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Reviews

Solid-Phase Synthesis of Biologically Active Benzoannelated Nitrogen Heterocycles: An Update

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1. Introduction

Heterocycles have a central position in organic chemistry[1−3] and considerable attention has been focused on their syntheses. Nitrogen heterocycles in particular exhibit diverse biological and pharmacological activities due in part to the similarities with many natural and synthetic molecules with known biological activity.[4] Furthermore, compounds that contain heterocyclic moieties often exhibit improved solubilities and can facilitate salt formation properties, both of which are known to be important for oral absorption and bioavailability.[5] In recent years, design and synthesis of pharmacologically relevant heterocyclic molecules by combinatorial techniques have proven to be a promising strategy in the search for new pharmaceutical lead structures.[6,7] For these reasons, combinatorial chemistry has emerged as a powerful methodology for the preparation of libraries of small organic compounds to accelerate the drug discovery process.[8,9] Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. As a result, an increasing range and number of pharmaceutically useful heterocyclic compounds have been prepared using the solid-phase strategy.[10−13] This approach permits the rapid synthesis of large numbers of individual compounds as well as mixture-based combinatorial libraries in a short time frame and facilitates their use in high-throughput screening.[14] The design and synthesis of novel scaffolds as core structures for the library generation of small molecules on solid-phase are essential steps in accessing a wide variety of structurally complex derivatives.

Considerable work has been carried out in both academia and pharmaceutical industry to optimize many of useful reactions from the organic chemists' arsenal for solid-phase conditions and to design versatile linkers.[15−17] In this respect, methods that allow the cleavage of the synthesized compounds from the resin without leaving behind traces of the solid-phase synthesis are of particular interest.[18] They avoid the functional groups required for resin attachment remaining in the target molecules which may have an undesired effect on their biological activity. In addition, synthetic sequences are of particular interest, where the desired products are formed and simultaneously released into solution in the last step of the synthesis, that is, in the sense of a safety catch mechanism. Such a strategy ensures that only the desired compounds are released because unwanted side products not fulfilling the demand for safety catch release remain attached to the solid support.

Because solid-phase organic synthesis (SPOS) provides a powerful tool for the preparation of compound libraries, it has been successfully used for the construction of both oligomeric compounds and small molecules.[19−21] However

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SPOS still exhibits several shortcomings due to the nature of the heterogeneous reaction conditions.

The combination of SPOS with microwave heating to speed up drug discovery processes is very interesting.[22] Microwave-assisted SPOS (MASPOS) has become popular in recent years because of the advancement in instrumentation. Organic reactions can now be performed in closed vessels in a temperature- and pressure-controlled manner, providing reproducible results and speeding up the library preparation process.[23−25]

The analytical evaluation and structure determination is a critical step in the development of combinatorial approaches to produce a great diversity of substances.[6,26,27] The finding of efficient and fast techniques that allow monitoring reaction progress and chemical changes on solid-phase supported compounds has become of great importance.

In particular, the pharmaceutical industry has invested in and integrated numerous aspects of combinatorial chemistry into the drug discovery process with one goal being to provide novel ligands for the plethora of biological targets derived from the mapping of the human genome.[28]

This review is an update of our previous paper in the field[10] and summarizes the literature published from 2002 describing the methods for the solid-phase synthesis of benzoannelated nitrogen heterocycles, motivated by the fact that these heterocycles are a pivotal element in modern drug discovery programs. The chapters on the cyclization methods for the preparation of five-, six-, and seven-membered benzoannelated rings have been subdivided depending on the number of nitrogen atoms present in the ring system.

2. Benzoannelated Five-Membered Heterocycles

2.1. Indoles and Related Heterocycles. One particular molecular scaffold of interest is the indole because it is known to exhibit a broad range of biological activity. A plethora of indole-based biologically active natural products and indole-derived drugs span over an enormous range of biological activity. The essential amino acid tryptophan, the neurotransmitter Serotonin [**1**, 5-hydroxytryptamine, (5-HT)], and several groups of important alkaloids are indole derivatives (Figure 1). In fact, a number of approved drugs have this core in their structures, for example, the 5-HT_3 receptor antagonist Ondansetron (**2**) used for the treatment of chemotherapy-induced nausea and vomiting[29] and the $5HT_1$ receptor agonist Sumatriptan (**3**) used for the treatment of cluster headache.[30] Other examples are the antibiotic Indolmycin (**4**),[31] the antihypertensive Reserpine (**5**),[32] and the antineoplastic Vincristine (**6**).[33] In the present year, a series of potent indole derivatives have been prepared as CB_2 cannabinoid receptor ligands,[34] as a new class of antimitotic agents and tubuline inhibitors,[35] and 1-hexyl-indolactam-V10 (**7**) as a selective activator for novel PKC isozymes that play important roles in various cellular processes related to tumor promotion, ischemia-reperfusion injury in the heart, and Alzheimer's disease.[36]

Consequently, indoles or molecules containing the indole moiety have efficiently been synthesized for more than 100 years in solution. The first preparation of indoles dates from 1866, and the Fischer indole synthesis was introduced as a more versatile method for preparing indoles in 1883.[37] Efficient preparation on solid-phase, however, dates back only about 15 years.[38] There are many ways of synthesizing indoles, but only a few methods have been used on solid-phase.[39] Solid-phase syntheses of indoles have involved palladium-mediated heteroannulation of alkynes,[40] intramolecular Heck reaction,[41] intramolecular Wittig reaction,[42] and the Nenitzescu,[43] modified Madelung,[44] and Fischer indole syntheses.[45] Traceless solid-phase synthesis of indole derivatives has also been achieved.[46] The preparation of more diversely substituted indoles may lead to the discovery of yet more biologically active compounds, and further research in this area is important.

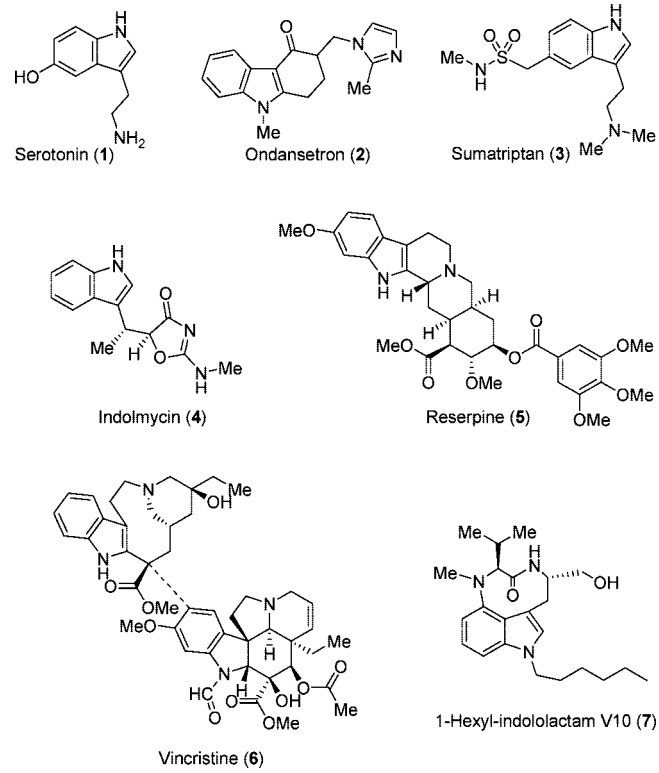
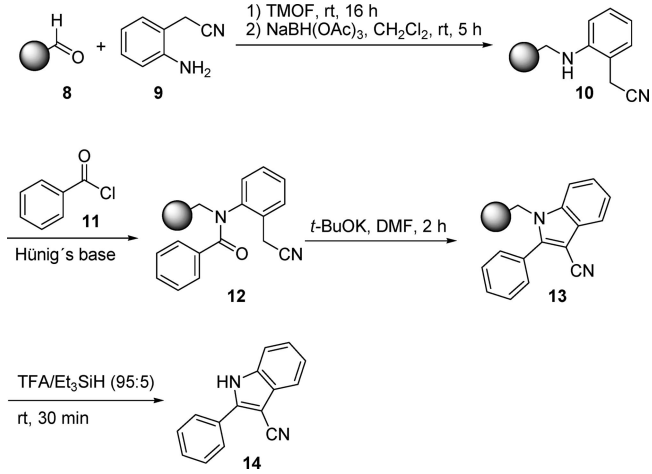


Figure 1. Relevant biologically active molecules with an indole moiety.

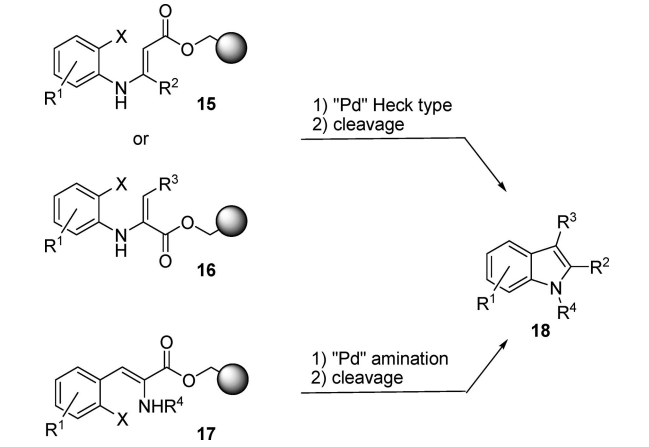
The modified Madelung indole synthesis provides an excellent methodology for the synthesis of 2,3-disubstituted indoles. This reaction is very modular and therefore allows the incorporation of multiple diversity points. Wacker and Kasireddy[44] have utilized this reaction successfully on solid-phase to obtain indoles in excellent yields and purities. The sequence was initiated with the reductive amination of Bal resin (**8**) using an ortho-substituted aniline **9**. The resin-bound aniline **10** was acylated with a variety of acid chlorides **11**, followed by cyclization with base to provide the desired indole **14** (yield 88%), after TFA-promoted cleavage from the resin (Scheme 1).

Immobilized enaminoesters were cyclized to indolecarboxylates by Yamazaki et al. via palladium-catalyzed reactions (Scheme 2).[41] They demonstrated that the intramolecular palladium-catalyzed cyclization of the α- or *β*-(2-halophenyl)amino-substituted α,*β*-unsaturated esters was effective in the solid-phase synthesis of indole 2- and 3-carboxylates with various functional groups on the benzene ring.[47,48] Moreover, the intramolecular palladium-mediated

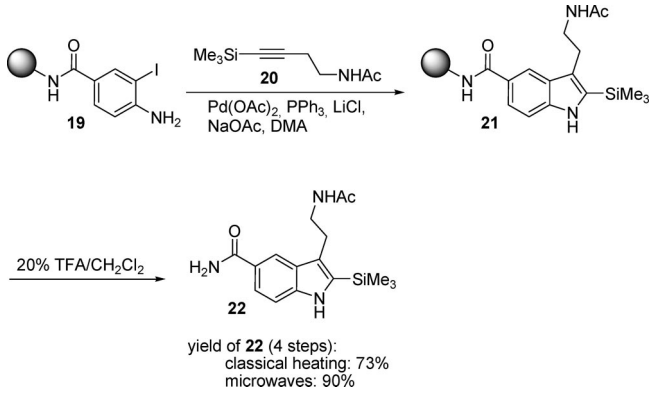
Scheme 1. Madelung Syntheses on Solid Supports by Wacker and Kasireddy[44]



Scheme 2. Palladium-Assisted Indole Synthesis by Yamazaki et al.[41]



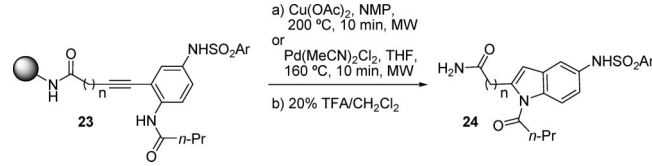
Scheme 3. Microwave-Assisted Solid-Phase Indole Synthesis by Finaru et al.[40]



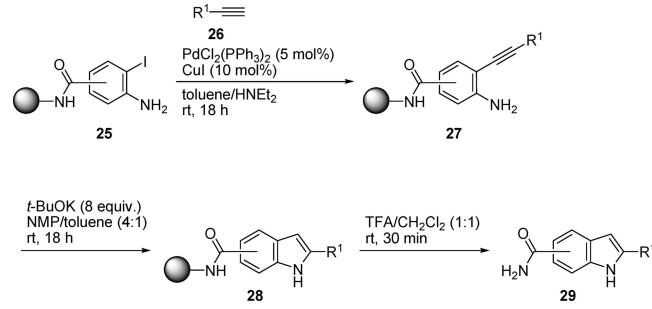
domino C−N-arylation[49] also provided a new one-pot method for solid-phase indole synthesis.

The combination of SPOS with microwave heating has proven to be an advantage for a rapid access to novel molecules. Finaru et al. employed both techniques to generate the indole skeleton of new melatonin analogues in five steps via a palladium-mediated reaction between 2-iodoaniline derivatives **19** and functionalized acetylenes **20** (Scheme 3).[40] They observed that exposition of the mixtures to microwave irradiation provided a substantial increase in yield and a striking reduction in the reaction time. Another example of microwave-assisted SPOS (MASPOS) was reported by Dai et al. to obtain, for the first time on solid-phase, a twelve-membered library of arenesulfamoyl-substituted indoles **24** (65−82% yield) (Scheme 4).[50]

Scheme 4. Microwave-Assisted Solid-Phase Indole Synthesis by Dai et al.[50]



Scheme 5. Synthesis of Polyfunctional Indoles by Koradin et al.[51]

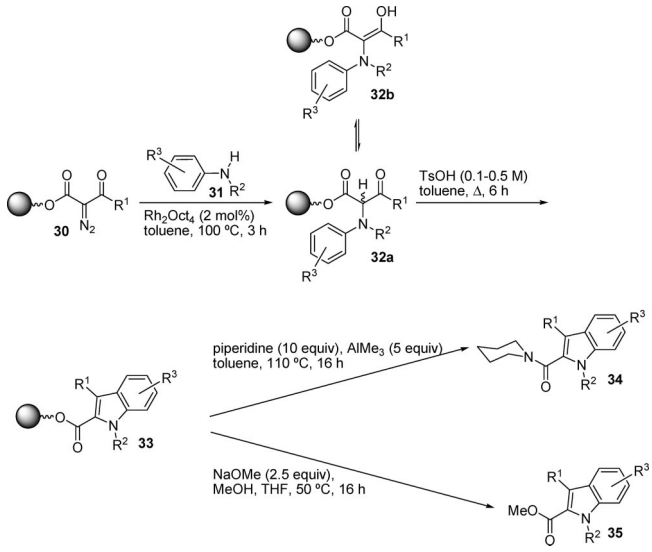


Koradin et al.[51] reported a base-mediated cyclization under mild reaction conditions of various 2-alkynylanilines leading to indoles. This method was also successfully adapted to the solid-phase by using the rink-MBHA-resin as solid support. A Sonogashira reaction of the immobilized iodoaniline derivative **25** under standard reaction conditions afforded the immobilized 2-alkynylamines **27** in nearly quantitative yields and high purities. The cyclization of **27** to the polymer-bound indoles **28** was accomplished with an excess of *t*-BuOK (8 equiv) in NMP/toluene (4:1) at room temperature. Under these conditions, the reactions provided eight indoles, **29**, in good yields and purities (Scheme 5). This base-mediated reaction was also used to synthesize the heterocyclic core of the marine alkaloid hinckdentine A.

