There are numerous biologically active molecules whose framework includes a six-membered ring containing two nitrogen atoms fused to a phenyl ring. Most of these molecules are based on the quinoxaline (**181**) or quinazoline (**182**) framework (Figure 16).

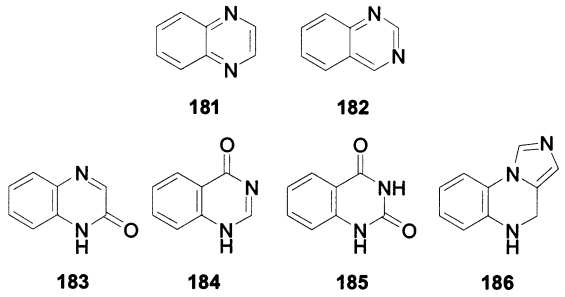


Figure 16. Privileged substructures based on the quinoxaline (**181**) and quinazoline framework (**182**).

These two structures may be considered to be privileged substructures in their own right. However, many of the biologically active molecules of this class contain a carbonyl group, such as the quinoxalinones (**183**), quinazolinones (**184**), and quinazolindiones (**185**), or possess a fused imidazole ring (**186**). As a result, this section will focus on derivatives of these molecules. Other nitrogen-containing fused [6−6] ring systems may also be considered to be privileged substructures. For example, isoquinoline alkaloids have been reported to be privileged substructures[111] and have been synthesized combinatorially.[111,346,347] However, they will not be discussed further in this review.

1. 3,4-Dihydroquinoxalin-2-ones (Benzopiperazinones)

3,4-Dihydroquinoxalin-2-ones (benzopiperazinones) (**187**, Figure 17) are useful scaffolds for drug development. This framework is closely structurally related to the benzodiazepine nucleus yet has been less

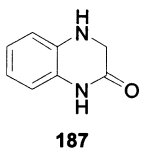
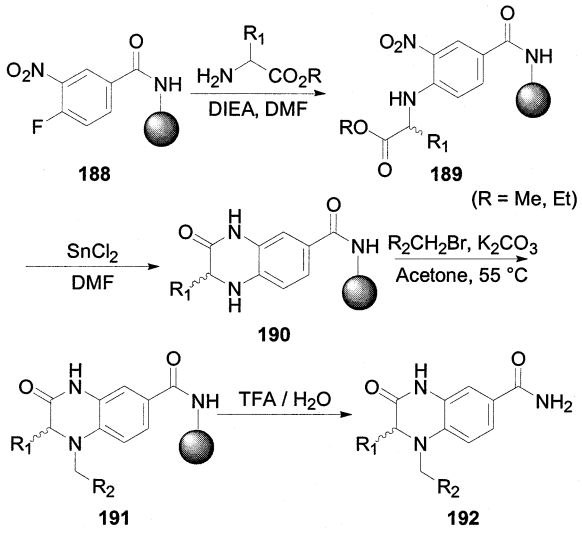


Figure 17. Benzopiperazinone.

widely utilized in drug discovery. These molecules have a wide range of biological activities, which includes inhibitors of aldose reductase and PDGF receptor tyrosine kinase, partial agonists and antagonists of the γ-aminobutyric acid (GABA)/benzodiazepine receptor complex, and antagonists of the AMPA and angiotensin II receptors. 4-(Acyloxy)-benzopiperazinones have also been shown to exhibit anti-HIV activity.[348−351] A recent report also described the utility of these molecules as multiple drug resistance antagonists, in which they target drug transport proteins such as P-glycoprotein (Pgp).[352] This framework may also be useful in cancer treatment as Pgp production is often increased in tumor cells from patients undergoing chemotherapy.

Conceptually, the simplest synthesis of molecules such as **187** is through the addition of an amino acid to an aniline analogue. Many groups have utilized this methodology for combinatorial synthesis.[349−351,353−355] The most common aniline analogue used for library synthesis is derived from *ortho*-fluoronitrobenzene, as displayed in Scheme 35.[350] The nitro group of the *ortho*-fluoronitrobenzene is critical, as it activates the aromatic ring for nucleophilic substitution and also serves as a precursor for the nucleophilic amine for cyclization. The synthesis begins with the removal of the Fmoc protecting group from Rink-amide resin and amino acid acylation of 4-fluoro-3-nitrobenzoic acid to generate **188**. Aromatic substitution of the activated aryl fluoride with various L- and D-amino esters was then accomplished using diisopropylethylamine (DIEA) in *N*,*N*-dimethylformamide (DMF) to yield **189**. This molecule was then treated with tin (II) chloride to reduce the nitro group and to facilitate cyclization, producing **190**. Selective alkylation of **190** using an alkylhalide in the presence of K_2CO_3 in refluxing acetone afforded **191**, which was subsequently cleaved from resin, producing **192**.

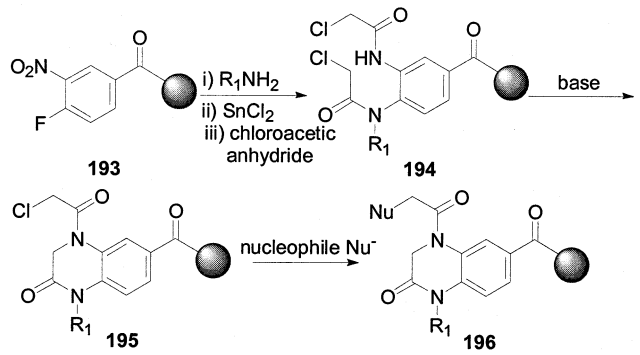
Scheme 35. 3,4-Dihydroquinoxalin-2-one Combinatorial Library Synthesis by Lee et al.[350]



A similar strategy was reported by Laborde and co-workers, which began with Fmoc−amino acids preloaded onto Wang resin.[351] Treatment of these deprotected amino acids with 4-fluoro-3-nitrobenzoic acid, subsequent derivatization of the product, and cyclization/cleavage from resin with tin (II) chloride yielded the 3,4-dihydroquinoxalinone. The advantage of this synthesis was the acid-free cleavage, which ensured that byproducts resulting from oxidation of the 3,4-carbon−nitrogen bond were not produced.

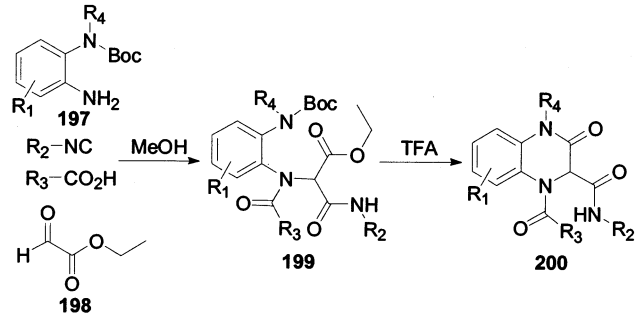
Another variation on this strategy was reported by Zaragoza and Stephensen.[348] The starting material was 4-fluoro-3-nitrobenzoic acid (**193**) supported on Wang resin (Scheme 36). Treatment of **193** with primary, aliphatic amines afforded an aromatic substitution reaction with fluorine. Subsequent reduction of the nitro group with tin (II) chloride and double acylation with an excess of chloroacetic anhydride then yielded **194**. Treatment with base cyclized **194** to the benzopiperazinone (**195**) followed by addition of a nucleophile yielded **196** via a substitution reaction.

Scheme 36. 3,4-Dihydroquinoxalin-2-one Combinatorial Synthesis by Zaragoza and Stephensen[348]



Hulme et al. has reported use of the Ugi reaction in the synthesis of a library of these compounds (Scheme 37).[288,289] Reaction of commercially available ethylglyoxalate (**198**) with the *N*-Boc amine **197**, an isonitrile, and a carboxylic acid yielded **199** through the Ugi reaction. Treatment with trifluoroacetic

Scheme 37. 3,4-Dihydroquinoxalin-2-one Combinatorial Library Synthesis by Hulme et al.[289]

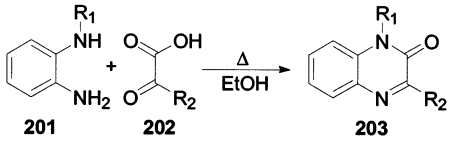


acid (TFA) removed the Boc protecting group and facilitated ring cyclization to produce the substituted 3,4-dihydroquinoxalin-2-one (**200**). This strategy allows more accessible substitution of the amide bond nitrogen than the strategy displayed in Scheme 35. Access to molecules such as **200** through intermediates of type **199** is also possible through other

means. Petasis and Patel reported a strategy for the combinatorial synthesis of these molecules through an organoboronic acid.[356] In this strategy, a similar two-step reaction was utilized, in which the starting materials were **197**, glycoxalate, and an organoboronic acid, which yielded a similar product to **199**.

