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BIOORGANIC & MEDICINAL CHEMISTRY

Review

The Recent Impact of Solid-Phase Synthesis on Medicinally Relevant Benzoannelated Nitrogen Heterocycles

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Dedicated to Professor Dr. Heinrich Wamhoff on the occasion of his 65th birthday

Abstract—Benzoannelated heterocycles such as benzodiazepines and indoles can be prepared efficiently through cyclization on solid supports, although no single approach is currently universal for the preparation of all benzoannelated *N*-heterocycle chemistries. In this review, a number of synthetic strategies for the generation of benzoannelated nitrogen heterocycles using resin-bound substrates have been described. Classical heterocycle forming reactions such as the Fischer indole, the Bischler–Napieralski tetrahydroisoquinoline, the Pictet–Spengler tetrahydro-β-carboline, the Tsuge, the Nenitzescu and the Richter cinnoline reaction are presented. In addition, the Heck, Sonogashira, Wittig, Diels–Alder, and olefin metathesis reactions have been also used. Multicomponent reactions such as the Grieco three-component assembly have been exploited for the synthesis of heterocycles. Cyclative cleavage from the solid support is particularly suitable for the synthesis of heterocycles while particular emphasis has been focused on the synthesis of libraries and the use of combinatorial chemistry techniques. In addition, the most relevant pharmacological properties of benzoannelated nitrogen heterocycles are included.

Contents

Abbreviations: Ac, acetyl; AMEBA, acid-sensitive methoxy benzaldehyde linker; BOP, benzotriazol-1-yloxy*tris*(dimethylamino)-phosphonium hexafluorophosphate; BSA, bis(trimethylsilyl)acetamide; CSA, 10-camphorsulfonic acid; DBU, 1,8-diazabicyclo[5,4,0]undec-7-ene; DCC, *N*,*N*-dicyclohexylcarbodiimide; DIC (DIPC), *N*,*N*′-diisopropylcarbodiimide; DMA, *N*,*N*′-dimethylacetamide; DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DNA, desoxyribonucleic acid; EDC, (3-dimethylaminopropyl)-3-ethylcarbodiimide; Fmoc, fluorenylmethyloxycarbonyl; HATU, *o*-(7-azabenzotriazol-1-yl)-1,1,4,4-tetramethyluronium-hexafluorophosphate; HBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HEPS, 2-hydroxyethyl polystyrene; HIV, human immunodeficiency virus; HOAt, 1-hydroxy-7-azabenzotriazole; HOBt, *N*-hydroxybenzotriazole; 5-HT, 5-hydroxytryptamine; HTS, high throughput screening; Ms, mesyl; NMP, *N*-methylpyrrolidinone; PyBroP, bromotris-pyrrolidino-phosphonium hexafluorophosphate; SPOS, solid phase organic synthesis; TBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; Tf, trifluoromethylsulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TMOF, trimethylorthoformate; TPCD, $[Co(pyridine)_4\ (HCrO_4)_2]$; Trt, trityl; Ts, tosyl.

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Introduction

One of the main objectives of organic and medicinal chemistry is the design, synthesis, and production of molecules having value as human therapeutic agents.

The development of High Throughput Screening (HTS) has increased dramatically the demand for substances to test, and the search for new drug-like molecules has recently taken on a new urgency.[1] In recent years, the synthesis of combinatorial libraries[2,3] has emerged as a valuable tool in the search for novel lead structures. The success of combinatorial chemistry in drug discovery is dependent, in part, on further advances in solid-phase organic synthesis (SPOS).[4] This offers the opportunity of synthesizing molecules via novel routes, which may be difficult or impossible using traditional solution phase methods, and offers also the possibility for rapidly synthesizing drug-like molecules without tedious and time-consuming purification.[5]

The generation of molecular diversity to create libraries for drug discovery was originally focused on the synthesis of the peptide and nucleotide libraries. However, the limitation of such libraries is that the pharmacokinetical properties of large polymeric and often hydrophilic structures make these molecules less suitable as leads in drug discovery. It is, therefore, desirable to develop methods to prepare small, non-polymeric molecules with sufficient diversity such, that they resemble classical drugs, for screening in different assay systems.[6] The rapid generation of such small molecule libraries can be executed effectively by employing combinatorial or simultaneous parallel synthesis on solid supports.[7]