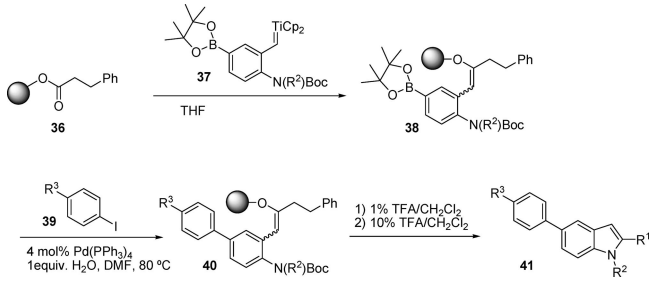
Lee et al. described a solid-phase indole synthesis using a N−H insertion reaction of *N*-alkylanilines **31** into a highly reactive polymer-bound rhodium carbenoid intermediate to yield the corresponding α-arylamino-β-ketoester **32a** (Scheme 6).[52] These insertion products were treated under acid-catalyzed cyclodehydration conditions to yield a series of 35 polymer-bound indole esters **33**, which were subsequently cleaved from the resin under Lewis acid-promoted amidation conditions to yield the desired indoles **34**−**35** in good yields and with excellent purities. In addition to the optimization of the reaction conditions, more diverse indoles were prepared by introducing additional substituents via a Suzuki-type coupling reaction.

The approach described by Macleod et al.[53,54] is both a novel strategy for the construction of indoles and the first example of a chameleon catch approach to this class of compounds. Basically, the general strategy involves the use of titanium carbenoids containing a masked nucleophile to convert acid-stable, resin-bound esters into acid-sensitive enol ethers. Treatment with mild acid leads to traceless cleavage

Scheme 6. Synthesis of a Diverse Array of Indoles by Lee et al.[52]



Scheme 7. Synthesis of 2,5-Disubstituted Indoles Using Titanium Carbenoids by Main et al.[55]



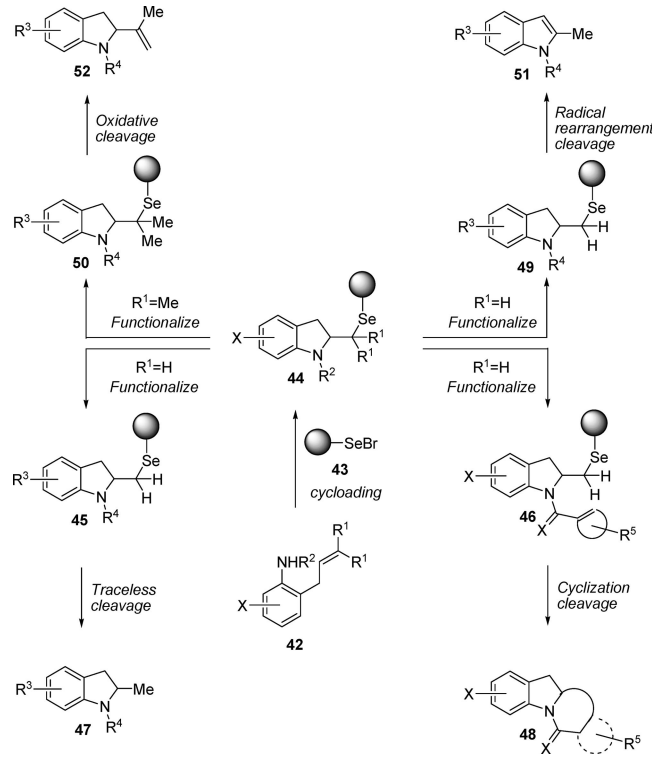
from resin with concomitant cyclization to generate bicyclic heteroaromatic compounds.

The use of new titanium carbenoid reagents bearing a boronate functionality **37** were used for the SPOS synthesis of 2,5-disubstituted indoles **41** in MiniKans. Suzuki cross-coupling, cleavage-cyclization sequence for introducing diversity was successfully employed for preparing 79 of the members of a potential 96-membered library of indoles (Scheme 7).[55]

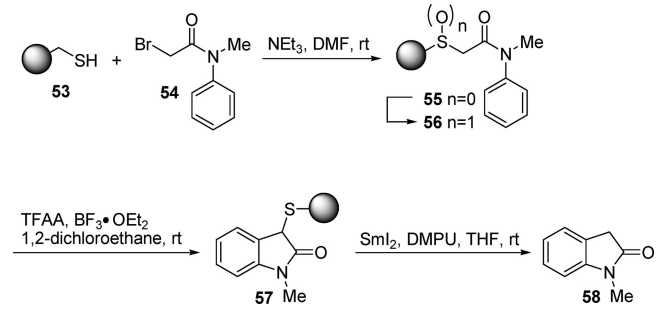
With the use of a polymer-bound selenyl bromide resin (**43**), *o*-allyl and *o*-prenyl anilines (**42**) were cycloadded to afford a series of solid supported indoline and indole scaffolds (Scheme 8).[56] Subsequently, Nicolaou et al. described the functionalization of these natural products-like templates cleavage via four distinct methods, namely, traceless reduction, radical cyclization, radical rearrangement, and oxidative elimination, to afford 2-methyl indolines **47** (nine-membered library in reasonable yields and purities), five polycyclic indolines **48** (five-membered library in moderate yields), 2-methyl indoles **51** (six-membered library in satisfactory yields), and 2-propenyl indolines **52** (twelve-membered library in good to excellent yields and purities).

The route to oxindoles reported by McAllister et al.[57] described the first Pummerer cyclizations on solid-phase by using a sulfur linker cleavable by SmI_2 (Scheme 9). They immobilized *N*-methyl-*N*-phenyl α-bromoacetamide (**54**) by stirring the amide with thiol resin (**53**) in DMF. The sulfur linker in immobilized amide **55** was then oxidized to give

Scheme 8. Solid-Phase Synthesis of Substituted Indolines and Indoles by Nicolaou et al.[56]



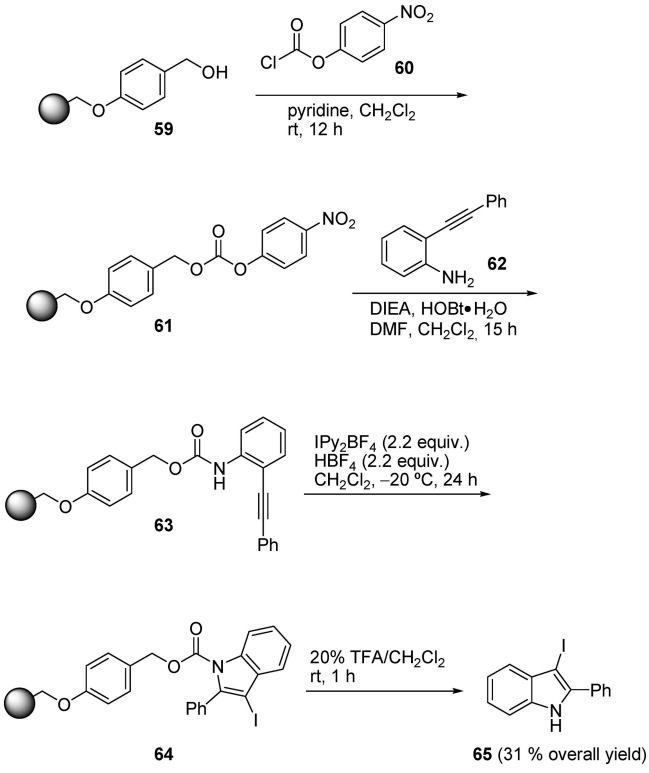
Scheme 9. Oxoindole Synthesis Using a Sulfur Linker by McAllister et al.[57]



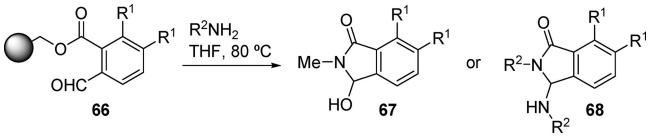
sulfoxide **56**. In this electronically unactivated substrate, the Pummerer cyclization was found to be most efficient when carried out using stronger activation with TFAA and $BF_3 \cdot OEt_2$. Finally, cleavage from the sulfur linker was carried out using SmI_2 and DMPU to obtain oxindole **58** in high purity and 47% yield after four steps. To increase the diversity of the oxindole library, a number of α-bromoamides were used in the sequence and further modifications were carried out after the Pummerer cyclization. Another route to oxindoles from thiol resin (**53**), aromatic amines and alkyl halides was reported by Xie et al.[58] The parallel traceless synthesis of trisubstituted oxindoles was carried out on solid phase using the "tea-bag" methodology.

Barluenga et al.[59] used for the first time the addition of anilines to internal alkynes facilitated by a simple iodinated reaction to prepare 3-iodoindoles (Scheme 10). For the solid-phase based approach, *p*-nitrophenyl-carbonate-modified Wang resin (**61**) was used to prepare the desired carbamates **63** from *o*-alkynylaniline (**62**). The C−N bond formation required only a simple activation of the iodinating agent (IPy_2BF_4) to yield 3-iodoindoles **64**. Because of the versatile

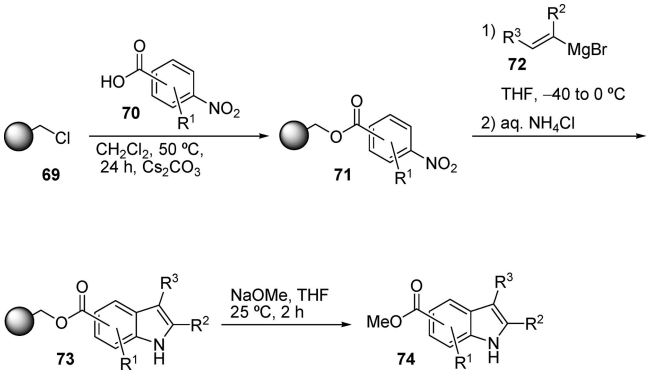
Scheme 10. Synthesis of 3-Iodoindoles by Barluenga et al.[59]



Scheme 11. Solid-Phase Synthesis of Isoindolinones by Knepper et al.[60]



Scheme 12. Bartoli Indole Synthesis on Solid Supports by Knepper and Bräse.[61]



iodine functionality can be transformed on the resin using organometallic chemistry, this direct assembly of 3-iodoindole offers additional synthetic potential.

The synthesis of naturally occurring 3-hydroxy-isoindolinones **67** or 3-alkylamino-isoindolinones **68** after addition reactions of primary amines to polymer-bound 2-formyl benzoic acids **66** was reported by Knepper et al. (Scheme 11).[60]

In 2003, Knepper and Bräse[61] were the first to report the Bartoli indole synthesis on solid supports (Scheme 12). Immobilization of five nitro benzoic acids **70** was performed starting from Merrifield resin (**69**). The addition of four different alkenyl Grignard reagents **72** and basic cleavage led to substituted methyl indole carboxylates **74** (19 examples) in excellent purities and moderate yields. In addition, palladium-catalyzed reactions have been demonstrated on immobilized indoles.

The Fischer indole synthesis is still the most important preparative method for indoles in solution. During the Fischer indole cyclization, arylhydrazones of aldehydes or ketones are converted to indoles by a process that involves ortho-substitution via a sigmatropic rearrangement. Although Fischer indole synthesis on solid supports has been already reported,[45] new applications to obtain new kinds of indoles are presented here. Mun[62] and Rosenbaum[46] described two different traceless solid-phase indole syntheses employing the Fischer indole synthesis as key step. Both groups immobilized the hydrazine on solid support, and Mun obtained the indole core by using a silicon linker (Scheme 13). Moreover, Ohno[63] and Koppitz[64] reported an on-resin Fischer indole cyclization reaction starting from immobilized ketones, which provided 16 N-substituted naltrindoles (potential δ-opioid receptor ligands) and highly diverse tetrahydrocarbazole libraries, respectively.