The structurally related quinoxalinones have also been used as a core scaffold for a combinatorial library. This simple one-step process, reported by Lawrence et al., utilizes a double condensation-cyclization reaction from the 1,2-diamine (**201**) and the α-ketocarboxylic acid (**202**) to yield the desired scaffold **203** (Scheme 38).[352]

Scheme 38. Quinoxalinone Combinatorial Library Synthesis by Lawrence et al.[352]



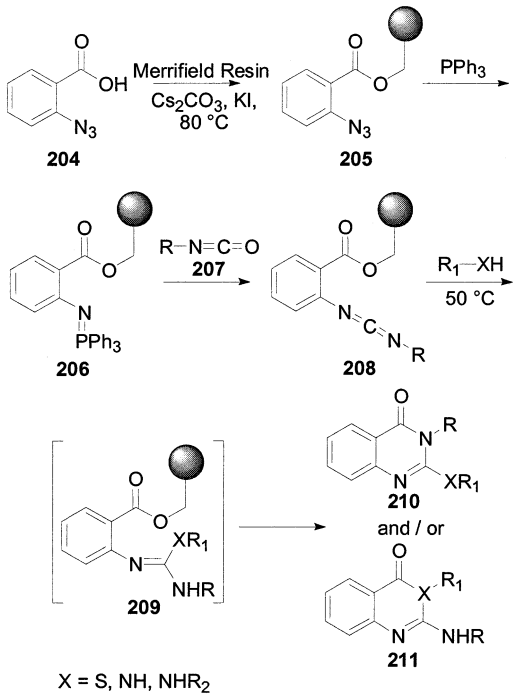
2. Quinazolinones

The quinazolinones (**184**) have been reported to possess a vast range of biological activities. They have a range of central nervous system (CNS) effects, including analgesic, antiparkinsonian, CNS depressant, and CNS stimulant activities, as well as tranquilizing, antidepressant, and anticonvulsant effects. These compounds also act as psychotropic, hypnotic, cardiotonic, and antihistamine agents[357] and possess cardiovascular activity (includes antihypertensive, antiarrhymic, vasodilatory, and lipid-lowering effects), and antiinflammatory activity (includes inhibition of cyclooxygenase activity and leukocyte function).[357,358] Quinazolinones also inhibit monoamine oxidase, aldose reductase, tumor necrosis factor α, thymidylate synthase, pyruvic acid oxidation, and acetylcholine−esterase activity and are antitumor, antiulcer, antiplatelet aggregation (glycoprotein IIb/IIIa inhibitors),[359,360] and hypoglycemic agents.[357,361] In addition to all of this, they are also potent antibacterial, antifungal, antiviral, antimycobacterial, and antimalarial agents and possess anthelmintic activity.[357]

Many different synthetic strategies have been described in the literature. The first achieves ring closure through the amide bond,[362] and the second uses carbodiimide formation on *N*1 to drive ring closure between the amide nitrogen (*N*3) and *C*2.[360] Other strategies involve the reaction between isatoic anhydride and thiourea derivatives to affect ring closure[361,363] and the use of orthoformates to react with both nitrogen atoms.[364] Other groups have also utilized the quinazolinone scaffold in combinatorial synthesis.[358,365]

Quinazolinones of type **184** were synthesized by Villalgordo et al. using an aza Wittig-mediated annulation strategy (Scheme 39).[362] After alkylative esterification of the *ortho*-azido benzoic acid **204** with Merrifield resin, the product (**205**) was treated with triphenylphosphine to yield the iminophosphorane

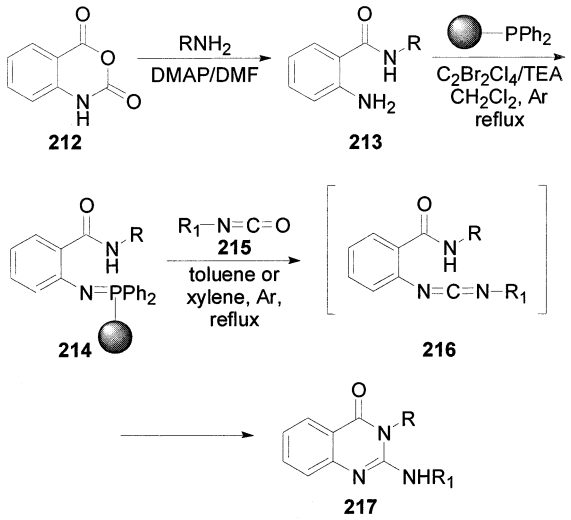
Scheme 39. Quinazolinone Synthesis by Villalgordo et al.[479]



(**206**). Division of the resin beads and subsequent aza Wittig reaction with different isocyanates (**207**) afforded a variety of carbodiimides (**208**). Further division of the resin and treatment with various nucleophiles yielded **209**, which underwent intramolecular cyclization and simultaneous cleavage from resin to form the quinazolinones **210** and **211**. Unfortunately, the control over the ratio of products **210** and **211** decreases to 1:1 when sterically less hindered groups are used at R_1.

A similar synthesis was reported by Zhang and co-workers.[360] As can be seen in Scheme 40, the basic premise is very similar to that described by Villalgordo et al.[362] and provides far more control over the product produced. Treatment of isatoic anhydride (**212**) with substituted primiary amines in *N*,*N*-di-

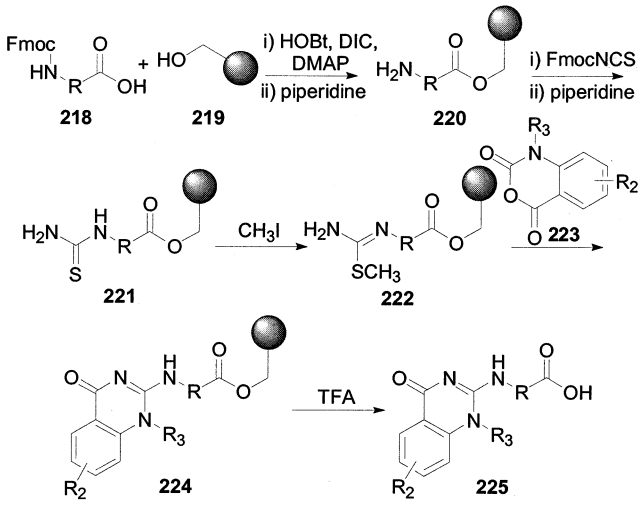
Scheme 40. Quinazolinone Synthesis by Zhang et al.[360]



methylformamide (DMF) with *N*,*N*-(dimethylamino)-pyridine (DMAP) produced the *N*-substituted benzamide (**213**). Using a modified Kirsanov reaction, **213** was then treated with polystyryl triphenylphosphine in the presence of dibromotetrachloroethane and triethylamine in dry dichloromethane at reflux under argon to produce the resin-bound iminophosphorane (**214**). Heating of this product with isocyanates (**215**) in dry toluene or xylene under argon cleaved the product from resin, producing the carbodiimide intermediate (**216**). Intramolecular cyclization then occurred to yield the 4-quinazolinone (**217**) in good yield (68−89%) and purity (61−96%) across seven quinazolinones.

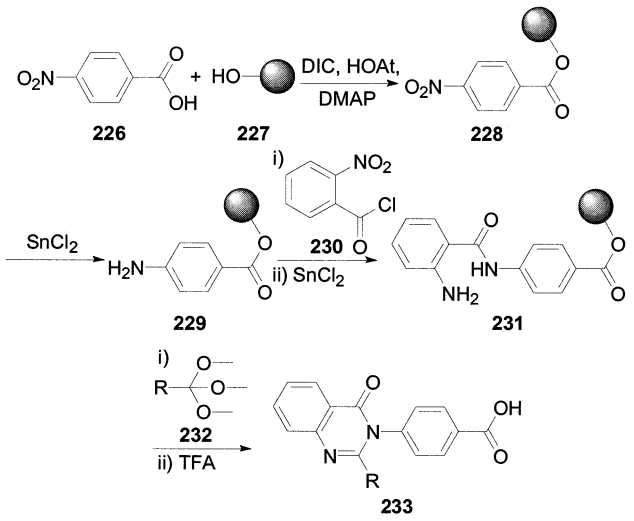
A different strategy, in which isatoic anhydride was treated with pseudothioureas, was reported by Gopalsamy and Yang (Scheme 41).[361] The Fmoc protected amino acid **218** was attached to Wang resin **219** using 1-hydroxybenzotriazole (HOBt) and *N*,*N*-diisopropylcarbodiimide (DIC) in the presence of *N*,*N*-(dimethylamino)pyridine (DMAP) to provide the resin bound Fmoc protected amino acid in quantitative yield. Following Fmoc deprotection (to yield **220**), the product was treated with Fmoc-isothiocyanate and again deprotected to afford **221**. Treatment with methyliodide yielded the corresponding *S*-methylthiopseudourea (**222**). Reaction of this compound with isatoic anhydride (**223**) in a polar aprotic solvent led to the formation of the quinazolinone ring on resin (**224**). Subsequent cleavage with trifluoroacetic acid then liberated the quinazolinone (**225**). A similar strategy was presented by Yang and Kaplan in which solid-supported isothioureas (connected to resin via the sulfur) were treated with isatoic anhydrides. This traceless synthesis allowed cyclization and resin cleavage in a single step, producing 2-amino-4(3*H*)-quinazolinones.[363]

Scheme 41. Quinazolinone Combinatorial Synthesis by Gopalsamy and Yang[361]