Experience has shown that compounds with biological activity are often derived from heterocyclic structures, such as indolines,[8] tetrahydroquinolines[9] or hydrobenzofuranes[10] that appear frequently in natural products. Substituted heterocyclic compounds can offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. For this reason, it is not surprising that this structural class has received special attention in combinatorial synthesis.[11–13] Since the disclosure of the benzodiazepine libraries by Ellman's group in 1992,[14] the development of strategies for the generation of heterocyclic libraries on solid support has sparked a great deal of interest.[15]

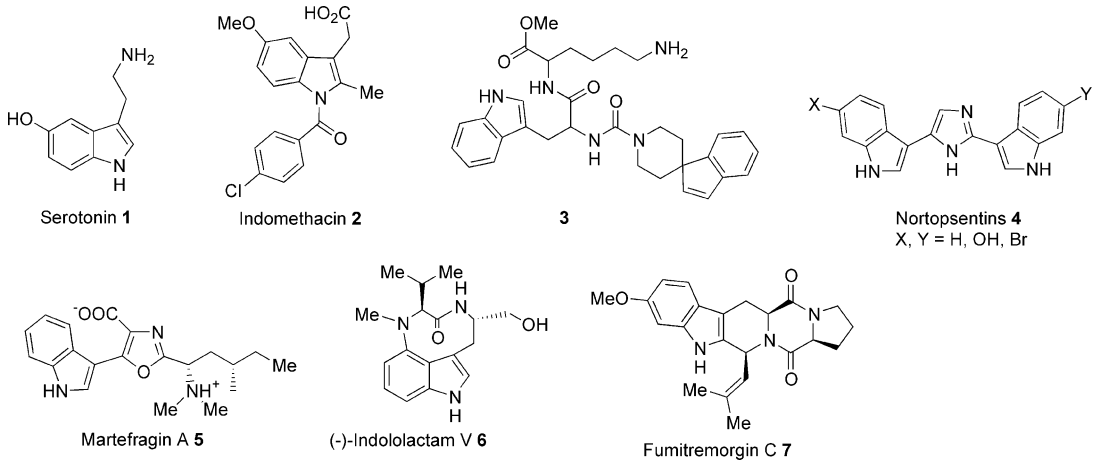


Figure 1. Relevant molecules with an indole moiety.

The results of such studies impact pharmaceutical research both in the area of new lead discovery and in the generation of rapid structure–activity relationship specifically through the combinatorial chemistry approach. In this review, we focus on methods for the synthesis of benzoannelated rings on solid support, because benzannelation[16] is an efficient method for the diversificiation of heterocycles. The benzo moiety is an integral part of numerous heterocyclic target molecules (e.g., benzimidazoles, benzodiazepines, quinoxalines, quinazolines, etc.). The chapters on the cyclization methods for the preparation of five-, six-, seven- and eight-membered benzoannelated rings have been subdivided depending on the number of nitrogen atoms in the ring system.

In this review, modification of polymer-bound heterocycles without a ring-forming step will not be included.

Benzoannelated Five-Membered Heterocycles

Indoles and related heterocycles

The indole nucleus is a fundamental constituent of a number of natural and synthetic products with biological activity. This basic skeleton for example present in the neurotransmitter Serotonin [**1**, 5-hydroxytryptamine, (5-HT)], which plays an important role in a variety of processes through the activation of 5-HT receptors.[17] Other indoles are present in drugs with a remarkable range of activities as demonstrated by the non-steroidal anti-inflammatory agent Indomethacin (**2**),[18] the peptidal mimetic somatostatin agonist **3**,[19] selective dopamine D_4 receptor agonist cyanoindole derivatives[20] and potent and selective factor Xa inhibitors.[21] A variety of natural products containing the indole ring have been identified such as the antitumoral Nortopsentins (**4**),[22] the potent inhibitors of lipid peroxidation Martefragin A (**5**)[23] and other 5-(3-indolyl)oxazoles,[24] the protein kinase C activator Indololactam V (**6**),[25] as well as Fumitremorgin C (**7**),[26] that was recently identified as a specific reversal agent for the breast cancer resistance protein transporter (Fig. 1).

Some indole-related heterocycles have well recognized pharmacological properties. For example some indolizines are antiarrhytmic,[27] while some oxindoles exhibit anti-rheumatic properties,[28] and are inhibitors of mandelonitrile lyase[29] and proteintyrosine kinases.[30] Derivatised indolines have also been shown to be potent and selective 5-HT_3 receptor antagonists.[31]

Due to the remarkable range of biological activities that have been displayed by indoles, several useful solid phase approaches to the construction of these heterocyclic core structures such as the 2-arylindole nucleus **8**,[32,33] spiroindolines **9**[34] and 2-oxindoles derivatives **10**[35] have been reported (Fig. 2).