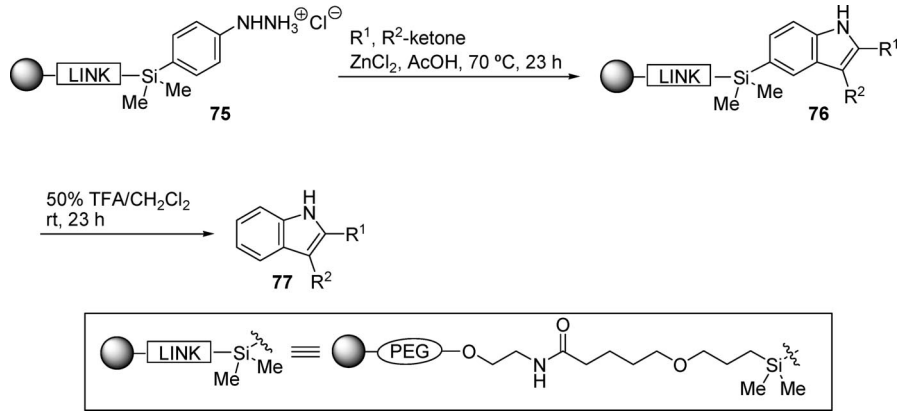
2.2. Benzimidazoles. This ring system has been extensively described in the literature as an important class of compounds with a wide variety of known pharmacological properties (Figure 2). Notable clinical examples are the antihistaminic Astemizole (**78**),[65] the antiulcerative Omeprazole (**79**),[66] the antihelmintic Albendazole (**80**),[67] or the angiotensin II type-1 receptor antagonist Candesartan (**81**).[68] In addition, benzimidazole-based compounds, like oxobenzimidazoles, have been shown to possess interesting properties, such as dopamine receptor antagonists Droperidol[69] and Domperidone.[70]

Furthermore, this class of compounds has recently shown activity as respiratory syncytial virus inhibitors,[71] nonnucleoside HIV-1 reverse transcriptase inhibitors,[72] or inhibitors of VEGFR-2 and TIE-2 kinase receptors, both of which are implicated in angiogenesis.[73]

In the solid-phase synthesis of benzimidazoles, one key step is the reduction of the nitro group to a primary amine and subsequent cyclization reaction. For example, the resin-bound *o*-nitroaniline **83** was treated with tin(II) chloride dihydrate to reduce the aromatic nitro group to generate the *o*-dianilino compound **84**, which was treated with thiocarbonyldiimidazole ($CSIm_2$) to yield dihydroimidazolyl dihydrobenzimidazol-2-thione **85**. Compound **85** was treated with an alkyl halide, and the alkylated derivative **86** cleaved using anhydrous HF to give dihydroimidazolyl 2-alkylthiobenzimidazole **87**. Twelve individual compounds were obtained in moderate yield and good purity. In addition, **87** can be converted in dihydroimidazolyl 2-alkylthiobenzimidazole **88** after treatment with hydrogen peroxide under weakly basic conditions (Scheme 14).[74]

A similar procedure was carried out in parallel by Hoesl et al.[75] who used Houghten's "tea-bag" method, in which the resin is contained within sealed polypropylene mesh packets. To obtain a large number of different resin-bound 2-aminobenzimidazoles **91**, they coupled 4-fluoro-3-nitrobenzoic acid either to an amino acid linked to MBHA

Scheme 13. Fischer Indole Synthesis on Solid Supports by Mun et al.[62]



resin or directly to MBHA resin. The second position of diversity was introduced by nucleophilic displacement of the fluoro atom with a variety of different amines. Quantitative reduction of the nitro group was achieved in this case using sodium hydrosulfite in combination with 1,1′-dioctadecyl-4,4′-bipyridinium dibromide. This reduction reagent was preferable to tin(II) chloride dihydrate, which is widely used for the reduction of solid-phase bound nitro groups and which

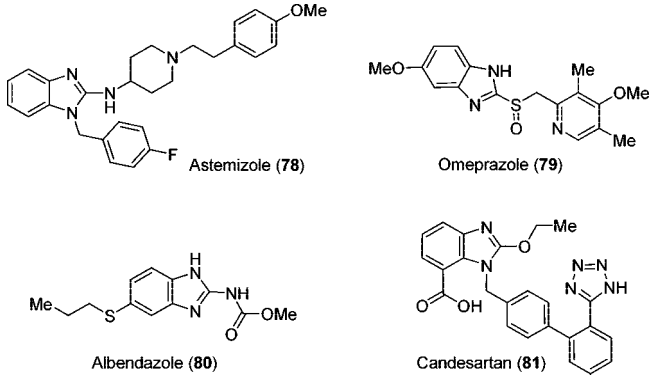
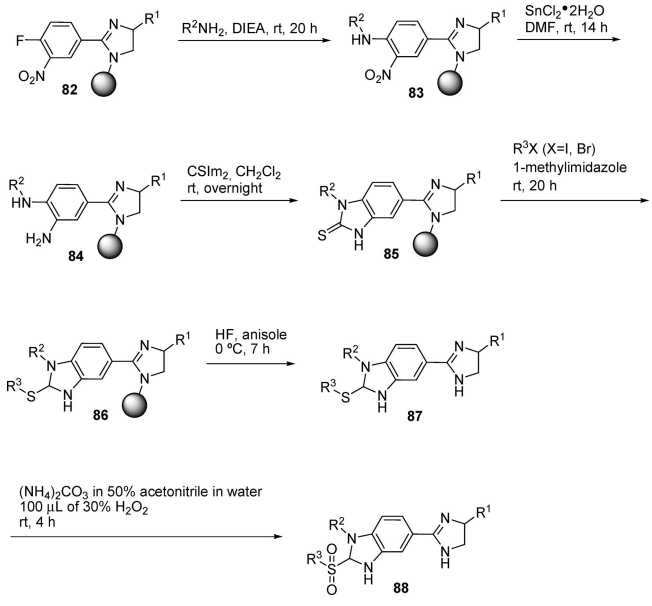
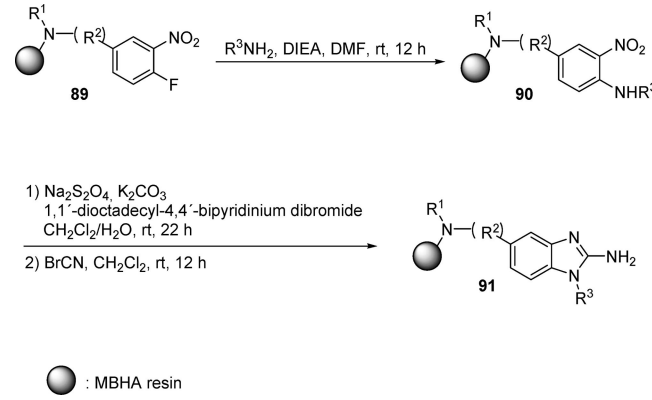


Figure 2. Pharmacological relevant molecules with a benzimidazole moiety.

Scheme 14. Synthesis of Thiobenzimidazole by Acharya et al.[74]



Scheme 15. Parallel Synthesis of Aminobenzimidazoles by Hoesl et al.[75]

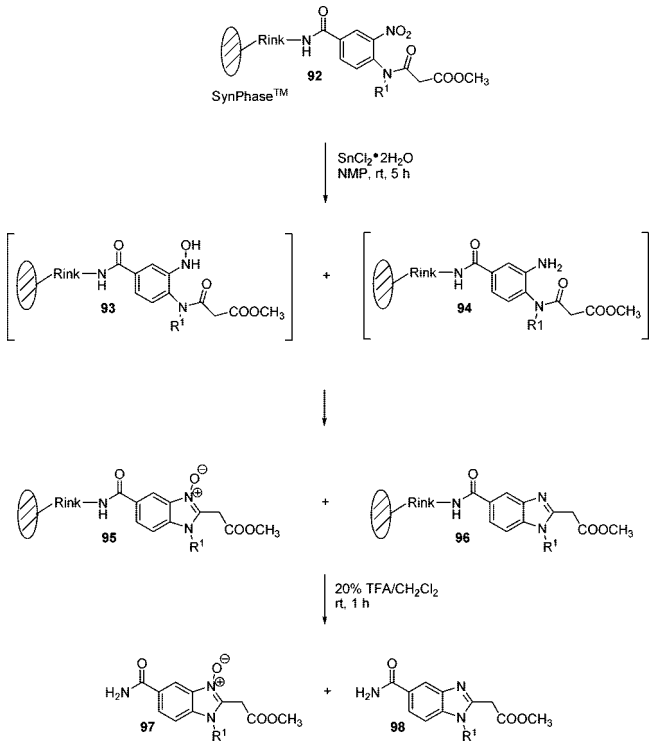


is reported to be problematic due to toxic tin species remaining within the resin.[76] Finally, cyclization with cyanogen bromide yielded a wide range of 2-amino-benzimidazoles **91** bound to the MBHA resin either by an amide or amino acid linkage in purities greater than 95% (Scheme 15).

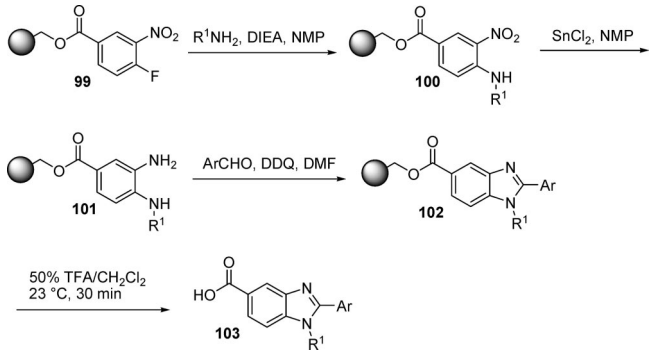
A set of nine benzimidazole *N*-oxides was prepared for the first time on SynPhase Lanterns by Wu et al. (Scheme 16).[77] The authors used a reduction-cyclization methodology which involved the reduction of an arylnitro **92** to a hydroxyamino intermediate **93**, which subsequently condensed with an internal carbonyl group to give a benzimidazole *N*-oxide **95**. Moreover, the benzimidazole *N*-oxides **97** were contaminated by a small amount of benzimidazole **98** because of cyclization of the arylaniline **94** obtained as a secondary product after the reduction of the arylnitro derivative **92**. In an attempt to eliminate the minor product, the reduction-cyclization was optimized by varying reaction solvent, concentration of tin(II) chloride dihydrate and reaction time. Although formation of the benzimidazole **98** could not be completely eliminated, the final purity of benzimidazole *N*-oxides **97** ranged from 59 to 85% while the average yield of the library was about 70%.

Vourloumis et al.[78] accomplished the formation of the benzimidazole nucleus by the treatment of anilines **101** with aromatic aldehydes in the presence of DDQ, furnishing **102** (Scheme 17). Anilines **101** were previously formed after reduction of the nitro-functionality in resin **100** with $SnCl_2$ in NMP. Later has been shown that inclusion of DDQ is

Scheme 16. Synthesis of Benzimidazole *N*-Oxides by Wu et al.[77]



Scheme 17. Synthesis of Benzimidazole on Solid Supports by Vourloum is et al.[78]

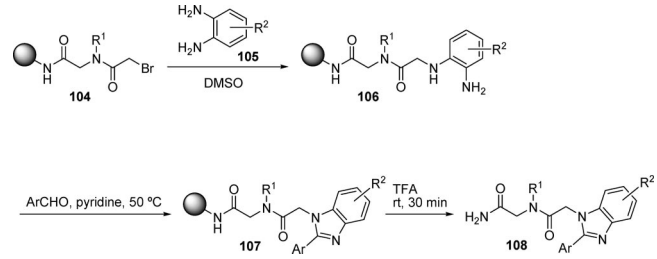


not necessary and that exposure to air overnight is sufficient to induce the oxidative cyclocondensation, producing the desired benzimidazoles on solid-phase. Cleavage from the solid support was performed by the use of a 50% TFA solution in CH_2Cl_2, furnishing benzimidazoles in 41% overall average yield and 94% average purity, which were evaluated against a variety of different bacterial and viral RNA-targets.

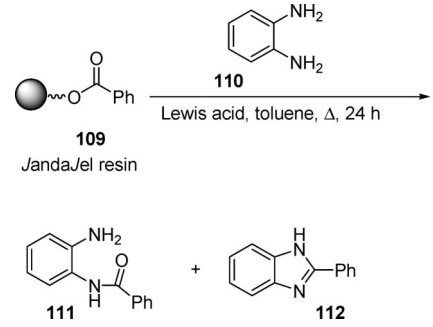
In a similar way, the nucleophilic aromatic displacement was also the key step to obtain 1-pyrazol-3-ylbenzimidazoles from 4-fluoro-3-nitrobenzoate derivatives and 3-amino-5-subtituted-1*H*-pyrazoles.[79]

Another simple and efficient method for the solid-phase synthesis of benzimidazole libraries was described by Akamatsu et al.[80] In this case, monoalkylation of various *o*-phenylenediamines on resin-bound bromoacetamide **104** proceeded smoothly to give the monoalkyl resin-bound *o*-phenylenediamines **106** in high yields. Subsequent cyclization of the diamines with various aldehydes afforded solid-supported benzimidazoles **107** (Scheme 18). Cleavage

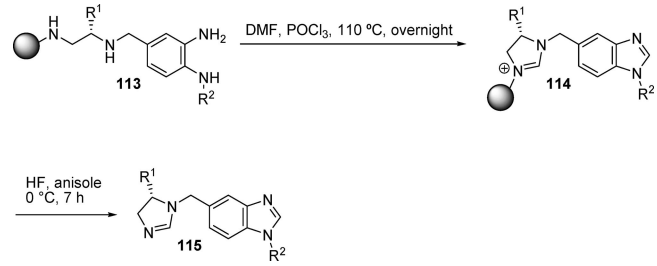
Scheme 18. Solid-Phase Synthesis of Benzimidazoles by Akamatsu et al.[80]



Scheme 19. Solid-Phase Synthesis of Benzimidazoles from Polymer-Bound Esters by Matsushita et al.[81]



Scheme 20. Solid-Phase Synthesis of Imidazolylbenzimidazoles by Acharya et al.[82]



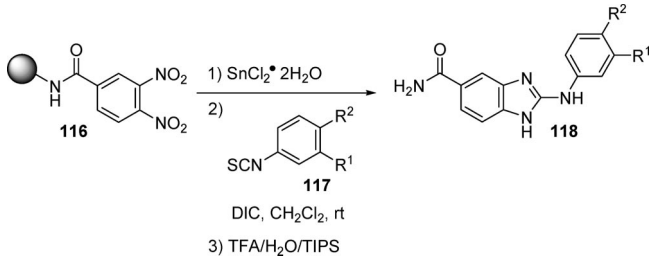
from the resin gave a library of thirty benzimidazoles **108** in good yields. This method allowed diversity to be introduced on the benzene ring of the benzimidazoles by using commercially available aromatic diamines.

Matsushita et al. described the conversion of polymer-bound esters **109** into the corresponding benzimidazoles by reaction with 1,2-phenylenediamine (**110**) in the presence of a Lewis acid (Scheme 19). The effects of the type of Lewis acid and the ratio of amino substrate **110** to Lewis acid were also studied.[81]

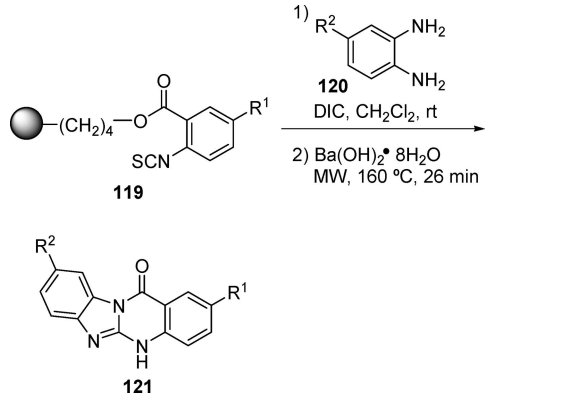
A straightforward one-pot cyclization of a tetraamine having two secondary amines and an *o*-dianiline using Vilsmeier reagent (DMF in the presence of phosphorus oxychloride) to yield disubstituted 4,5-dihydro-1*H*-imidazolylbenzimidazoles **114** was reported by Acharya et al.[82] The cleavage from the solid support was accomplished by using anhydrous HF. Twelve derivatives **115** were obtained in moderate yield and good purity (Scheme 20). The authors also highlighted the introduction of diversity at the N1 position of the dihydroimidazole moiety.