As neither strategy described above could produce 2-alkylquinazolinones, a different synthesis was developed by Makino et al. (Scheme 42).[364] This procedure utilizes mild acidic conditions and allows the use of compounds sensitive to oxidation. The scheme begins with the attachment of 4-nitrobenzoic acid

Scheme 42. Quinazolinone Combinatorial Synthesis by Makino et al.[364]



(**226**) to a Synphase Lantern (**227**) using 1-hydroxy-7-azabenzotriazole (HOAt), DIC, and DMAP. Treatment of the resultant compound (**228**) with tin chloride then produced the amine (**229**), which could then be treated with the nitrophenyl acid chloride **230**, and the nitro group reduced with tin chloride, yielding **231**. Addition of an orthoformate (**232**) cyclized the resin bound quinazolinone to yield the product (**233**), which was subsequently cleaved from the resin with trifluoroacetic acid. A similar solid-phase strategy has also been used by Theoclitou et al.[366]

3. Quinazolindiones

Like the quinazolinones, quinazolin-2,4-diones (**185**) exhibit a wealth of biological activity, much of which resides in the central nervous system. Quinazolin-2,4-diones interact with many G-protein coupled receptors, including adrenergic, serotonergic, dopaminergic, and endothelin (ET_A) receptors.[367,368] In addition, this scaffold may also inhibit various enzymes, including cyclooxygenase, collagenase, aldose reductase, and carbonic anhydrase.[367,368] These molecules also show potential as coagulants, as they are fibrinogen receptor antagonists.[359]

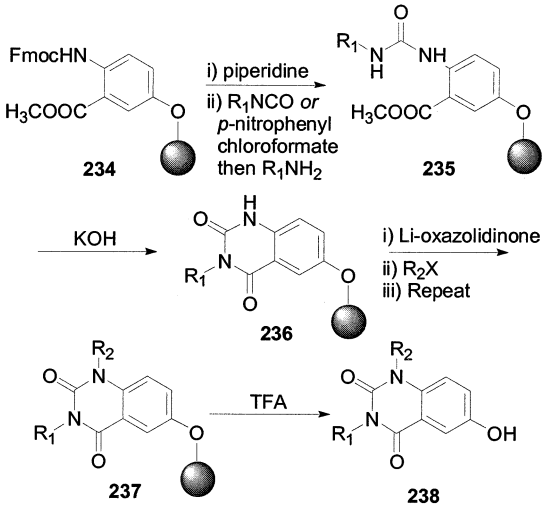
In addition to quinazolin-2,4-diones, quinazolin-2,3-diones may also be privileged substructures. Of these molecules, perhaps DNQX (6,7-dinitroquinoxalin-2,3-dione) and CNQX (6-cyano-7-nitroquinoxalin-2,3-dione) are the best known. They are competitive antagonists at the AMPA/KA receptor (glutamate α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), kainate (KA)) and may be useful for a variety of neurological and psychiatric disorders.[369,370] These two drugs have also been reported to be calcium channel blockers with application to Alzheimer's disease.[371] Unfortunately, few, if any, combinatorial syntheses of molecules of this type have been attempted.

The major strategy utilized for combinatorial synthesis of quinazolin-2,4-diones employs a ring closure reaction through attack of an amine on an ester, to form an amide bond. Various groups have achieved

this, all of them making use of solid-phase synthesis. Two reports have described a cyclization-cleavage strategy based on this principle,[367,368] another two achieved cyclization and cleavage in two separate steps.[372,373]

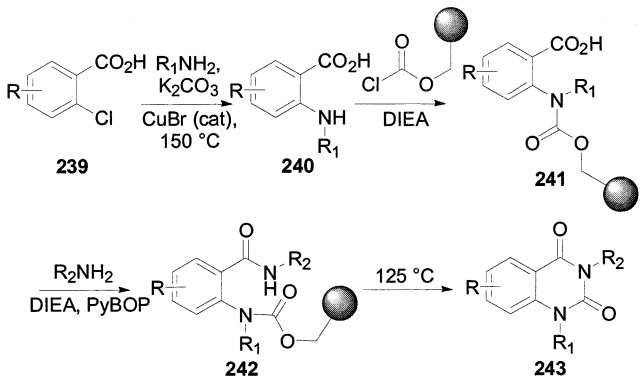
Buckman and Mohan reported a solid-phase combinatorial synthesis of quinazolin-2,4-diones via a strategy in which cyclization and cleavage occurred in two separate steps (Scheme 43).[372] The synthesis begins with the attachment of an acid cleavable linker to Tentagel resin. After attachment of an Fmoc protected anthraniliate to the linker, **234** was obtained. Treatment of this compound with piperidine to remove the Fmoc group was followed by either addition of an isocyanate (for alkyl, alkenyl and aryl R groups) or *para*-nitrophenyl chloroformate (affording the carbamate) followed by a primary amine yielding the urea (**235**). These compounds were then cyclized to the quinazolin-2,4-dione (**236**) by treatment with ethanolic potassium hydroxide. Alkyl substituents could then be added to the secondary amide by addition of lithium oxazolidinone to form the enamine, followed by treatment with activated alkyl halides, to afford resin bound **237**. Treatment of this compound with trifluoroacetic acid liberated the quinazolindione, yielding **238**. Gordeev et al. reported a similar strategy, except that the solid-support was attached through R_1 (in molecule **238**), which allowed a greater variety of substituents on the benzene ring.[373]

Scheme 43. Quinazolin-2,4-dione Combinatorial Synthesis by Buckman and Mohan[372]



A cyclization-cleavage strategy has been reported by Smith et al. and Shao et al.[367,368] Both of these syntheses were achieved on the solid phase, and strategically the major difference between them was the linker chosen for the synthesis. Smith et al. chose a carbamate linker, and cyclization through attack of a secondary amide. In contrast, Shao et al. utilized an ester linkage, which necessitated the formation of the urea prior to cyclization-cleavage. The strategy utilized by Smith et al. is displayed in Scheme 44.[368] If the desired anthranilic acid (**240**) was not available commercially, it could be synthesized from **239** and primary amines through treatment with K_2CO_3 and

Scheme 44. Quinazolin-2,4-dione Combinatorial Synthesis by Smith et al.[368]



catalytic CuBr at 150 °C. Following this, treatment with diisopropylethylamine (DIEA) and a chloroformate-functionalized polystyrene resin afforded the carbamate (**241**). Coupling of the carboxylic acid of this compound with a primary amine using DIEA and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) yielded **242**. Heating at 125 °C provided the quinazolin-2,4-dione (**243**) with purities in excess of 95%.

4. Imidazoquinoxalines

Imidazoquinoxalines possess a broad range of pharmacological activities. These molecules include 4,5-dihydroimidazo[1,5-*a*]quinoxalines (**186**), 4,5-dihydroimidazo[1,2-*a*]quinoxalines (**244**), 4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoxalines (**245**) and 4,5-dihydro[1,2,4]triazolo[1,5-*a*]quinoxalines (**246**) (Figure 18). Although scaffolds **244**,[374−378] **245**[374,375,379] and **246**[376] may be privileged substructures and all of these molecules have been synthesized combinatorially (**244**,[378] **245**,[374,379] and **246**[376]), they will not be discussed further here. However, both the biology and the combinatorial chemistry utilized to synthesize the 4,5-dihydroimidazo[1,5-*a*]quinoxalines (**186**) will be discussed in depth.

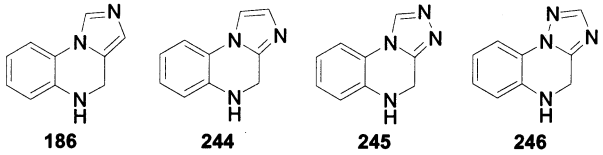
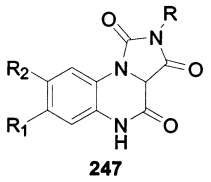


Figure 18. Imidazoquinoxalines.