As demonstrated in Scheme 1, the indole moiety can be constructed using the Fischer,[32,34,36] Nenitzescu[37] or Wittig[38] indole synthesis. It is also feasible to use a combination of the Sonogashira and Heck reactions,[39–41] the Heck reaction with 1,3-dienes,[42] cycloaddition reactions (**20**→**21**)[43] or *C*-arylation of substituted acetonitriles and 1,3-dicarbonyl compounds.[44]

Collini and Ellingboe[39] described the palladium-catalyzed solid-phase synthesis of trisubstituted indoles (Scheme 2). Therefore, Wang resin (**25**) was converted to chloro Wang resin (**26**). After coupling with an iodoaminobenzoic acid **27**, Sonogashira coupling with a terminal alkyne **29** gave the resin **30**. Heck cyclization with concomitant loss of the trifluoroacetyl group yielded the indole unit **31**. Following cleavage from the solid phase, the indoles **32** were isolated in 34–76% yield. Using this approach, three substituents are available for variation and the preparation of a combinatorial library.

The solid-phase Nenitzescu indole synthesis was described by Ketcha, Wilson and Portlock[37] (Scheme 3). Fmoc-protected ArgoPore® Rink NH_2 resin **33** was used in

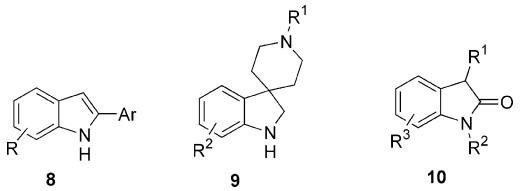
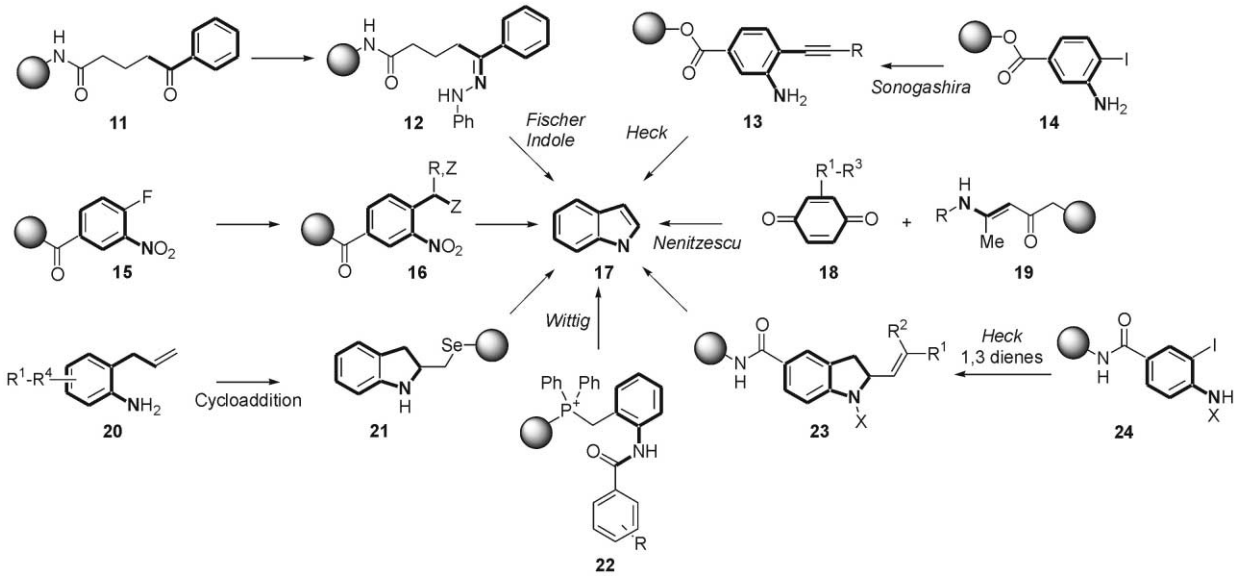
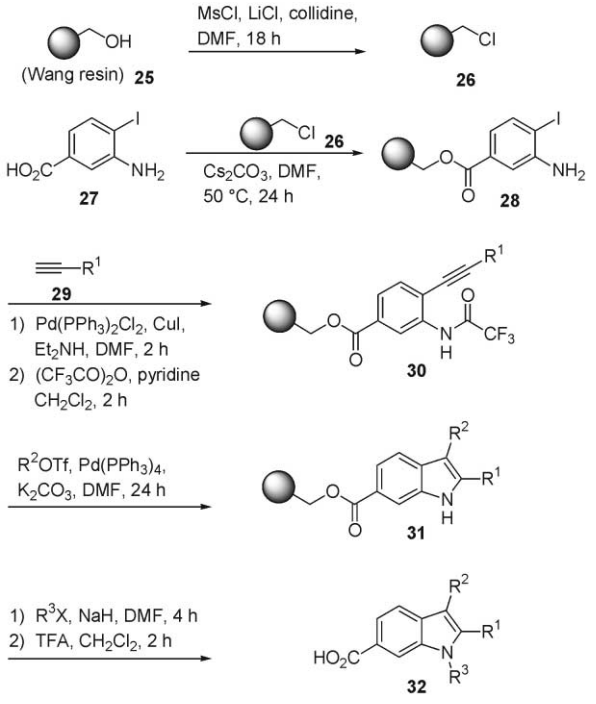