Furthermore Carpenter et al.[83] have demonstrated a mild, one-pot solid-phase synthesis to four *N*-2-arylamino-benzimidazoles **118** by condensation of intermediate thioureas by carbodiimide reagents (Scheme 21). On solid supports, carbodiimide reagents are generally used because

Scheme 21. Carbodiimide-Based Benzimidazole Library by Carpenter et al.[83]



Scheme 22. Microwave-Assisted Synthesis of Benzimidazoquinazolinones by Carpenter et al.[86]



of the ease of washing away DIC and the thiourea byproduct as the resin is filtered. This simple, quite general one-pot aryl isothiocyanate to benzimidazole approach delivers the benzimidazole system in good yields from commercially available materials, and mild reaction conditions enable heterocycle construction in either solution- or on solid-phases.

Microwave-assisted synthesis has been applied successfully to obtain benzimidazoles. Su and Sun[84] have reported the first multistep microwave-assisted method for the bismuth chloride catalyzed synthesis of 1,2-disubstituted benzimidazoles on soluble polymer supports. Biologically interesting benzimidazoles were readily assembled using a S_NAr reaction, followed by reduction and finally a bismuth(III)-mediated cyclization under microwave irradiation. The desired products were then liberated from the soluble matrix in excellent yield and purity. All steps in the synthesis were performed under microwave conditions. The microwave irradiation proved also highly effective for the condensation of resin-bounds esters with 1,2-phenylenediamines, 2-aminophenols, and 2-aminothiophenol to yield benzimidazoles, benzoxazoles, and benzothiazoles libraries, respectively.[85]

An effective route to eight benzimidazo[2,1-*b*]quinazolin-12(5*H*)-ones **121** (85−93% overall yield) from commercially available *o*-aryl isothiocyanate esters **119** and *o*-phenylenediamines **120** has been reported.[86] This method accommodates a variety of substituents on both of the starting materials and proceeds under microwave irradiation in the presence of barium hydroxide (Scheme 22). The pharmacologically important benzimidazoquinazolinone heterocycle can be achieved in excellent yield and purity via both solution- and solid-phase protocols, the latter involving traceless cleavage from the resin.

New strategies have been developed to the simultaneous synthesis of two different scaffolds called "one-bead-two-compound", in which via a single synthetic sequence the scaffold diversity of small molecule heterocycles is doubled. In this way, Ji et al.[87] achieved a solid-phase approach to six fluorobenzimidazoles **130** and six fluoro-2-hydroxyquinoxalines **132** in moderate yields but good purities (Scheme 23). The precursor, 6-nitro-2,3,4,5-tetrafluorobenzoic acid (NTFBA), was tagged to Rink amide MBHA resin via an α-amino acid linker. The first nucleophilic substitution generated two regioisomers in which the second active fluorine atom underwent a subsequent nucleophilic substitution with a primary amine. The reduction of the aryl nitro groups with $SnCl_2 \cdot 2H_2O$/NMM and the formation of a five-membered ring with aldehydes afforded **129**. Fluorobenzimidazoles **130** were directly furnished by cleavage using TFA; then, the stable six-membered ring **132** was produced by concomitant intramolecular cyclization and thermal dehydrogenation. In addition to the introduction of fluorine into the heterocycles, two scaffolds could be simultaneously synthesized with this method.

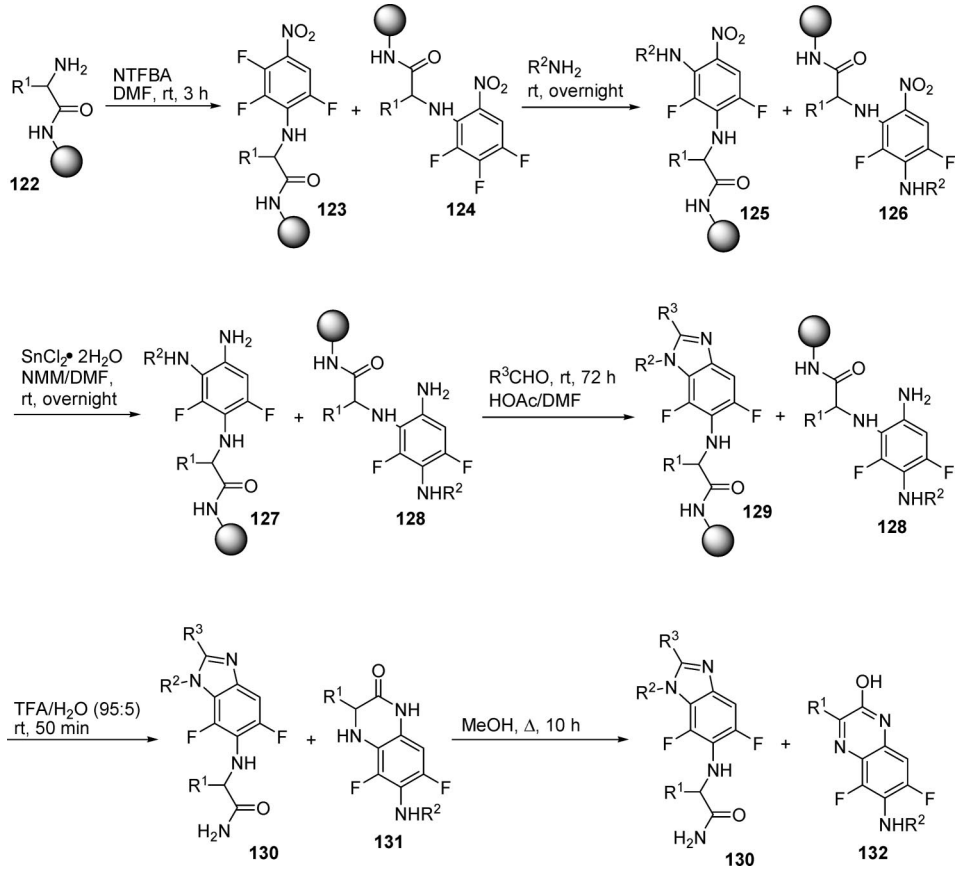
Kou et al.[88] described another method for the simultaneous solid-phase synthesis of a quinoxalinone **136** (10−60% yield) and benzimidazole **137** (over 80% yield) scaffold library of 240 members (Scheme 24). The library was generated by using the solid-phase "split and pool" approach and the IRORI sorting system.

Purandare et al.[89] reported a novel and efficient solid-phase methodology for the synthesis of benzimidazole derivatives from *o*-fluoronitrobenzoic acid (Scheme 25). The intermediate *o*-nitroaniline **138**, proceeded from the displacement of a fluorine atom with a primary amine. To access the benzimidazole core, the nitro group in compound **138** was reduced with tin (II) chloride in DMF to furnish the phenylenediamide **139**. Finally, the cyclization was efficiently carried out using triphosgene and upon cleavage the benzoimidazol-2-one **140** derivative was achieved (65−79% yield). Heating the suspension of **139** in trimethylorthoformate, followed by cleavage from the resin, gave the benzoimidazole **141** (72−84% yield). Wang et al.[90] reported the solid-phase synthesis of benzimidazolones after the introduction of one of the nitrogens by nucleophilic substitution of a carbamate to an *o*-fluoronitrobenzene and spontaneous cyclization and detachment from the resin under reductive conditions.

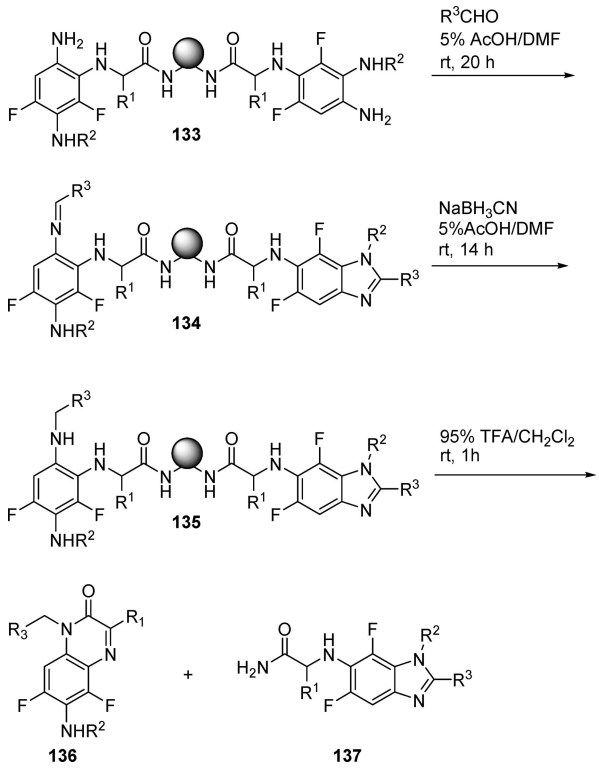
Combinatorial synthesis of 2-arylbenzothioazoles and 2-arylbenzimidazoles was described by Hioki et al.[91,92] using a traceless aniline linker. This synthetic method has the advantage that the products are cleavable without the aid of oxidants under neutral conditions.

Using the 4-chloro-7-fluoro-6-nitroquinazoline scaffold as the core structure, Zhang et al.[93] have demonstrated a novel approach for the parallel solid-phase synthesis of seventeen 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines **144** from common building blocks, such as arylamines (R^1), alkylamines (R^2), and alkylaldehydes (R^3) using the "tea-bag" methodology (Scheme 26). The yields and purities of the products were dependent on the nature of the substituents of arylamines.

Scheme 23. Solid-Phase Synthesis of Fluorobenzimidazoles and Fluoro-2-hydroxyquinoxalines by Ji et al.[87]



Scheme 24. Solid-Phase Synthesis of Benzimidazoles and Quinoxalinones by Kou et al.[88]



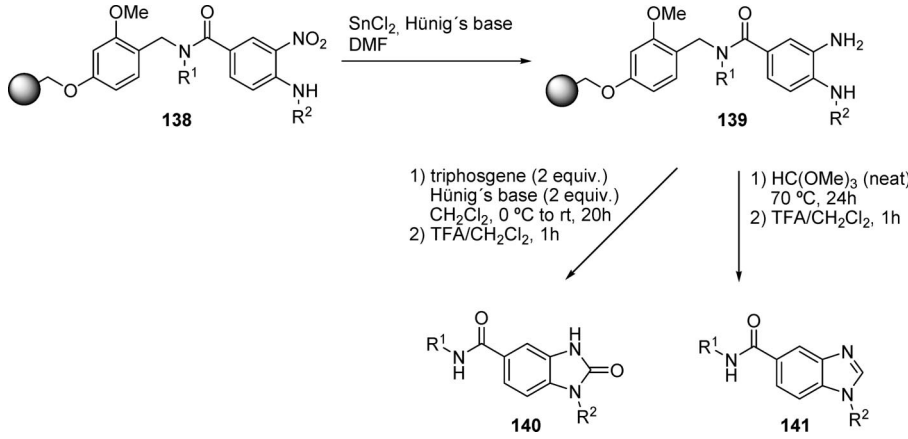
In 2004, Roy et al.[94] developed an efficient method for the synthesis of a new benzoimidazole-based intermediate that resulted from an unusual rearrangement on solid-phase observed during the *S*-alkylation of benzoimidazole-2-thione with α-haloacetophenone.

Vickerstaffe et al.[95] described an efficient, fully automated, multistep polymer-assisted solution phase approach to benzimidazoles. Individual synthesis steps were integrated on a single synthesis robot that was able to perform multiple steps in an unattended manner and thereby maximize the advantages inherent in the use of polymer-supported reagents. These methods have been exemplified by the preparation of a 96-membered 2-alkylthiobenzimidazole library (average isolated yield 72%) and a 72-membered *N*,*N*′-dialkylbenzimidazolin-2-one library (average isolated yield 57%).

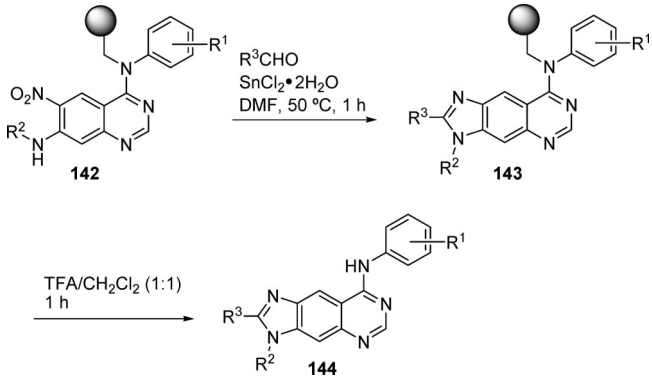
2.3. Benzotriazoles. The nonsteroidal aromatase inhibitor Vorozole (**145**)[96] and also the antiemetic Alizapride (**146**)[97] are benzotriazole derivatives (Figure 3). Recently, 1-substituted benzotriazole carboxylic acids have been identified as the first reported examples of selective small-molecule agonists of the human orphan G-protein-coupled receptor GPR109b (HM74).[98] New benzotriazole derivatives have also demonstrated inhibitory properties against different kinases.[99,100]

The preparation of 1-alkyl and 1-aryl benzotriazoles from symmetrical and unsymmetrical diamines by diazotation is well-known, and a solid-phase approach was reported by Lormann et al. (Scheme 27).[101] They investigated the conversion of the polymer-bound fluoronitroaryl triazenes **147** to 1-alkyl benzotriazoles. The cleavage of triazene-bound anilines **147** with trifluoroacetic acid in dichloromethane proceeded smoothly at room temperature within minutes to give the desired 1-alkyl-5-nitro-1*H*-benzotriazole **149** in

Scheme 25. Solid-Phase Synthesis of Benzimidazoles by Purandare et al.[89]



Scheme 26. Synthesis of imidazoquinazolines on solid supports by Zhang et al.[93]

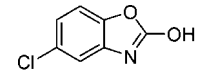


excellent yields and purities. Lormann et al. also demonstrated the reduction of nitroarenes on solid-supports, the subsequent cyclative cleavage to aminobenzotriazoles,[76] and a versatile route to 1-alkyl- and 1-aryl-1*H*-benzotriazoles based on Hartwig−Buchwald amination.[102] The report on the reductive amination of triazene-bound anilines to give benzotriazoles after cleavage has allowed the extension of the chemical transformation to be carried out on solid supports.[103]

2.4. Benzoxazoles. Besides the well-known anti-inflammatory Benoxaprofen[104] and skeletal muscle relaxant Chlorzoxazone (**150**),[105] new biological properties has been found for this kind of heterocycles (Figure 4). They have shown to be promising antimicrobials,[106] DNA topoisomerase I and II inhibitors,[107] or vascular endothelial growth factor-2 receptor tyrosine kinase inhibitors.[108]

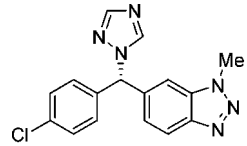
Berta et al.[109] have developed a highly effective route for the synthesis of 2-(3-aryl-1*H*-pyrazol-4-yl)-1,3-benzoxazoles using a stepwise solid-phase path with a dehydrative Mitsunobu cyclization as the key step (Scheme 28). *N*-(2-hydroxyphenyl)amides **151** were cyclized by Mitsunobu reactions to form four variants of the pyrazolyl-benzoxazole core template **152** as protein kinase inhibitors.