Much research has been undertaken on the 4,5-dihydroimidazo[1,5-*a*]quinoxalines (**186**), and this scaffold is without doubt a privileged substructure. These molecules range from being antagonists to full agonists on the γ-aminobutyric acid A ($GABA_A$) chloride ion channel complex, without displaying typical benzodiazepine side effects.[380−385] These imidazoquinoxalines also exhibit adenosine A_1- and A_{2a}-receptor activity,[376] inhibit cAMP and cGMP phosphodiesterase,[377] and IgE-mediated passive cutaneous anaphylaxis (PCA) (antiallergic properties).[378] A small combinatorial library of molecules based on the scaffold **247** (Figure 19) has also yielded glycine/NMDA receptor antagonists and AMPA receptor antagonists.[386]

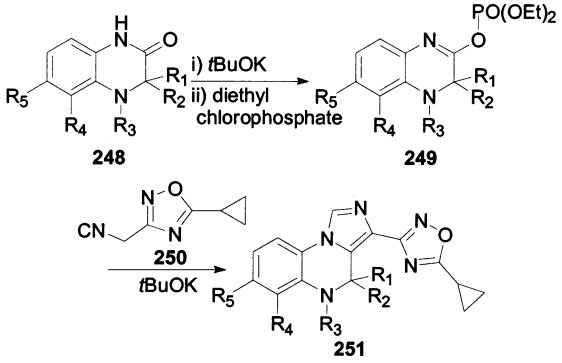


247

Figure 19. 5*H*-Imidazo[1,5-a]quinoxalin-1,3,4-trione scaffold used for combinatorial synthesis.[386]

Three different strategies have been reported for the combinatorial synthesis of imidazo[1,5-*a*]quinoxalines (**186**). The first involves the addition of a methyl isocyanide to a preformed quinoxaline template to construct the template through the formation of the imidazole ring. Many combinatorial libraries have been synthesized through this route. An example synthesis is displayed in Scheme 45.[380,381,383] After synthesis of the desired quinoxaline template (**248**), treatment with potassium *tert*-butoxide, followed by diethyl chlorophosphate, yielded the intermediate enol phosphonate (**249**). Without isolation, this enol was treated with 5-cyclopropyl-3-(isocyanomethyl)-1,2,4-oxadiazole (**250**) to generate **251** via a 1,3-dipolar cycloaddition reaction and subsequent phosphonate elimination. If *N*5 had not been derivatized prior to this reaction, it could also be accomplished afterward if desired. All of these libraries were constructed using solution-phase combinatorial chemistry.

Scheme 45. 4,5-Dihydroimidazo[1,5-*a*]quinoxaline Combinatorial Synthesis at the Upjohn Laboratories[380,381,383]



Solution-phase combinatorial libraries have also been constructed using other 1,3-dipoles to construct the imidazole ring. Jacobsen et al. utilized a substituted phenyl methyl isocyanide 1,3-dipole to generate compounds such as **252**,[382] and both Jacobsen et al. and TenBrink et al. both reported the use of a *tert*-butyl isocyanoacetate to create molecules based on **253** (Figure 20).[381,384]

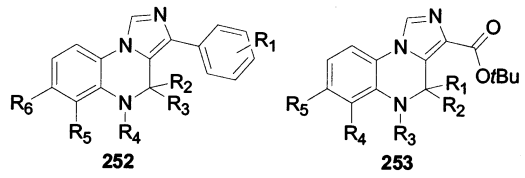
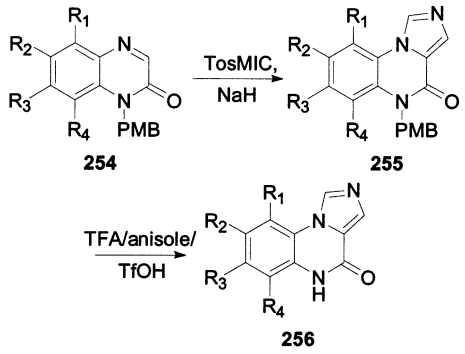


Figure 20. Solution-phase combinatorial scaffolds created using other 1,3-dipoles.[381,382,384]

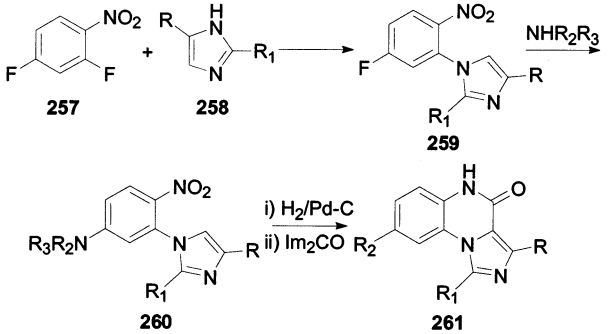
A different strategy based on this type of 1,3-dipolar cycloaddition was developed by Chen et al. in order to synthesize both 1- and 3-unsubstituted imdiazo[1,5-*a*]quinoxalines (Scheme 46).[387] Unlike the methods above, this technique does not utilize a phosphonate intermediate. After synthesis of the N-*para*-methoxybenzyl (PMB) protected quinoxalinone (**254**), treatment with TosMIC (tosylmethyl isocyanide) in the presence of a base such as sodium hydride provided the imidazoquinoxalinone (**255**) in >68% yield. Following this, removal of the PMB group afforded the imidazoquinoxalinone (**256**) in >90% yield. The major difference in the strategy used for imidazole ring closure between Scheme 45 and Scheme 46 is that in Scheme 45, the phosphonate is the leaving group (at *C*5 of the imidazole ring), whereas in Scheme 46, the tosylate is the leaving group (at *C*4 of the imidazole ring).

Scheme 46. Imdiazo[1,5-*a*]quinoxalinone Combinatorial Synthesis by Chen et al.[387]

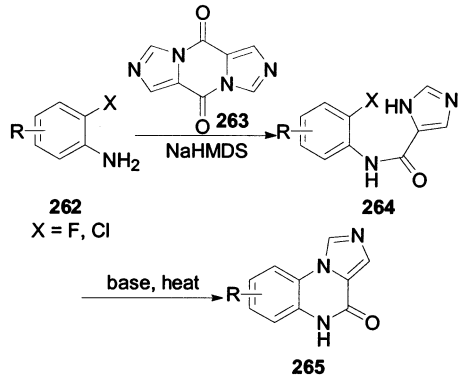


A second strategy has been reported by Davey et al. for the combinatorial synthesis of imidazoquinoxalines (Scheme 47). This was achieved using a ring closure reaction in which cyclization occurred through the piperazinone ring to generate the desired tricyclic scaffold.[377] This strategy begins with the addition of fluorobenzenes (**257**) to substituted imidazoles (**258**) to form **259**. Following this, a second amine may be added to substitute the remaining fluorine yielding **260**. Reduction of the nitro group to the amine, followed by treatment with carbonyldiimidazole (Im_2CO) yielded the desired imidazoquinoxalinone (**261**). This synthesis is useful for the preparation of 1-substituted imidazo[1,5-*a*]quinoxalinones (**261**, $R_1 \neq H$), but not their 1-unsubstituted counterparts, as the use of the corresponding 2-unsubstituted imidazole (**258**, $R_1 = H$) will lead to exclusive formation of the of imidazo[1,2-*a*]quinoxalin-6-ones.[387]

Scheme 47. Imdiazo[1,5-*a*]quinoxalinone Combinatorial Synthesis by Davey et al.[377]



Scheme 48. Imdiazo[1,5-*a*]quinoxalinone Synthesis by Norris et al.[388]



A final strategy applicable to combinatorial synthesis is that described by Norris et al.[388] This strategy also features ring closure through the piperazinone ring and will form both 1- and 3-unsubstituted imdiazo[1,5-*a*]quinoxalines (Scheme 48). An *ortho*-halogenated aniline derivative (**262**) was acylated with carbonyl−imidazole dimer (**263**) in the presence of sodium bis(trimethylsilyl)-amide (NaHMDS) to yield **264**. Treatment with base and heat yielded the imidazoquinoxaline (**265**) regiospecifically in good to excellent isolated overall yields (>56%).

V. Fused [5–6] Ring Systems

There are a range of fused [5,6] ring systems that exhibit biological activity. For example, the indole ring is one of the most ubiquitous heterocyclic structures found in nature. As a result, it is not surprising that a number of frameworks based upon this type of structure have been used as the core scaffold in combinatorial libraries. In contrast to the larger systems described previously, fused [5,6] ring systems are much more commonly utilized as substituents of other scaffolds. Fused [5,6] ring systems discussed here include indole (**266**), benzimidazole (**267**), benzofuran (**268**) and benzothiophene (**269**) (Figure 21).

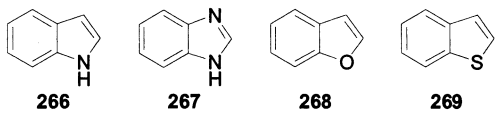


Figure 21. Indole (**266**), benzimidazole (**267**), benzofuran (**268**), and benzothiophene (**269**).

A. Indoles

Indoles (**266**) probably represents the most important of all structural classes in drug discovery.[389] Indeed, there are so many compounds containing this ring that it is nearly impossible to catalog their complete range of biological activity. As a result, only some indication as to the scope of activities possible shall be discussed.