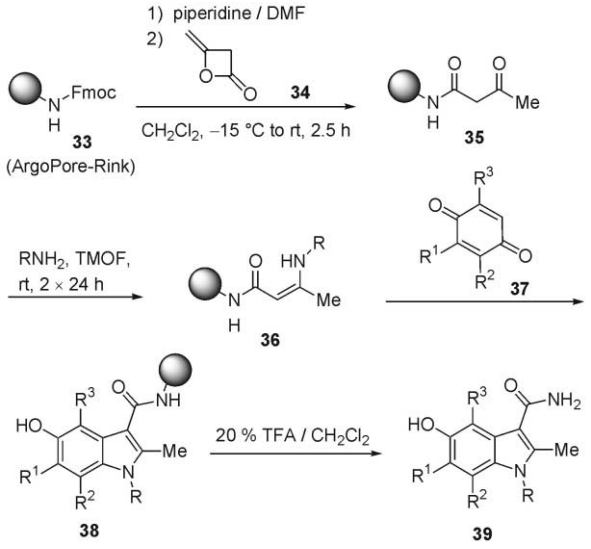
Figure 2. Indole-related heterocycles.



Scheme 1. Solid-phase pathways towards the indole core structure.



Scheme 2. Palladium-catalyzed synthesis of indoles **32** by Collini and Ellingboe.[39]



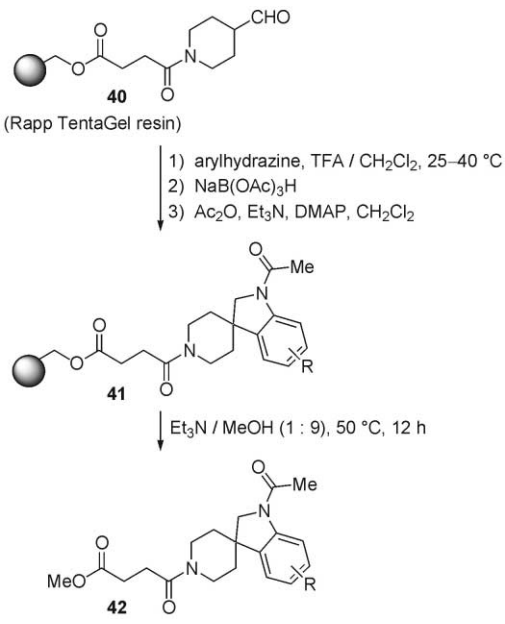
Scheme 3. Nenitzescu indole **39** synthesis on solid support by Ketcha et al.[37]

this case as the solid support. In the first step, the resin was deprotected and the acetoacetamide **35** prepared using diketene (**34**). Treatment with primary amines forms the polymer bound enaminones **36**. The indole skeleton **38** was formed by Michael addition. Cleaving of the solid phase resulted in a library of indoles **39** with a high purity (>99%).

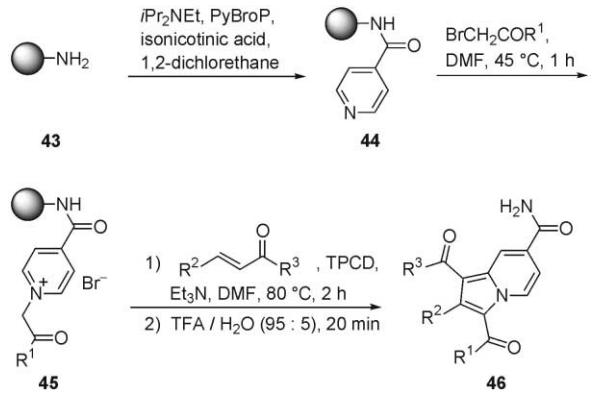
A solid-phase Fischer indole synthesis was described by Cheng and Chapman[34] (Scheme 4). TentaGel resin was used as the solid support. In the Fischer indole reaction, the polymer bound aldehyde **40** reacted with arylhydrazines to give an enolenine. Following reduction and acylation, the spiroindolines **42** were cleaved from the resin in good yields and purities.