The combination of a parallel synthesizer and a microwave reactor allowed the synthesis of a collection of substituted benzoxaxoles in high purities and satisfactory yields.[110] A 28-membered library was obtained in one-pot and two-step protocol. The reaction of different polymer-bound esters

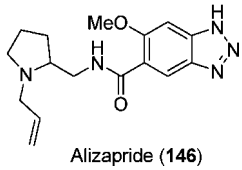


Chlorzoxazone (**150**)

Figure 4. Structure of Chlorzoxazone (**150**).



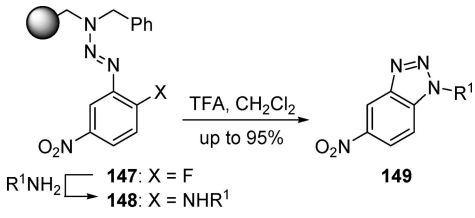
Vorozole (**145**)



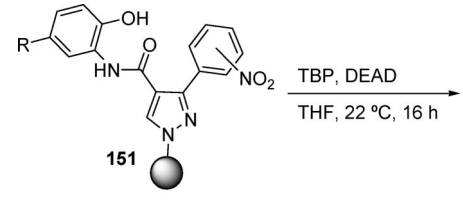
Alizapride (**146**)

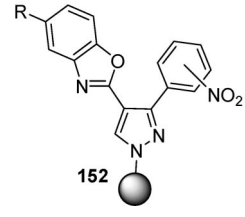
Figure 3. Structures of Vorozole (**145**) and Alizapride (**146**).

Scheme 27. Solid-Phase Synthesis of Benzotriazoles by Lormann et al.[101]

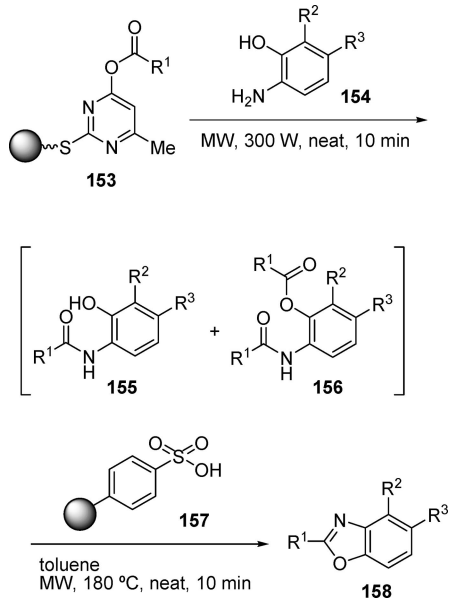


Scheme 28. Synthesis of Pyrazol-4-yl-1,3-benzoxazoles on Solid Supports by Berta et al.[109]





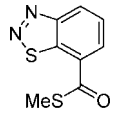
Scheme 29. Microwave-Assisted Solid-Phase Synthesis of Benzoxazoles by Radi et al.[110]



(**153**) with an excess of different aminophenols **154** shifted the equilibrium toward the formation of the uncyclized intermediates (**155** and **156**). The PTSA polymer bound (**157**) added in the second step allowed to scavenge the unreacted basic species and to catalyze the cyclodehydration reaction. Final removal of the combined solid supports by filtration allowed to isolate the pure products (**158**) (Scheme 29).

2.5. Benzothiadiazoles. 1,2,3-Thiadiazoles are heterocycles of great practical and theoretical interest in the agriculture. Derivatives of benzo[1,2,3]thiadiazoles have been recognized as the first synthetic chemical plant activators, which can induce disease resistance in plants, the so-called systemic acquired resistance. The *S*-methyl ester of benzo-[1,2,3]thiadiazole-7-thiocarboxylic acid (acibenzolar-*S*-methylester) (**159**) was introduced as Bion or Actigard, respectively, as the first commercial product of this type (Figure 5).[111]

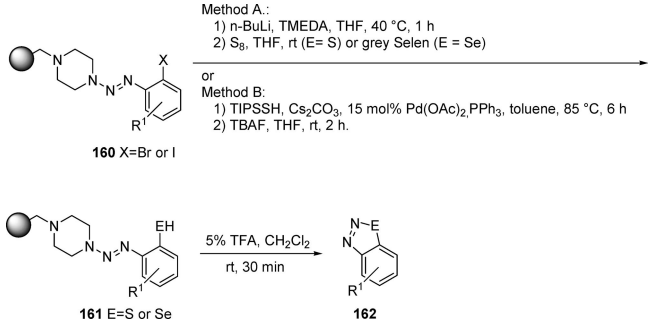
The first solid-phase synthesis of benzo[1,2,3]thiadiazoles was achieved from resin-bound *ortho*-bromo- or -iodo



Bion® (**159**)

Figure 5. Structure of Bion (**159**).

Scheme 30. Solid-Phase Synthesis of Benzo[1,2,3]thiadiazoles by Kreis et al.[112]



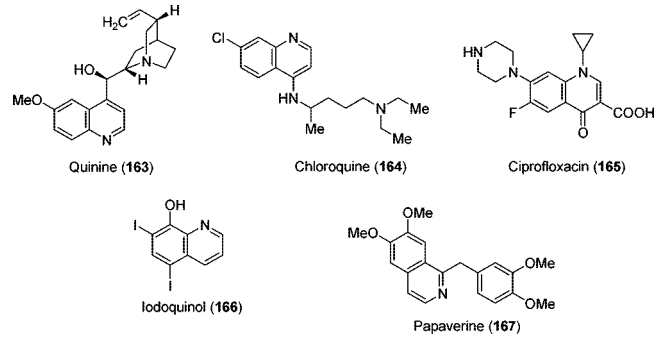


Figure 6. Structures of medicinally relevant quinolines.

triazenes **160** (Scheme 30).[112] Cleavage from the resin with diluted trifluoroacetic acid resulted spontaneously in the desired cyclization reaction yielding benzo[1,2,3]thiadiazoles **162** (E = S) in good yields. Both, *ortho*-bromo and *ortho*-iodo anilines are excellent substrates for the synthesis of this kind of heterocycles. Considering the success of the methodology, the authors employed the strategy in the synthesis of benzo[1,2,3]selenadiazole **161** (E = Se), which could be synthesized by the lithiation protocol in a good yield (63%) and purity. Benzo[1,2,3]selenadiazoles are only scarcely found in literature and show antioxidative as well as antibacterial activities.[113,114]

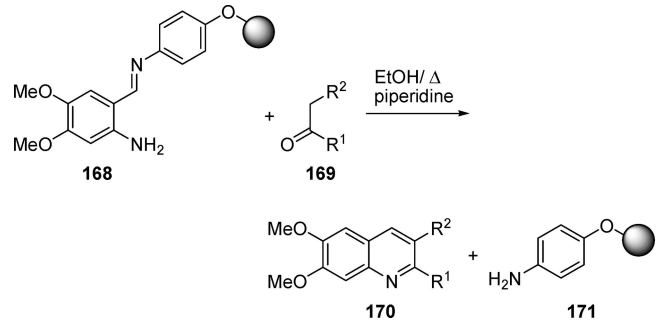
2.6. Benzofuroxanes. Avemaria et al.[115] reported the solid-phase synthesis of benzofuroxanes. The key step is the cleavage of *ortho*-nitroazides from polymer-bound triazenes and subsequent thermolysis.

3. Benzoannelated Six-Membered Heterocycles

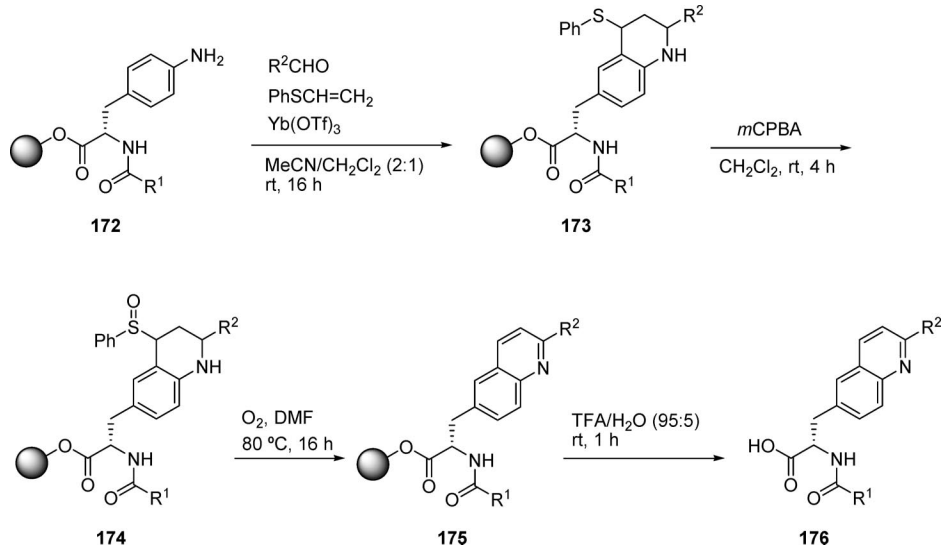
3.1. (Tetrahydro)quinolines and (Tetrahydro)isoquinoline. The quinoline nucleus is widespread among natural and synthetic products with significant biological activities (Figure 6). There are a number of commercial drugs containing this core, for example the antimalarials Quinine (**163**) and Chloroquine (**164**) and derivatives,[116] the fluorinated quinolone antibacterials as Ciprofloxacin (**165**),[117] the antiamebic Iodoquinol (**166**)[118] or the cerebral vasodilator Papaverine (**167**) found in opium.[119] Compounds with this scaffold were also recently reported as promising nicotic ligands,[120] nonsteroidal inhibitors of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1),[121] or potent CB_2-selective cannabinoid receptor ligands.[122]

Because quinoline derivatives are found in many medicinally interesting compounds, researchers have continued to improve traditional methods and develop new strategies for

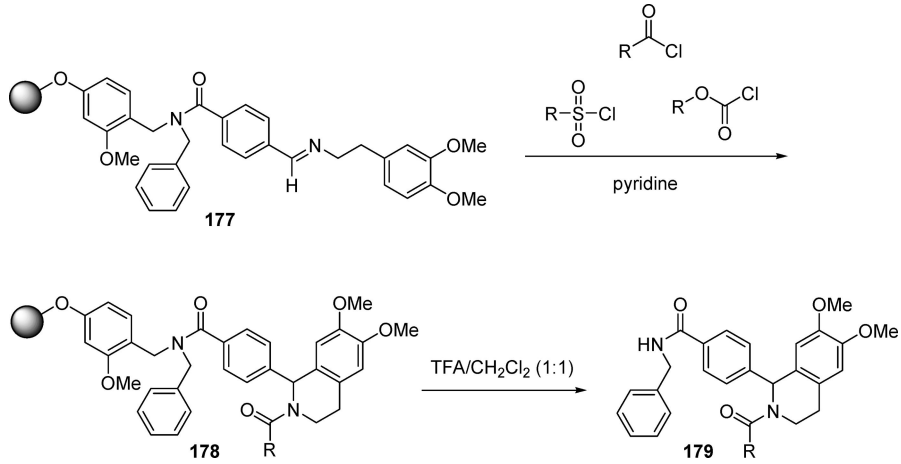
Scheme 31. Solid-Phase Synthesis of Quinolines by Patteux et al.[123]



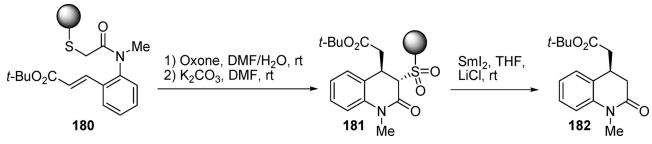
Scheme 32. Synthesis of Tetrahydroquinolines by Demaude et al.[124]



Scheme 33. Solid-Phase Synthesis of Tetrahydroquinolines via Pictet−Spengler Reaction by Sun and Kyle.[127]



Scheme 34. Solid-Phase Approach to Tetrahydroquinolones Using a Sulfur Linker by Procter et al.[130]



their preparation. Despite advances in methodologies for the synthesis of quinoline derivatives, it is still challenging to explore new and efficient synthetic routes, especially for library production and solid-phase applications. In this sense, Patteux et al.[123] described a new solid-phase synthesis of quinolines based on a Friedländer-type reaction between the resin-bound azomethine **168** and ketone **169** (Scheme 31). This cyclative cleavage approach affords six quinolines **170** in 50−80% yields. An additional advantage of this procedure is that the polymer-bound aniline equivalent (**171**) easily can be recycled and reused with comparable performance.

An interesting synthetic pathway to 2-substituted quinolines was reported by Demaude et al.[124] by using 1,2,3,4-tetrahydroquinolines as intermediates based on a multicomponent reaction and its application to library production, both in liquid phase and on solid phase. The solid-phase approach used L-4-nitrophenylalanine as starting material. By using Kobayashi's modification of the Grieco reaction, the authors obtained tetrahydroquinolines **173** that were subsequently transformed in quinolines **175** (Scheme 32). This method permits the condensation of anilines, aldehydes, and electron-rich alkenes using lanthanide triflates as Lewis acid catalysts. A 16-membered library was synthesized according to this methodology with isolated yields from 18 to 47% and purities >95% in all cases. Several members displayed high potency as VLA-4 (very late antigen-4) antagonists, which could be useful for the treatment of inflammatory diseases.