Aside from the role of the indole ring as the key substructure in the amino acid tryptophan (and the multitude of molecules containing this amino acid), this bicycle is also frequently found in natural products. One of the most prominent of these, serotonin (5-hydroxytryptamine) (**270**), is a key neurotransmitter in the central nervous system, regulates smooth muscle function in the cardiovascular and gastrointestinal systems, and regulates platelet function.[390] The hallucinogen D-lysergic acid diethylamide (LSD) (**271**) also contains an indole ring and is a potent nonselective serotonin receptor agonist.[390] Other well-known drugs such as the nonsteroidal antiinflammatory drugs indomethacin (**272**) and etodolac (**273**) also contain the indole ring (Figure 22).[391] In addition to this, molecules containing an indole scaffold are partial agonists and antagonists of neurotensin (8−13),[392] agonists of the somatostatin receptor,[193] and also thrombin receptor antagonists[393] and selective factor Xa inhibitors,[394] to name a few. Many other indole alkaloids with biological activity also exist, including those that cause cell cycle arrest at the G_2/M transition.[395]

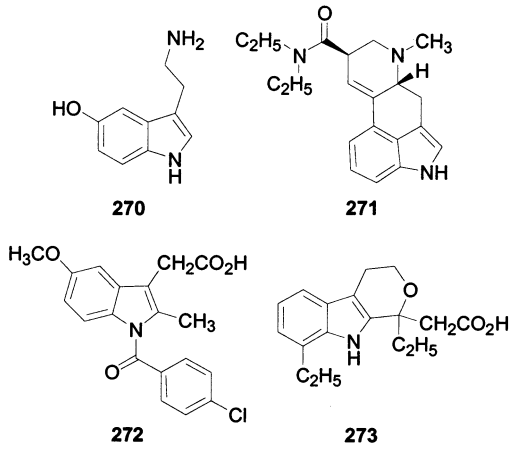
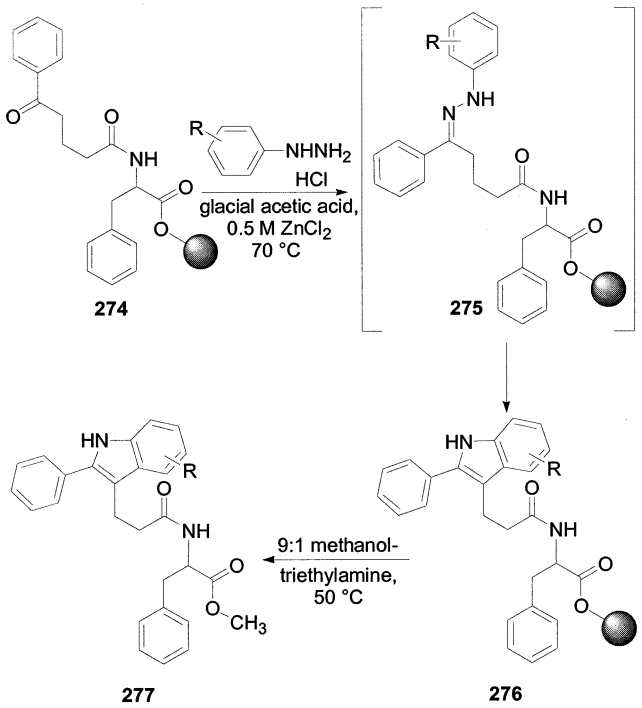


Figure 22. Examples of biologically active indoles.

The combinatorial syntheses of small molecule libraries involving indoles are frequently described in the literature. Many of these utilize the indole ring as a substituent on a small molecule scaffold.[31,193,396,397] This is to be expected, as the small size and favorable properties of the indole ring make it ideal for this use. Other groups have constructed small-molecule combinatorial libraries based on an indole scaffold through the derivatization of a preformed indole ring.[207,393−395,398−404] Despite the commercial availability of many indole derivatives, many groups synthesize combinatorial libraries from simpler starting materials in order to append the desired functionality. Combinatorial libraries based on the indole scaffold have been synthesized by the Fischer indole synthesis,[213,403,405,406] the Heck reaction,[407,408] through the palladium-catalyzed coupling of alkynes,[389,409−412] various condensation reactions,[413] or alternatively through the intramolecular attack of amines on nitriles.[414,415]

One of the best known strategies by which the indole ring has been synthesized is the Fischer indole synthesis. In 1996, Hutchins and Chapman reported the application of this reaction to solid-phase combinatorial synthesis (Scheme 49).[405] The reaction begins with the ketone (**274**) which is attached to a polystyrene resin through the 4-hydroxymethylbenzoic acid (HMB) linker. **274** was treated with various substituted phenylhydrazines in the presence of zinc chloride in glacial acetic acid for 18 h to yield the indole (**276**) through the hydrazine intermediate (**275**). Cleavage was then accomplished using a 9:1

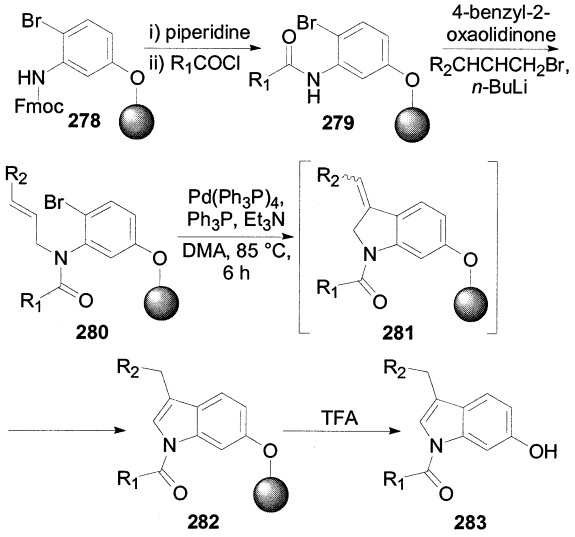
Scheme 49. Indole Combinatorial Synthesis by Hutchins and Chapman[405]



mixture of methanol/triethylamine to yield **277**. Use of monosubstituted alkyl- and halophenylhydrazines was well tolerated yielding cleaved product purities >96 %. Disubstituted phenylhydrazines yielded cleaved indole derivatives in purities >74%. Only electron deficient 4-substituted phenylhydrazines failed to produce the desired indole products. It should also be noted that meta-substituted phenylhydrazines produced both the 6- and 4-substituted indoles in an average ratio of 7:3, respectively. Other combinatorial libraries have also been synthesized using the Fischer indole synthesis as a key step.[213,403,406] Font et al. and Tois et al. both synthesized 2-carboxyindoles through a Japp-Klingemann reaction followed by Fischer indolization.[213,406] Font and co-workers synthesized a solution phase combinatorial library, while Tois and co-workers attached the indole template to resin and synthesized their library on solid phase.

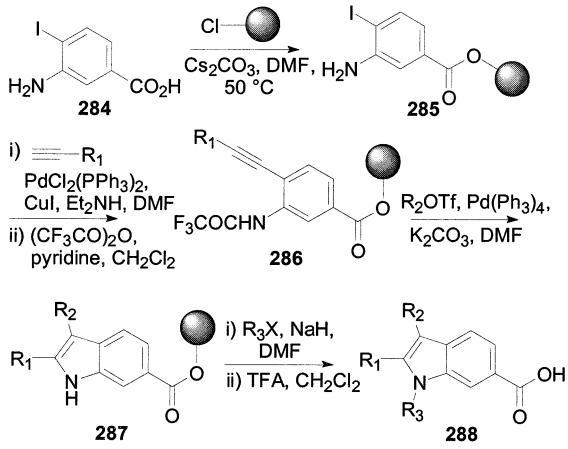
Another avenue by which the indole ring may be synthesized combinatorially is through a Heck-type cyclization. There have been at least two reports of solid-phase combinatorial syntheses utilizing this reaction.[407,408] The method reported by Yun and Mohan is displayed in Scheme 50.[407] After attachment of derivatized Fmoc-protected 3-amino-4-bromophenol to TentaGel S−NH_2 resin to yield **278**, removal of the Fmoc group with piperidine followed by acylation with an acid chloride yielded **279**. The nitrogen was then alkylated with an allylic bromide in the presence of lithium benzyloxazolidinone which afforded **280**. Treatment with a catalytic amount of $Pd(PPh_3)_4$ with triphenylphosphine and triethylamine in anhydrous *N*,*N*-dimethylacetamide (DMA) at 85 °C under inert gas produced **282** via a 5-*exo*-trig transition state (**281**). The indole scaffold was then cleaved from the resin with trifluoroacetic acid, yielding **283**.

Scheme 50. Indole Combinatorial Synthesis by Yun and Mohan[407]



The indole ring may also be synthesized through the palladium-catalyzed coupling of alkynes. This has been achieved many times in the synthesis of solid-phase combinatorial libraries.[389,409−412,416−418] The starting materials for this type of reaction usually include a resin-bound *ortho*-iodoaniline derivative and substituted acetylene. The method reported by Collini and Ellingboe is no exception and is displayed in Scheme 51.[411] 3-Amino-4-iodobenzoic acid (**284**) was attached to a modified Wang resin as the cesium salt to yield **285**. Following this, palladium-catalyzed coupling of a terminal acetylene was achieved, followed by trifluoroacetylation to yield **286**. Cyclization

Scheme 51. Indole Combinatorial Synthesis by Collini and Ellingboe[411]