The use of a novel and versatile resin-bound (succinimid-1-yloxycarbonylmethyl)triphenylphosphonium ylide under microwave heating, was reported by Henkel[125] as an excellent tool for rapid access to diverse heterocycles as quinolin-2(1*H*)-ones.

Widespread interest in this core structure has stimulated the conception of many synthetic approaches, several of which described the solid-phase synthesis of tetrahydroisoquinolines. Spaller et al.[126] reported the utility of the *aza*-Diels−Alder reaction to afford a series of configurationally and functionally diverse heterocyclic compounds as different tetrahydroquinoline products. Sun and Kyle[127] reported an

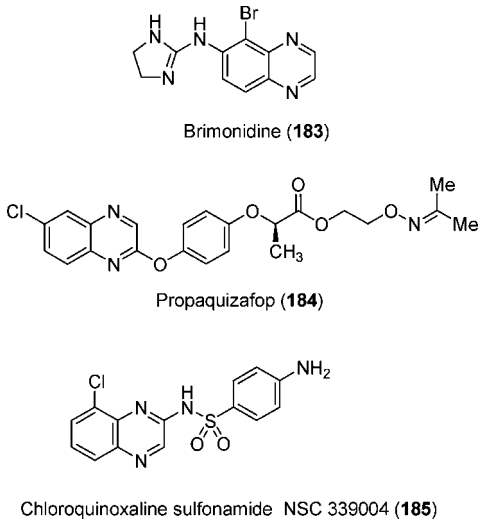


Figure 7. Structures of biologically relevant quinoxalines.

efficient parallel solid-phase synthesis, where the key reaction step is 3,4-dimethoxyphenethylimines **177** reacting with acid chlorides to form an *N*-acyliminium ion intermediate, which undergoes Pictet−Spengler condensation to give ten desired products in >80% yield (Scheme 33). In addition, Nielsen et al.[128,129] expanded the scope of the solid-phase intramolecular *N*-acyliminium Pictet−Spengler reaction toward the synthesis of pharmacologically interesting pyrroloisoquinolines, which were explored in on-bead screening for agonistic activity at G-protein coupled receptor.

A new linker system that used a sulfur α-heteroatom-substituted carbonyl (HASC) in a solid-phase approach to tetrahydroquinolones was developed by Procter et al.[57,130] (Scheme 34). The route illustrates the compatibility of the linker system with palladium-catalyzed transformations and its utility for library synthesis. The linker is cleaved by electron transfer from samarium(II) iodide and allowed the isolation of the desired compound **182** in a yield of 57%.

3.2. Quinoxalines. This kind of heterocycle is present in the antiglaucoma drug Brimonidine (**183**),[131] the herbicide Propaquizafop (**184**),[132] or the antitumor agent chloroquinoxaline sulfonamide NSC 339004 (**185**)[133] (Figure 7).

An efficient methodology for the solid-phase synthesis of isomerically pure quinoxalines of high purity was reported by Shing et al.[134] (Scheme 35). Polymer-linked 2-nitrophenyl carbamate was treated with α-bromoketones, followed by reduction of the nitro group, which underwent spontaneous intramolecular cyclization afforded polymer-bound quinoxalines **188**. Finally acidolytic cleavage gave fourteen desired compounds **190** via aerial oxidation in high yields and good purities.

An efficient approach for the solid-phase synthesis of dihydroimidazolyl dihydroquinoxalin-2(1*H*)-ones **193** was described by Acharya et al.[74,135] (Scheme 36). Substituted dihydroimidazoles were prepared from the resin-bound reduced amino acid amides via cyclization of the in situ formed imidoyl chloride intermediate. The dihydroquinoxalines **192** were obtained after reduction of the aromatic nitro group and the concomitant intramolecular cyclization. Eighty individual quinoxalines were cleaved from the solid-support using anhydrous HF in moderate yield and in high purity.

Dixon et al.[136] reported a synthetic route to dihydroquinoxalines **195** (Scheme 37). In this case, the fused heterocyclic system was achieved via a benzyne heterocyclization initiated by dehydrofluorination with lithium tert-butoxide. Acid treatment released the quinoxaline **195** in 68% yield.

As we commented in the benzimidazole section, using the "one-bead-two-compound" strategy, Ji et al.[87] reported a solid-phase approach to fluorobenzimidazoles **130** and fluoro-2-hydroxyquinoxalines **132** (Scheme 23). In addition to benzimidazoles, Purandare et al.[89] reported a solid-phase synthetic methodology for quinoxaline derivatives starting from *ortho*-fluoronitrobenzoic acid.

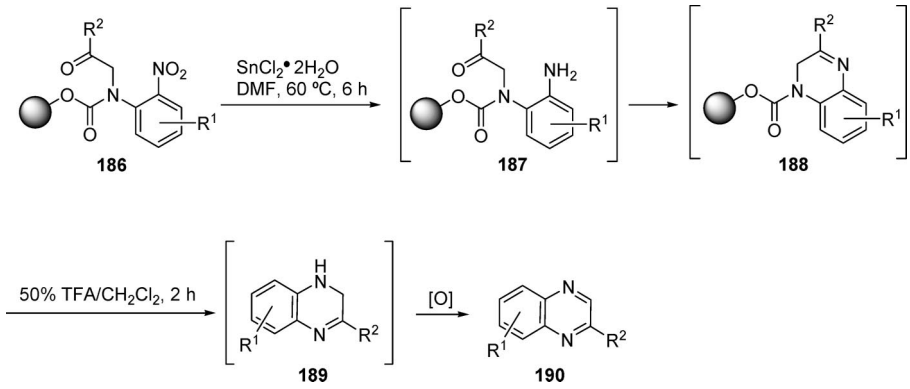
3.3. Quinazolines. Related heterocycles of the quinazoline ring have significant antihypertensive properties as the specific serotonin ($5HT_2$)-receptor antagonist Ketanserin (**196**) or the α_1-adrenergic blocker Prazosin (**197**) and related derivatives (Figure 8). Trimetrexate is another interesting quinazoline used for the treatment of *Pneumocystis carinii.*

Molecules containing the quinazoline moiety have efficiently been synthesized for more than 140 years in solution, and more recently solid-phase approaches have been described.[137] In this way, Yu et al.[138] described a traceless parallel solid-phase synthesis of 2-arylamino-substituted quinazolinones **199**. Acylation of MBHA resin with *o*-nitrobenzoic acid derivatives, followed by reduction of the nitro group with tin (II) chloride, generated a resin-bound *o*-anilino derivative. Reaction of resin-bound *o*-anilino derivative with arylisothiocyanates yielded resin-bound thioureas, which reacted with amines in the present of Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) to afford resin-bound guanidines **198**. After an intramolecular cyclization of the resin-bound guanidines, and cleavage from the resin by treatment with HF/anisole, eleven quinazolines **199** were obtained in good yields and purities (Scheme 38). Another traceless approach to 18 quinazolines was reported by Hioki et al.[139] using 4-alkoxy aniline linker.

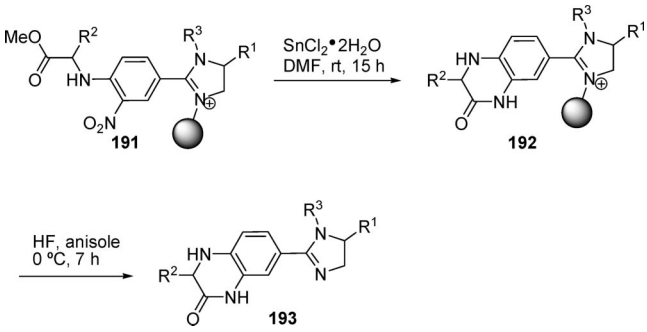
Makino et al. have worked extensively on the solid-phase synthesis of quinazoline-2,4-diones and their analogues starting from resin-bound compounds with primary amines (Scheme 39).[140]

They developed the first solid-phase synthesis of 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides **207** (Scheme 40).[141,142] Synthesis of the title compounds was achieved as follows: sulfonylation of solid-supported primary amines with 2-nitrobenzenesulfonylchlorides, reduction of the nitro group, cyclization with thiocarbonyldiimidazole (formation of thiourea **205**), and finally, *S*-alkylation or *S*-arylation of the thiourea. In addition to the excellent purities and the good yields of the derivatives **207**, a large-sized library can be synthesized with the method because this synthesis includes three diversity points. In a similar way, they developed a method for the synthesis of quinazoline-2,4-diones with electron-withdrawing substituents on the aromatic ring in which the immobilized anthranilamides were cyclized with carbonyldiimidazoles.[143] In addition, an efficient solid-phase synthesis of diverse 2-aminoquinazolin-4-ones from resin-bound anilines was reported by the same group.[144]

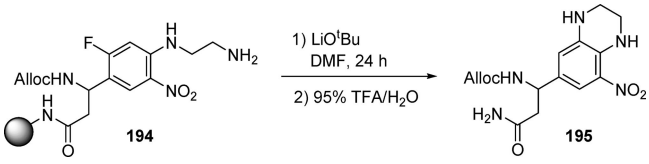
Scheme 35. Solid-Phase Synthesis of Quinoxalines by Shing et al.[134]



Scheme 36. Synthesis of Dihydroquinoxalinones by Acharya et al.[135]

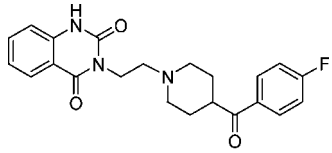


Scheme 37. Dihydroquinoxaline Synthesis by Dixon et al.[136]

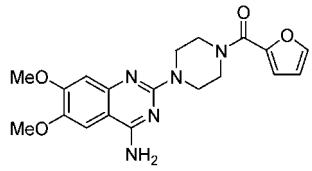


A 42-membered library of 3-aryl-2,4-quinazolinediones with various substitution on aromatic rings has been prepared in reasonable yields by Choo et al.[145] by cyclization of urethanes **208** with triethylamine in methanol at 60 °C for 24 h (Scheme 41). Several compounds showed selective cytotoxicity on human colon carcinoma (Col2).

A versatile method for the solid-phase synthesis of 2-aminoquinazoline-based derivatives, 3-substituted-3,4-dihydroquinazolin-2-amines and imidazoquinazolines, has been developed by Srivastava et al. (Scheme 42).[146] These



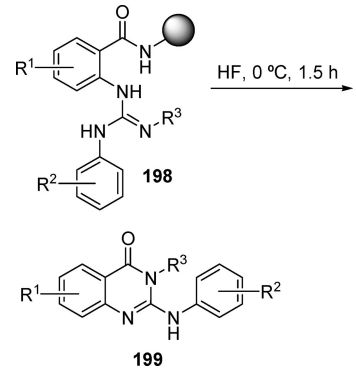
Ketanserin (**196**)



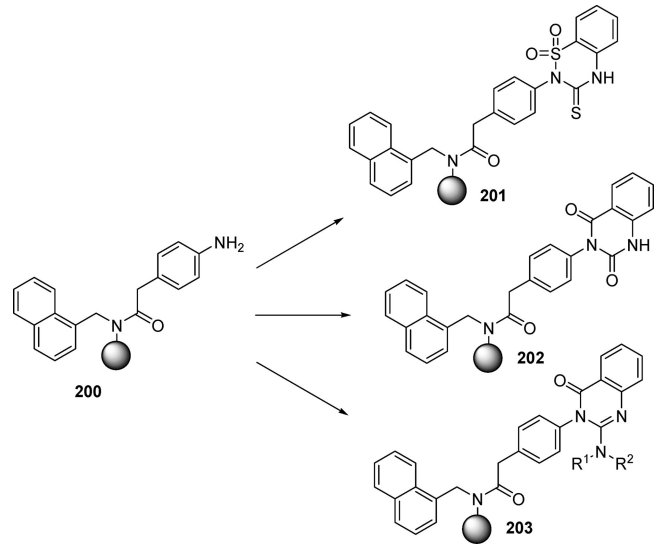
Prazosin (**197**)

Figure 8. Antihypertensive quinazolines.

Scheme 38. Solid-Phase Synthesis of 2-Arylamino Quinazolinones by Yu et al.[138]



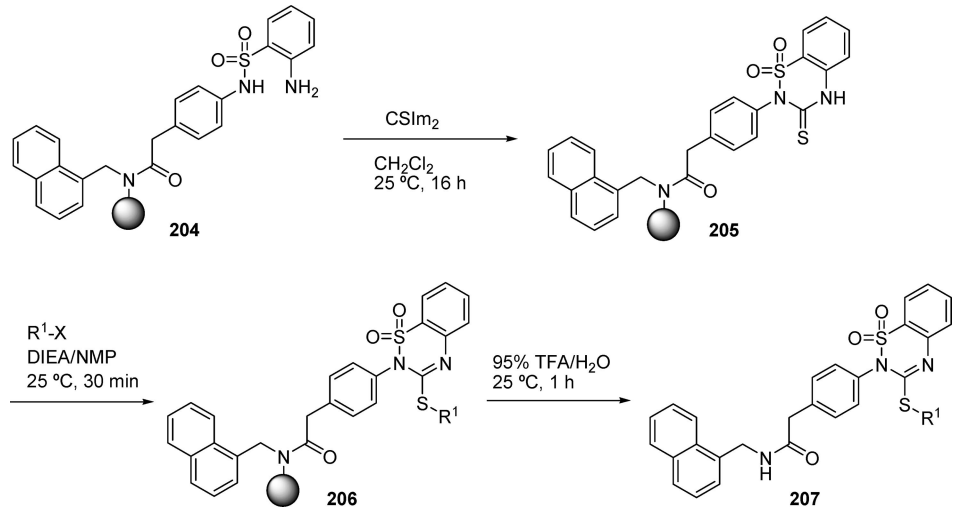
Scheme 39. Solid-Phase Synthesis of Quinazolinones by Makino et al.[140]



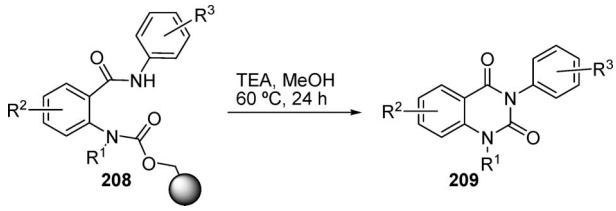
heterocycles were obtained by treating the amino group of polymer-linked amino acids with 2-nitrobenzaldehyde, followed by reduction of the nitro group to an amine. Cyclization of the resulting immobilized intermediates **210** with cyanogen bromide followed by acidic/basic cleavage yielded five desired quinazoline-based compounds **212** in excellent yields and purities.