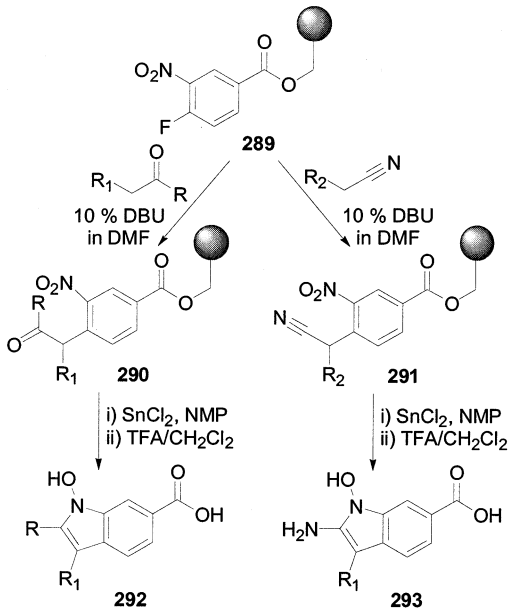


of the indole along with the incorporation of a vinyl group from a vinyl triflate at the indole 3-position gave the resin-bound disubstituted indole **287**. Alkylation of the nitrogen using an alkyl halide and sodium hydride followed by cleavage from the resin with trifluoroacetic acid yielded **288** in modest yields (33−76%). This reaction has also been used for the traceless solid-phase synthesis of indoles, in which the indole nitrogen was attached to the resin via a sulfonamide bond. This bond can be cleanly cleaved once the scaffold is fully assembled through treat-

ment with tetrabutylammonium fluoride (TBAF) or potassium *tert*-butoxide.[416−418]

A similar strategy for solid-phase combinatorial synthesis was reported by Stephensen and Zaragoza (Scheme 52).[413] Beginning with 4-fluoro-3-nitrobenzoic acid ester attached to resin (**289**), either a carbonyl or a nitrile was used to form **290** or **291**, respectively. Reduction of the nitro group with tin

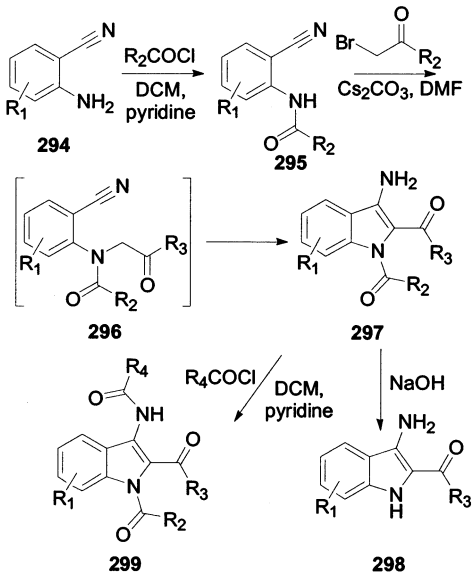
Scheme 52. Indole Combinatorial Synthetic Strategy by Stephensen and Zaragoza[413]



(II) chloride in 1-methyl-2-pyrrolidinone and subsequent cleavage from polystyrene resin formed the *N*-hydroxyindole (**292**, **293**). Various attempts to reductively cleave the N−O bond were unsuccessful.

A final strategy utilized for the synthesis of indole derivatives was reported by Nettekoven.[414,415] This method was used to synthesize various combinatorial libraries of indole compounds in solution phase (Scheme 53). Treatment of an aminobenzonitrile

Scheme 53. Indole Combinatorial Synthesis by Nettekoven[414,415]



(**294**) with an acid chloride in pyridine yielded **295**, which reacts cleanly with various α-bromoketones in *N*,*N*-dimethylformamide (DMF) with Cs_2CO_3 as a base to yield the indole (**297**) via **296**. At this point, the amide bond may be cleaved using 6N NaOH to yield a 2-acyl-3-amino-indole derivative (**298**), or alternatively, the primary nitrogen may be acylated to yield **299**. In the synthesis of **298** a benzoyl substituent attached in **295** is necessary (R_2) and may be regarded as an activating group for the nitrogen (*N*-unsubstituted aminobenzonitriles did not directly react with α-bromoketones to yield the desired indole **298**).

B. Benzimidazoles

Benzimidazoles (**267**) are structurally related to one of the most ubiquitous privileged substructures, the indole ring. As would be expected from their close structural similarity, benzimidazoles are also privileged substructures and have also seen extensive use in medicinal chemistry. Molecules containing the benzimidazole scaffold exhibit antiarrhythmic, antihistamine, antiulcer, anticancer, inotropic, fungicidal, anthelmintical, and antiviral activities.[165,419−423] In addition to this, benzimidazoles also show diverse biological activities, inhibiting phosphodiesterase IV and the integrin $\alpha_{IIb}\beta_3$ receptor, and antagonism of angiotensin I and neuropeptide Y.[423−425] 2-Alkylthiobenzimidazoles and their corresponding sulfoxides have also been shown to be proton-pump inhibitors, antiulcer compounds and antivirals.[426] In addition to this, the purine framework, which is one of the key structures in DNA (Figure 23), is also closely related to the benzimidazole framework. The purine motif is a privileged substructure and is recognized by an enormous number of proteins such as reductases, polymerases, G-proteins, methyltransferases, and protein kinases.[57] Although these molecules have been synthesized combinatorially,[57−60,427−437] they will not be discussed further in this review.

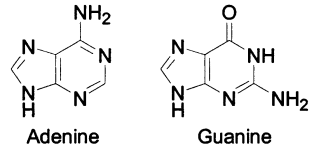


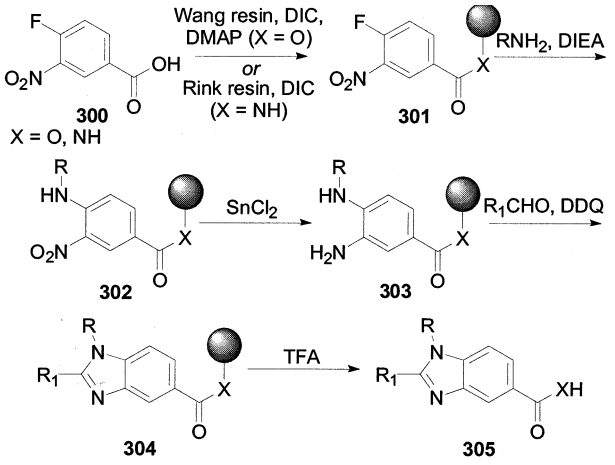
Figure 23. Purines found in DNA.

The simplest disconnection to make when considering how to synthesize the benzimidazole scaffold is across *C*2, so that the starting materials would be an *ortho*-aminoaniline derivative and a reagent that allows insertion of the required carbon, such as phosgene or an aldehyde component. Most, if not all, groups that have synthesized combinatorial libraries based on the benzimidazole scaffold have chosen variations on this strategy.

Obviously, the type of substituents desired at *C*2 of the imidazole ring dictates the choice of reagent to cyclize the ring. The most common reagents are aldehydes (for an intermolecular cyclization) or ketones (for an intramolecular cyclization). There are many reports of the synthesis of combinatorial libraries using either strategy. An example of a combinatorial library of benzimidazoles using an aldehyde to

affect ring closure is displayed in Scheme 54.[423] 4-Fluoro-3-nitrobenzoic acid (**300**) was either coupled to Wang resin using diisopropylcarbodiimide (DIC) and *N*,*N*-(dimethylamino)pyridine (DMAP) or a Rink derivatized polystyrene resin using DIC, to yield **301**. Following this, treatment of **301** with a variety of primary aliphatic, benzyl, and 2-alkylbenzylamines in a 5% solution of *N*,*N*-diisopropylethylamine (DIEA) in *N*,*N*-dimethylformamide or *N*-methylpyrrolidine yielded **302**. Reduction of the nitro group was achieved through treatment with a tin (II) chloride solution, which afforded **303**. A 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated cyclocondensation reaction of the *ortho*-aminoaniline and various aldehydes furnished **304**, which could then be cleaved with trifluoroacetic acid (TFA) to yield **305**. Other

Scheme 54. Benzimidazole Combinatorial Synthesis by Mayer et al.[423]



groups have also used an aldehyde to cyclize the imidazole ring in solid-phase combinatorial synthesis.[165,438−440] An intramolecular cyclization strategy through amides is also common in both solution-[441] and solid-phase[422,442−444] combinatorial synthesis. Carbamates of *ortho*-aminoanilines have also been used for a traceless synthesis involving simultaneous intramolecular cyclization-cleavage on solid phase.[445] Another traceless solid-phase synthesis was reported by Krchňák and co-workers who utilized an intramolecular attack of the thiourea derivative of an *ortho*-aminoaniline derivative to yield 2-arylaminobenzimidazoles.[446]

Many other reagents aside from aldehydes and ketones have been used to cyclize the imidazole ring from *ortho*-aminoaniline derivatives such as **303**. Solid-phase combinatorial syntheses from these derivatives have been achieved using a trimethylorthoformate/TFA solution (yielding a 2-unsubstituted benzimidazole),[419] ethyl benzimidate hydrochloride (yielding a 2-aryl substituted benzimidazole),[447] a isothiocyanate/DIC solution[448] or cyanogen bromide[449] (to afford 2-arylaminobenzimidazoles), and triphosgene (to yield the benzimidazolone)[450] to affect cyclization. A solution-phase combinatorial synthesis of benzimidazoles with three points of diversity has also been achieved from an *ortho*-aminoaniline using a carboxylic acid and the coupling reagent, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), to affect ring closure.[451]

Combinatorial libraries of the structurally related 2-alkylthiobenzimidazoles (**306**) can readily be obtained through cyclization of the imidazole ring from a structure similar to **303** with an appropriate reagent (Figure 24). Solution-[421,452] and solid-phase[420,426] combinatorial libraries of these molecules have been synthesized using thiophosgene as well as TCD (1,1′-thiocarbonyldiimidazole, **307**).