The solid-phase synthesis of 3-alkyl-2-arylamino-3,4-dihydroquinazolines using an *N*-Fmoc-β-amino-2-nitrobenzenepropanoic acid scaffold was described by Song et al. (Scheme 43).[147] The resin-bound scaffold was reductively

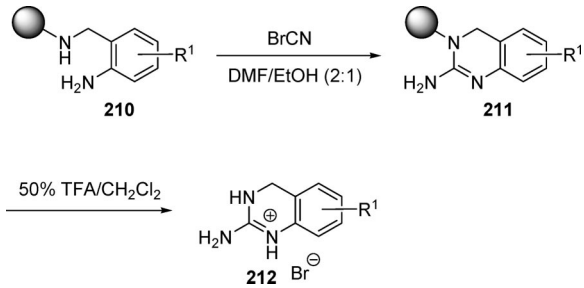
Scheme 40. Solid-Phase Synthesis of 1,2,4-Benzothiadiazine 1,1-Dioxides by Makino et al.[141]



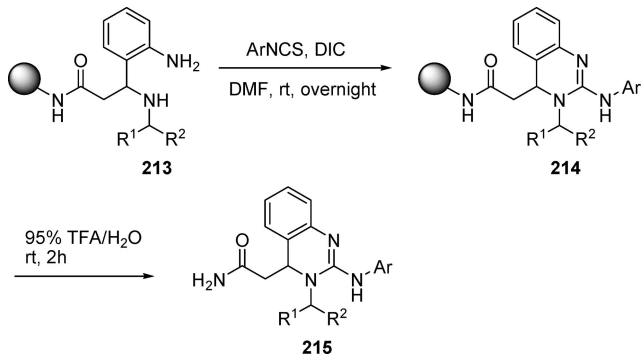
Scheme 41. Synthesis of 3-Aryl-2,4-quinazolinediones by Choo et al.[145]



Scheme 42. Solid-Phase Synthesis of 2-Aminoquinazolines by Srivastava et al.[146]

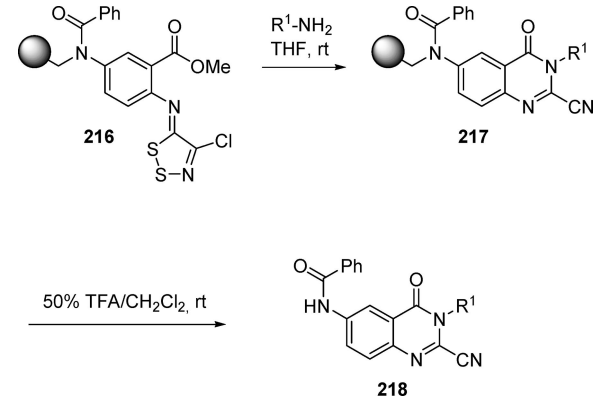


Scheme 43. Synthesis of Dihydroquinazolines Using DIC-Mediated Cyclization by Song et al.[147]



alkylated with aldehydes or ketones after Fmoc deprotection, followed by reduction of the nitro group with tin(II) chloride. Subsequent cyclization of the 1,3-diamine intermediates **213** with aryl isothiocyanates in the presence of 1,3-diisopropylcarbodiimide (DIC) afforded 19 desired products **215** in high purities with moderate to good yields after trifluoroacetic acid (TFA) cleavage of **214**. By using this DIC-mediated cyclization, Wang et al.[148] described a similar synthesis of 1,2-disubstituted-6-nitro-1,4-dihydroquinazolines.

Scheme 44. Synthesis of 2-Cyanoquinazolin-4(3*H*)-ones by Jeon et al.[149]

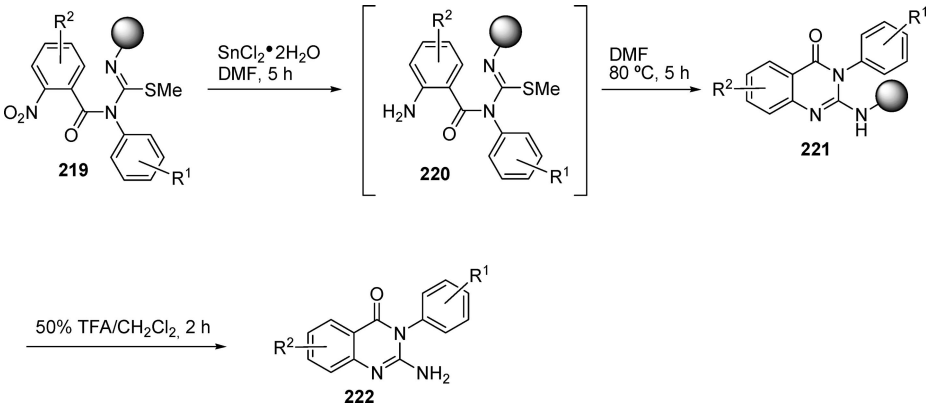


Jeon et al.[149] were able to obtain eight different 2-cyanoquinazolin-4(3*H*)-ones **218** in moderate yields from polymer-bound anthranilic acid derivatives via dithiazole resin **216** (Scheme 44).

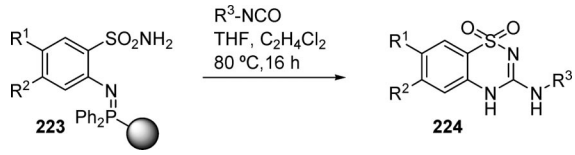
Kundu et al.[150] described a versatile solid-phase method for the synthesis of various substituted 2-amino-4(3*H*)-quinazolinones with two- and three-points of diversity (Scheme 45). The synthesis commenced with the generation of polymer-bound *S*-methylisothiourea, followed by N-acylation with different substituted *o*-nitrobenzoic acids. Finally, reduction of the nitro group triggered intramolecular cyclization via formation of guanidine to afford 2-amino-4(3*H*)-quinazolinone **222** and its derivatives in high yields and purities.

Blackburn et al.[151] have shown that reaction of *o*-azidobenzenesulfonamides with polymer-supported triphenylphosphine affords iminophosphoranes **223** that undergo a domino *aza*-Staudinger−Wittig heterocumulene annulation with isocyanates or sulfonylisocyanates releasing sixteen different 3-amino-1,2,4-benzothiadiazine 1,1-dioxides **224** into solution in good yields (Scheme 46).

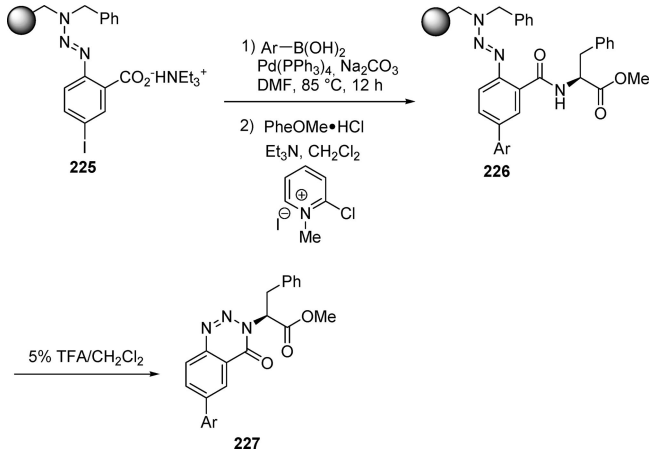
Scheme 45. Solid-Phase Synthesis of 2-Amino-4(3*H*)-quinazolinones by Kundu et al.[150]



Scheme 46. Synthesis of 3-Amino-1,2,4-benzothiadiazine 1,1-dioxides by Blackburn et al.[151]



Scheme 47. Synthesis of 1,2,3-Benzotriazin-4-ones Using Polymer-Bound Triazenes by Gil et al.[156]



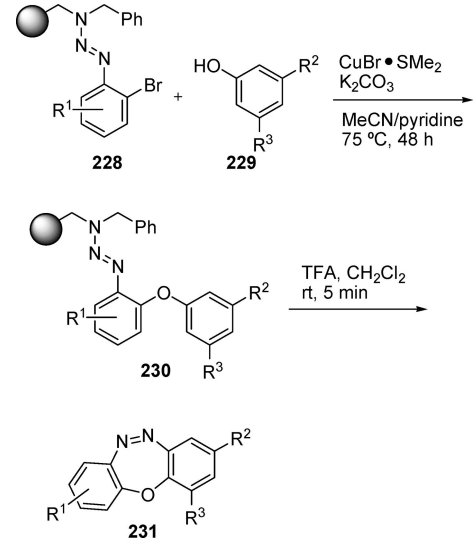
3.4. Benzotriazinones. Compounds containing this core have displayed biological activity as for example affinity for 5-HT_{1A} [152,153] or cytotoxicity.[154]

Solid-phase synthesis of benzotriazinone heterocycles has been developed by two approaches. Okuzumi et al.[155] achieved the synthesis of 1,2,3-benzotriazin-4-ones via cyclization of 2-aminobenzamides through diazotization, while Gil et al.[156] presented the synthesis using polymer-bound triazenes, upon cyclization of 38 suitable substituted benzamides (Scheme 47). The latter ones are accessible from carboxylate resins **225** and amines by peptide coupling methods. A second point of diversity was established in this case via a Suzuki-type reaction with arylboronic acids to yield a library of 6-aryl-3*H*-benzo-[*a*][1,2,3]triazinones **227** after cleavage in good overall yields.

4. Benzoannelated Seven-Membered Heterocycles

4.1. Benzazepines. During the search for inhibitors of the 17α-hydroxylase-C17,20-lyase and the testosteron-5α-reductase, which are target enzymes for the development of drugs used for the treatment of prostate cancer caused by hormones, two fluorinated to benzazepine type compounds were identified.[157]

Scheme 48. 5-Oxa-10,11-diazadibenzo[*a,d*]cycloheptenes by Intramolecular azo-Coupling by Knepper et al.[158]



Knepper et al.[158] described the solid-phase synthesis of fourteen 5-oxa-10,11-diazadibenzo[*a,d*]cycloheptenes **231** after a cyclization cleavage reaction in good overall yields. The diaryl ether moiety was constructed efficiently by coupling of aryl halides immobilized as triazenes **228** with 3,5-dimethoxyphenol and 3-dimethyl aminophenol, respectively, under basic conditions in presence of copper salts (Scheme 48).

4.2. Benzodiazepines. This molecular framework is one of the classical examples of privileged structures present in a number of bioactive molecules.[159] Since the disclosure of Chlordiazepoxide (**232**),[160] these kinds of compounds have shown remarkable potency in various biological targets and favorable pharmacokinetical properties.[161] Well-known

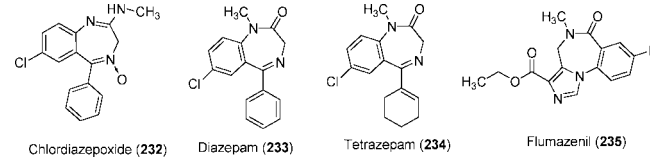
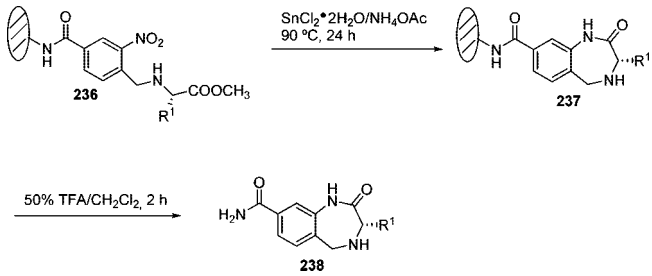
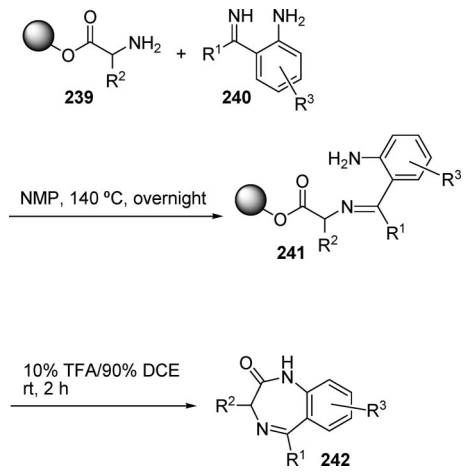


Figure 9. Structure of relevant molecules with benzodiazepine moiety.