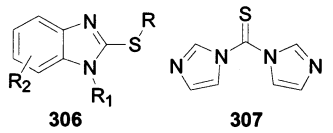


Figure 24. 2-Alkylthiobenzimidazole (**306**) and TCD (1,1′-thiocarbonyldiimidazole, **307**).

C. Benzofurans

Molecules containing the benzofuran scaffold (**268**) possess a wide range of biological activities. They are active as antifungals,[453] κ-selective opioid receptor analgesics,[454] angiotensin II antagonists (hypertension)[455] and inhibit platelet aggregation through fibrinogen receptor antagonism.[456] Molecules containing this scaffold also find use as antioxidants and brightening agents and in agriculture.[457] Due to their small size, the benzofuran group has also been appended to other scaffolds to form molecules that inhibit tubulin (antimitotic activity),[458] sodium-independent atypical dopamine D-2 receptors (antipsychotic activity),[459] and EP_3 prostanoid receptors.[460] The benzofuran group is also present in larger heterocyclic structures such as the furochromones (**308**), whose analogues inhibit cyclic AMP phosphodiesterase (inhibiting platelet aggregation),[461] and acyl CoA:cholesterol *O*-acyltransferase (ACAT) inhibitors (antiatherosclerotic activity) (Figure 25).[462] Benzo[*b*]-furo[3,4-*d*]furan-1-ones (**309**) also are a common scaffold found in many naturally occurring products, which have a wide range of biological effects.[463]

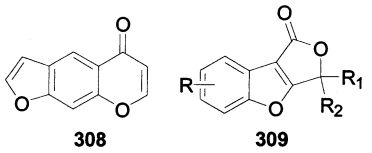


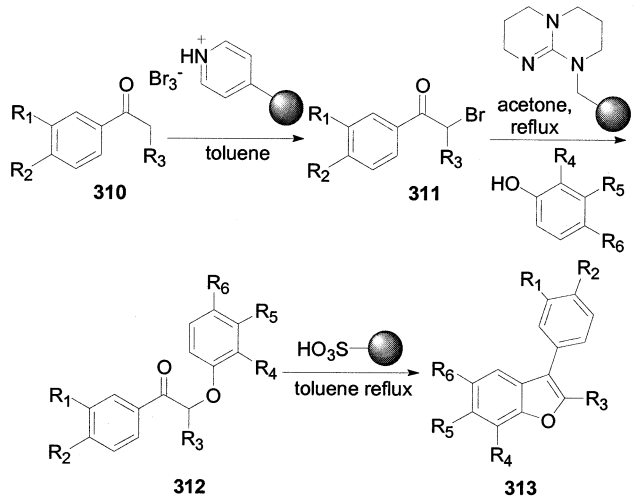
Figure 25. Molecules based on the benzofuran scaffold.

Combinatorial syntheses of these molecules have been achieved in a number of ways. As stated above, a number of groups have utilized the benzofuran moiety as a substituent on other scaffolds for combinatorial synthesis.[454,458−460] Other groups synthesized combinatorial libraries based upon the benzofuran scaffold, but started with a pre-synthesized benzofuran moiety.[455,456,462] Nevertheless, at least four different strategies have been reported for the synthesis of this structure.

The first methodology utilizes a condensation reaction between a ketone and a nucleophilic group. The nucleophile can take several forms. For example, Fecik et al. reported the use of a Wittig reaction to close the furan ring of the benzofuran moiety and generate a combinatorial library,[453] and Boehm and Showalter reported cyclization to the benzofuran ring

via an aldol-type reaction.[464] Habermann et al. reported a cyclization-dehydration reaction to yield the benzofuran (Scheme 55).[457] The synthesis begins with the bromination of commercially available acetophenones (**310**) to yield **311**. Following this, **311**

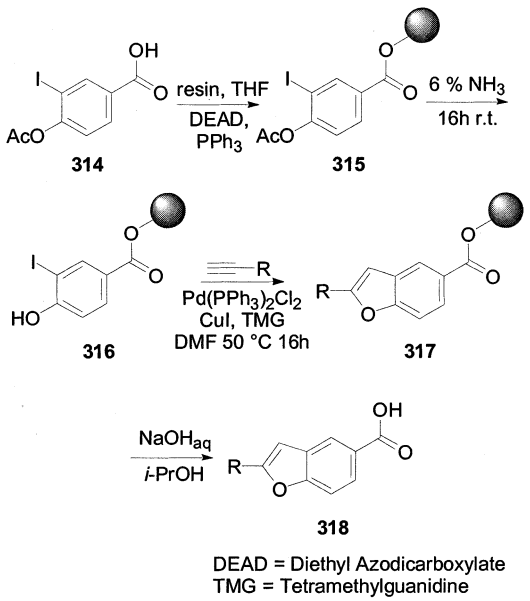
Scheme 55. Benzofuran Combinatorial Synthesis by Habermann et al.[457]



was reacted with commercially available phenols using 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD-P) as a base, affording **312** in fair to excellent yields (>30%) and good purities (>75%). The benzofuran ring system (**313**) was then assembled through a clean cyclodehydration reaction of the α-phenoxyacetophenones using Amberlyst 15 as a cyclizing agent (>57% yield, >90% purity). Interestingly, all reaction steps in this scheme utilized solid-supported reagents. This technique has shown to be a clean and efficient method for the generation of chemical libraries.[465,466]

The second methodology involves a palladium catalyzed heteroannulation reaction. Many syntheses suitable for combinatorial synthesis have been proposed using this reaction.[408,467] One procedure that

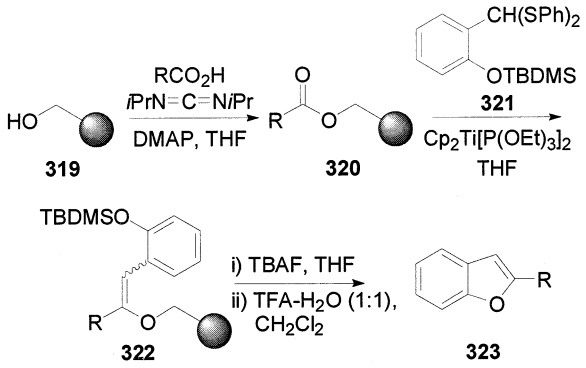
Scheme 56. Benzofuran Combinatorial Synthesis by Fancelli et al.[468]



has been reported by Fancelli et al. begins with the reaction between the starting carboxylic acid (**314**) and TentaGel resin via the Mitsunobu reaction, producing **315** (Scheme 56).[468] Following this, the acetate group was deprotected to allow further derivatization (**316**). A palladium-catalyzed heteroannulation of terminal acetylenes then followed to yield the benzofuran scaffold (**317**), which could be cleaved from resin to yield **318**.

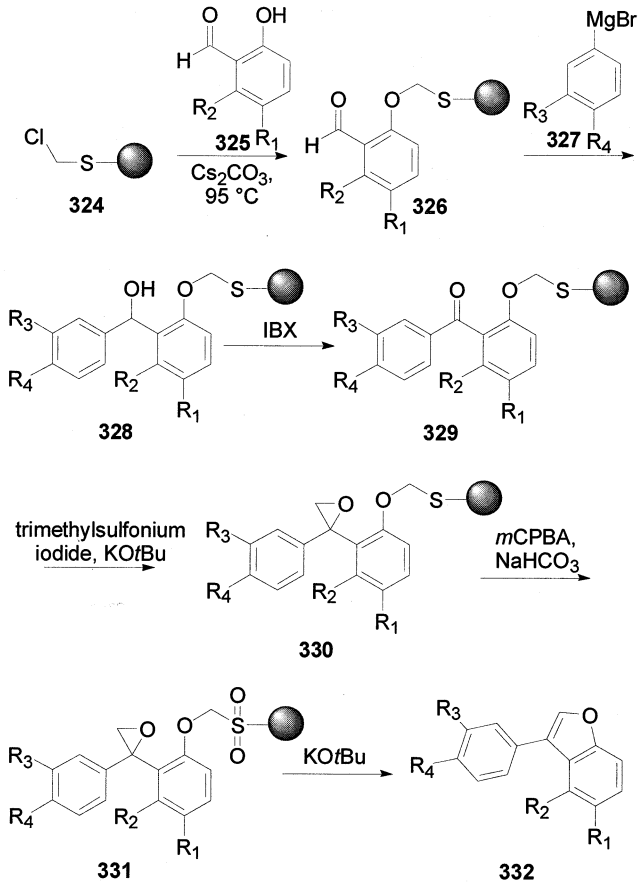
A third strategy was presented by Guthrie and coworkers who utilized a traceless solid-phase synthesis of 2-substituted benzofurans (Scheme 57).[469] Compounds synthesized via this route may theoretically be substituted at any site on the benzofuran ring. First, 1,3-diisopropylcarbodiimide was used to couple carboxylic acids to Wang-resin (**319**), producing **320**. **322** was then assembled through an alkylidenation reaction, using thioacetal (**321**) and the low-valent titanium complex $Cp_2Ti[P(OEt)_3]_2$. The workup of this reaction is relatively simple, merely requiring washing with various solvents. Deprotection of the phenol with tetrabutylammonium fluoride (TBAF) followed by treatment with 50% aqueous trifluoroacetic acid in dichloromethane then yielded the benzofuran (**323**).

Scheme 57. Benzofuran Combinatorial Synthesis by Guthrie et al.[469]



Last, Nicolaou and co-workers have reported the solution- and solid-phase synthesis of 3-arylbenzofurans by via a cyclofragmentation−release pathway (Scheme 58).[470] Previously synthesized chloromethyl sulfide resin (**324**) was treated with a series of functionalized salicylaldehydes (**325**) to produce **326**. These resin supported aldehydes were then treated with several arylmagnesium bromides (**327**) to yield **328**, which could subsequently be selectively oxidized with IBX (1-hydroxy-1,2-benziodoxol-3(1*H*)-one) to form benzophenones (**329**). Sulfur ylide epoxidation afforded **330** followed by *m*CPBA (*meta*-chloroperoxybenzoic acid) oxidation yielded the sulfone (**331**). Treatment with potassium *tert*-butyl alcohol deprotonated the methylene group adjacent to the sulfone, which the authors suggested attacked the quarternary carbon of the epoxide via a 5-*exo*-trig cyclization, which then collapsed to **332** expelling both formaldehyde and the resin phenylsulfinate anion. As can be seen, this synthetic strategy permits a great deal of diversity to be incorporated on either aromatic ring, and the cyclization-cleavage step not only allows for a traceless synthesis, but also increases the purity of the product, as only the desired benzofuran scaffold

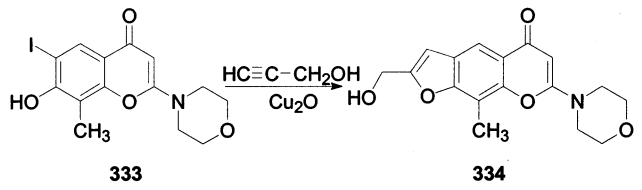
Scheme 58. Benzofuran Combinatorial Synthesis by Nicolaou et al.[470]



can undergo cleavage from resin. Unfortunately, both aryl groups appear to be required for regioselective epoxide opening.

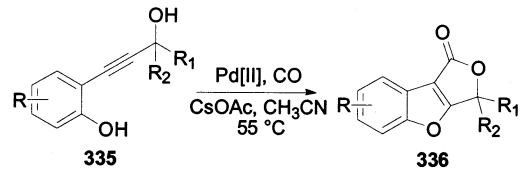
Larger scaffolds have been synthesized using variations on these themes. 7-Aminofurochromones (**334**) were made using a strategy similar to that described in Scheme 56.[461] The key step in this reaction is a copper catalyzed heteroannulation of prop-2-yn-1-ol with the 7-hydroxy-6-iodo-8-methylchroman-4-one (**333**) (Scheme 59). The benzo[*b*]furo[3,4-*d*]furan-1-

Scheme 59. 7-Aminofurochromone Combinatorial Synthesis by Morris et al.[461]



ones (**336**) may also be synthesized by a similar methodology (Scheme 60). This reaction utilizes a

Scheme 60. Benzo[*b*]furo[3,4-*d*]furan-1-one Combinatorial Synthesis by Hu and Yang[463]



palladium catalyzed carbonylative annulation of *ortho*-alkynylphenols (**335**).[463]

D. Benzothiophenes

Benzothiophenes (**269**) are privileged substructures that are closely related to the indole ring. Molecules with this scaffold are inhibitors of herpes simplex virus type I (HSV-1) replication,[471] tubulin (antimitotic activity),[458,472] cysteine proteases such as cathepsins K and L,[473] serine proteases such as thrombin,[474] and κ-selective opioid receptor analgesics[454] and when used in conjunction with an arylpiperazine moiety are 5-HT_6 antagonists (potential roles in schizophrenia and depression).[209] Benzothiophenes also form the core of molecules such as raloxifene (**337**, Figure 26) (raloxifene has been approved for use in Europe and the United States for the prevention of osteoporosis) which are selective estrogen receptor modulators.[475,476]

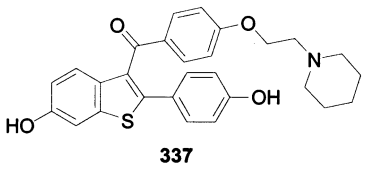
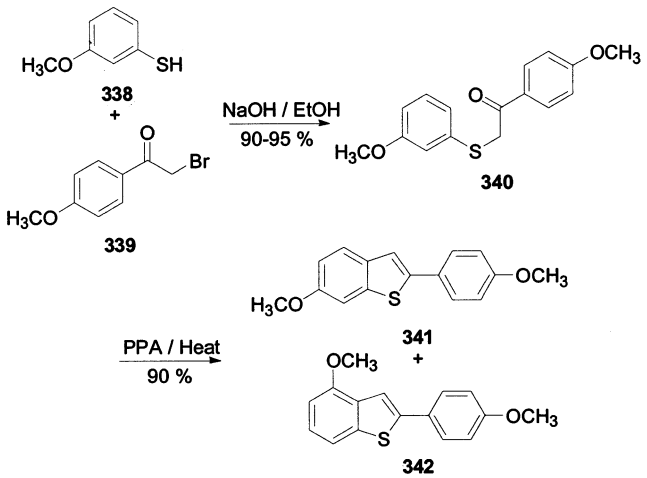


Figure 26. Raloxifene.

This scaffold has been the core framework of relatively few combinatorial syntheses, although it has frequently been used as a substituent on another scaffold.[209,458,473] Other groups have assembled libraries based on a benzothiophene core scaffold and have used a pre-assembled benzothiophene ring.[474,475] It appears that there are few, if any, groups that have reported the assembly of a large combinatorial library in which the initial synthesis of the benzothiophene moiety is integral.

Nevertheless, several strategies for the synthesis of this bicyclic ring have been reported, and these may be amenable to synthesis in a combinatorial fashion. One strategy has utilized a Friedel−Crafts aroylation as the key synthetic step (Scheme 61).[472] Reaction of the thiol (**338**) with bromoacetophenone (**339**) provided **340** in excellent yield. Subsequent cyclization and concomitant aryl ring migration in

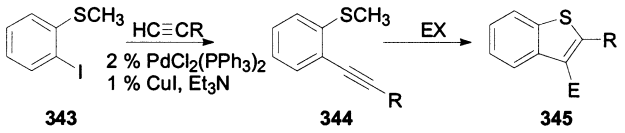
Scheme 61. Benzothiophene Synthesis by Pinney et al.[472]



the presence of polyphosphoric acid (PPA) then provided the regioisomers **341** and **342** in a 3:1 mixture respectively, which were available for further derivatization.

A different method reported by Larock and Yue synthesized benzothiophenes through an electrophilic cyclization reaction (Scheme 62).[477] In this scheme, the arylalkyne (**344**) is prepared through Sonogashira coupling of *ortho*-iodothioanisole (**343**) and terminal alkynes, which proceeded in high yields (93−100%). The benzothiophene (**345**) can then be prepared from **344** with an iodo, bromo, *para*-nitrophenylsulfyl, or phenylselenyl group in the 3- position through the use of iodine, bromine or *N*-bromosuccinimide (NBS), *para*-$O_2NC_6H_4SCl$ or PhSeCl, respectively. All of these cyclizations proceed in good to high yields (70 to 100%) for the R groups reported.

Scheme 62. Benzothiophene Synthesis by Larock and Yue[477]



VI. Conclusions

Privileged substructures are of potentially great importance in medicinal chemistry. These scaffolds are characterized by their ability to promiscuously bind to a multitude of receptors through a variety of favorable characteristics. This may include presentation of their substituents in a spatially defined manner and perhaps also the ability to directly bind to the receptor itself, as well as exhibiting promising characteristics to aid bioavailability of the overall molecule. It is believed that some privileged substructures achieve this through the mimicry of common protein surface elements that are responsible for binding, such as β- and γ-turns. As a result, these structures represent a promising means by which new lead compounds may be identified. Combinatorial libraries based upon these structures may be a means of easily generating multiple lead compounds for a variety of receptors.

VII. Acknowledgments

This review has attempted to be as comprehensive as possible; however, we apologize for any oversights in the literature that may have occurred and these emissions are the responsibility of the authors alone. The authors would especially like to thank Michael Ankersen, Chris Waller, Mike Hann, Marc Campitelli, Justin Coughlan, Peter Cassidy, and John Holland for their helpful discussions on the nature of privileged substructures. The authors would also like to thank present and past group members for their contributions to the concepts presented, particularly Tran Trung Tran, Stephen Love, Andrew McDevitt, Simon Golding, and Wim Meutermans. Various colleagues also contributed, particularly Alun Jones, Paul Alewood, Mike Waters, Garland Marshall and Peter Andrews. The authors also especially thank the reviewers for their helpful comments.

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