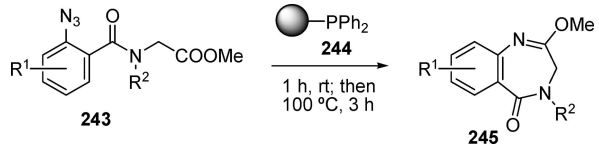
Scheme 49. Synthesis of Tetrahydro-1,4-benzodiazepine-2-ones on SynPhase Lanterns by Wu et al.[169]



Scheme 50. Synthesis of 1,3-Dihydro-1,4-benzodiazepine-2-one Derivatives by Laustsen et al.[170]

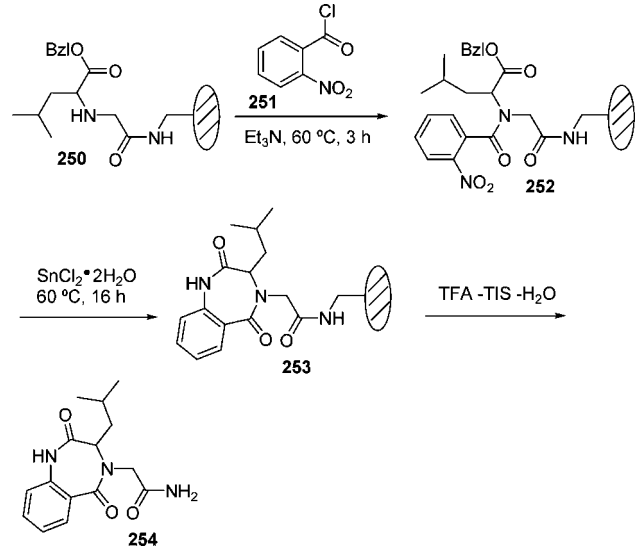


Scheme 51. Synthesis of 1,4-Benzodiazepine-5-ones by Gil and Bräse[171]



properties as anxiolytics, sedatives, anticonvulsants, or muscle relaxant have provided a plethora of trademarked drugs (Diazepam (**233**), Lorazepam, Midazolam, Triazolam, Clorazepate, Tetrazepam (**234**), Flunitrazepam, etc.) (Figure 9). Moreover, this scaffold continues to provide new ligands such as new agonist of melanocortin receptor,[162] selective inhibitors of falcipain-2,[163] selective checkpoint kinase 1 (Chk1) inhibitors,[164] or inhibitors of respiratory syncytial virus.[165] Also of great interest as antidote for the benzodiazepine toxicity is the antagonist Flumazenil (**235**).[166]

Scheme 53. Synthesis of Peptides Incorporating a Benzodiazepinone by Verdié et al.[174]

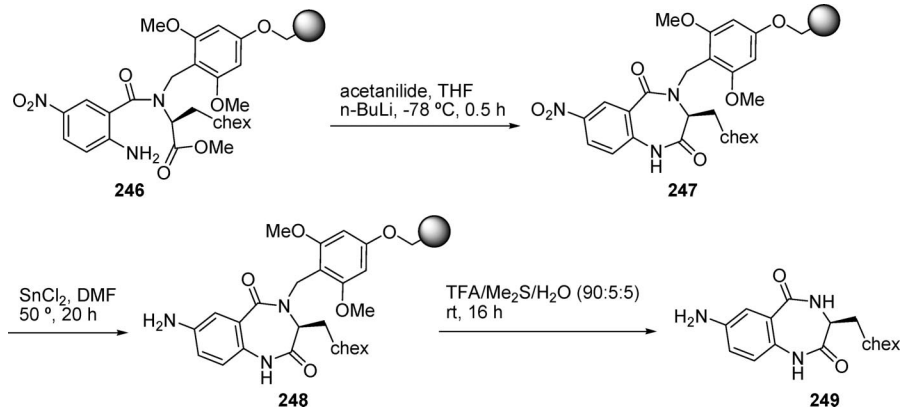


Since Ellman and co-workers published the landmark paper of solid-phase synthesis of 1,4-benzodiazepines in the early 1990s,[167] there has been increasing interest in solid-phase synthesis of both 1,4- and 1,5-benzodiazepines. Among 1,4-benzodiazepines, a great deal of work has been directed toward the synthesis of 1,4-benzodiazepin-2,5-diones, presumably as a result of relatively easy accessibility in comparison with the more difficult 1,4-benzodiazepine-2-ones. Most benzodiazepine libraries have limited diversity on the benzene ring because they use the benzene moiety to link to the resin or they introduced the benzene moiety in building blocks such as anthranilic acids to give diversity.[168]

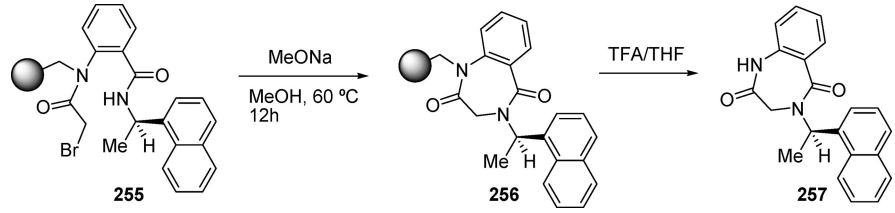
Wu et al.[169] reported a very convenient and straightforward solid-phase synthesis of seven different tetrahydro-1,4-benzodiazepine-2-ones **238** in good yields. The synthesis proceeded on the hydrophilic polyamide SynPhase lanterns by using a reduction-cyclization strategy (Scheme 49).

An efficient solid-phase method was developed by Laustsen et al.[170] for the parallel synthesis of 1,3-dihydro-1,4-benzodiazepine-2-one derivatives. By employing the catch and release principle crude 2-aminobenzoimines **240** were converted to benzodiazepine products **242**, which were

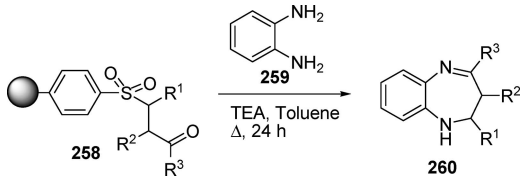
Scheme 52. Solid-Phase Synthesis of 7-Aminobenzodiazepin-2,5-dione by Ettmayer et al.[173]



Scheme 54. Synthesis of 4-*N*-Naphthylethyl-1,4-benzodiazepine-2,5-dione on Solid-Phase by Rivero et al.[175]



Scheme 55. Synthesis of Benzo[*b*][1,4]diazepine Using a Sulfone Linker by Kong et al.[176]



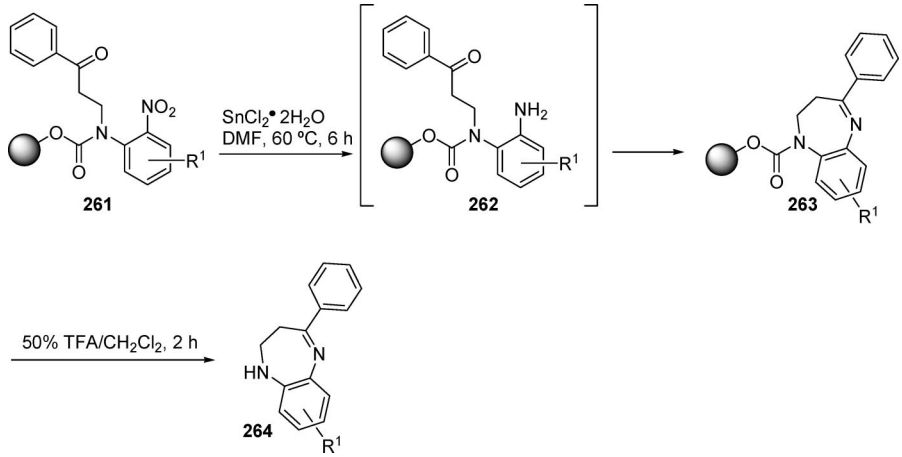
released from the resin in high purities. A key step in this procedure involves catching crude 2-aminobenzoimine products **240** on an amino acid Wang resin **239**. Mild acidic conditions then promote a ring closure and in the same step cleavage from the resin to give 27 pure benzodiazepine products **242** (Scheme 50).

After cyclization of azides **243** with polymer-supported triphenylphosphine, Gil and Bräse[171] obtained 1,4-benzodiazepine-5-ones **245** in 69−99% yield via the corresponding iminophosphoranes, at room temperature in toluene (Scheme 51). The azides were prepared starting from various substituted triazene resins. Cleavage in the presence of an azide donor, gave rise to aryl azides. Pyrrolo[2,1-*c*][1,4]-benzodiazepines were also synthesized by using this methodology. Lee and Park[172] developed an efficient solid-phase strategy to tetrahydro-1,4-benzodiazepines by using the Leuckart−Wallach reaction. A 96-membered library was obtained with excellent yields and purities.

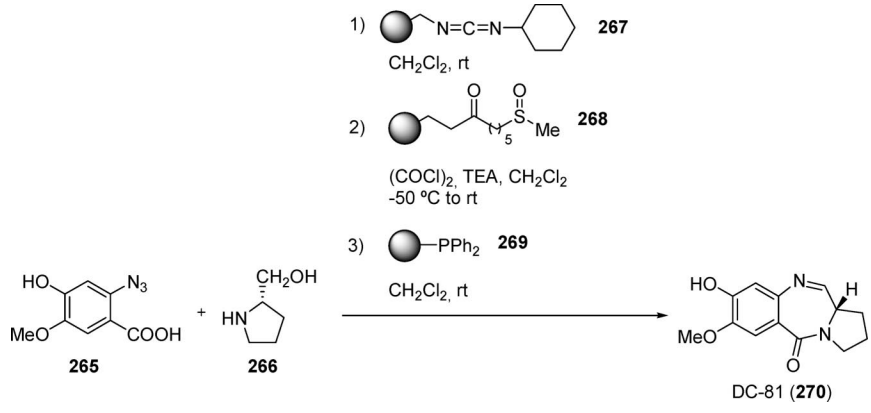
A method for the synthesis of polymer-bound 7-acylamino-benzodiazepine-2,5-diones was described by Ettmayer et al.[173] (Scheme 52). The amino group of an α-amino acid is linked to polystyrene or TentaGel resins via reductive amination of polymer-bound 4-alkoxy-2,6-dimethoxybenzaldehyde followed by base-catalyzed ring closure. Reduction of the nitro group yields enantiomerically pure 7-aminobenzodiazepin-2,5-dione **248** attached via the N-4 atom to the resin.

The synthesis of peptides with a benzodiazepinone moiety obtained directly during the course of solid-phase peptide synthesis was reported by Verdié et al.[174] Model compound **254**, [2-(2,3-dihydro-3-isobutyl-2,5-dioxo-1*H*-benzo1,4-

Scheme 56. Solid-Phase Synthesis of 4-Phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine by Shing et al.[134]



Scheme 57. Synthesis of Pyrrolobenzodiazepine Using Polymer-Supported Reagents by Kamal et al.[179]



diazepin-4(5*H*)-yl)acetamide], was synthesized on Fmoc-Rink amide polystyrene SynPhase lanterns (Scheme 53). Each reaction step was optimized using parallel arrays of lanterns. Several parameters including reaction time, solvent, temperature, concentration, and reactants were varied to determine the best experimental procedure which allowed the generation of a library of 54 peptides incorporating the benzodiazepinone moiety. The biological evaluation of the purified library members, with respect to their affinity for melanocortin receptor type 1, led to the identification of several micromolar ligands.

The synthesis of 4-*N*-naphthylethyl-1,4-benzodiazepine-2,5-dione (**257**) on solid-phase was described by Rivero et al. (Scheme 54).[175] The fluorescent naphthyl group is used as internal sensor for monitoring various stages on the synthetic reaction by spectral differences in fluorescence. Their results showed the efficacy of fluorescence as a direct method for the evaluation of reaction progress.

Using a traceless solid-phase sulfone linker strategy, Kong et al.[176] prepared four benzo[*b*][1,4]diazepine derivatives **260** in moderate yields (Scheme 55). The desired heterocycles were obtained after an elimination-cyclization reaction under basic conditions with *o*-phenylene diamine and triethylamine in toluene for 24 h. A Batrachotoxin (BTX) radioligand assay was used to assess the compound's binding affinities to neuronal sodium channels.

The solid-phase synthesis of 4-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine **264** was reported by Shing et al.[134] In this case, polymer-linked 2-nitrophenyl carbamate was alkylated with chloropropiophenone followed by reduction of the nitro group and acidolytic cleavage (Scheme 56).

The solid-phase synthesis of DNA-interactive pyrrolo[2,1-*c*][1,4]benzodiazepine imines and biologically important pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones was described by Kamal et al. On Wang resin, a reductive cyclization procedures of nitro and azido substrates was achieved using triphenylphosphine for the reductive cyclization[177] or Al/$NiCl_2 \cdot 6H_2O$ and Al/NH_4Cl.[178] This group also reported the generation of a combinatorial library of this kind of heterocycles by using polymer-supported reagents. This methodology involves intra molecular *aza*-Staudinger−Wittig reaction and has been extended for the synthesis of the natural product DC-81 (**270**) in good overall yields (Scheme 57).[179] To provide pyrrolobenzodiazepine dimers, an oxidative cyclization process was used.[180] Recently, they reported also an efficient synthetic procedure involving the *aza*-Staudinger−Wittig strategy and base-mediated cyclative cleavage.[181] From a generated library of 210 compounds, 142 have been selected and evaluated for in vitro activity against *Mycobacterium tuberculosis*, and some of these pyrrolo[2,1-*c*][1,4]benzodiazepines exhibited promising activity.

5. Conclusion

In the past decade, small-molecule heterocyclic compound libraries have attracted much interest for their promising biological and pharmacological activities. Substituted heterocyclic compounds exhibit a high degree of structural diversity that makes them attractive candidates for screening in drug discovery programs.

Combinatorial chemistry continues to be applied extensively within the pharmaceutical industry as one approach toward the discovery and optimization of research leads. Solid-phase synthesis is especially useful in library production because large numbers of compounds can be generated in short time. The choice of linker for the library scaffold to the polymer support is critical for successful library production, and a number of groups have devised elegant methods that enable additional diversity to be incorporated into the products during the cleavage reaction. The quality of solid supports and linkers has improved significantly. This, in turn, has expanded the number of synthetic transformations that can be successfully accomplished on solid-phase and has led to an improvement in the purities and yields of the targeted compounds.

Library design strategies have evolved from the rapid exploration of analogues of known leads to embrace the generation of collections of entirely novel compounds with "druglike" or other desirable properties.

Combinatorial chemistry has become an important tool in both drug discovery and chemical biology studies and its continued success is dependent, in part, on further advances in solid-phase organic synthesis.

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Abbreviations

Ac	acetyl
Alloc	allyloxy carbonyl
Ar	aryl
Bal-resin	backbone amide linker resin
Boc	*tert*-butyloxycarbonyl
Bu	butyl
chex	cyclohexyl
$CSIm_2$	thiocarbonyldiimidazole
DCE	dichloroethylene
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DIC	1,3-diisopropylcarbodiimide
DIEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DMF	dimethylformamide
DMPU	dimethylpropylene urea
equiv	equivalents
Et	ethyl
Fmoc	fluorenylmethyloxycarbonyl
HASC linker	(α-heteroatom-substituted carbonyl) linker
HOBt	*N*-hydroxybenzotriazole
5-HT	5-hydroxytryptamine
MASPOS	microwave-assisted SPOS
MBHA-resin	*p*-methylbenzhydrylamine resin
*m*CPBA	*meta*-chloroperoxobenzoic acid
Me	methyl

MW	microwave
NMM	*N*-methylmorpholine
NMP	*N*-methylpyrrolidinone
NTFBA	6-nitro-2,3,4,5-tetrafluorobenzoic acid
Nu	nucleophile
Oct	octanoate
PEG	polyethylene glycol
PG	protecting group
Ph	phenyl
Pr	propyl
PTSA	*p*-toluenesulfonic acid
Rh_2Oct_4	rhodium octanoate
S_NAr	nucleophilic aromatic substitution
SPOS	solid-phase organic synthesis
TBAF	tetrabutylammonium fluoride
TBP	tri-*n*-butylphosphine
Tf	trifluoromethylsulfonyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilane
TIPSSH	triisopropylsilylthiol
TIS	triisopropyl silane
TMEDA	tetramethylethylenediamine
TMOF	trimethylorthoformate
TsOH	*p*-toluenesulfonic acid

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