Combinatorial chemistry also offers a solid supported synthesis for indolizines.[45,46] Scheme 5 shows the synthetic pathway used by Goff.[45] In the first step, isonicotinic acid was coupled to the deprotected Rink amine resin followed by treatment with 2-bromoacetophenones, structure **45** was assembled. A [3 + 2]-dipolar cycloaddition gave the indolizines **46** after cleavage. A small library of indolizines with high yields and purities was produced using this route.

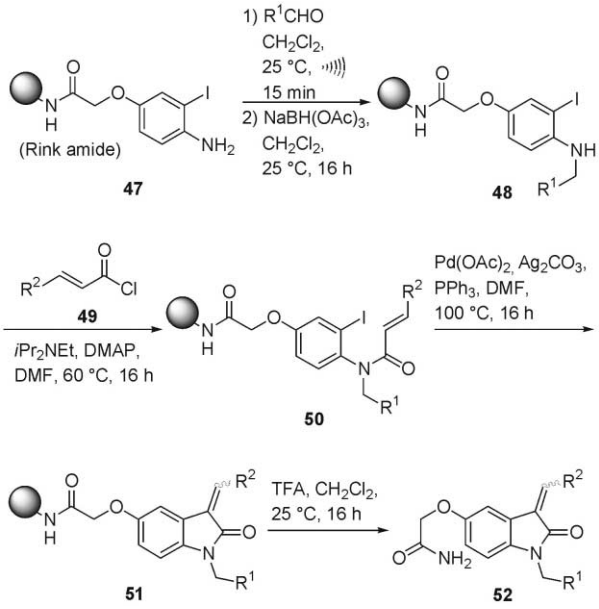
The synthesis of 2-oxindole derivatives on solid support was published by Arumugam et al.[35] in 1997. As shown



Scheme 4. Synthesis of spiroindolines **42** by Cheng and Chapman.[34]



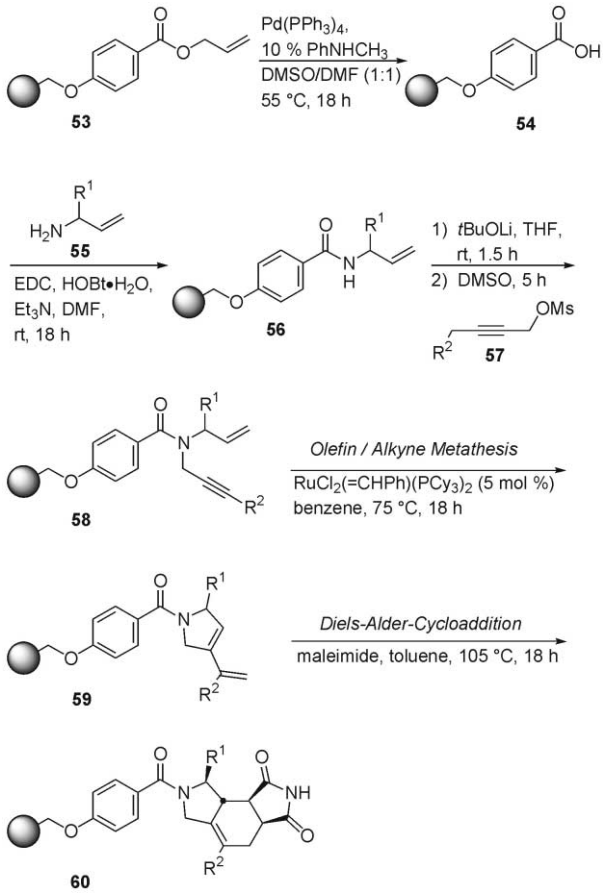
Scheme 5. Synthetic pathway for indolizines **46** by Goff.[45]



Scheme 6. Synthesis of 2-oxindole **52** derivatives by Arumugam et al.[35]

in Scheme 6, the synthesis started with reductive alkylation of an aniline **47**. After construction of the tertiary amide **50**, an intermolecular Heck reaction formed the oxindoles **51** as a mixture of (*E*)- and (*Z*)-isomers.

The solid-phase synthesis of isoindoles and hydroindoles is only described in one publication.[47] Heerding et al. used an intramolecular olefin/alkyne metathesis in combination with a Diels–Alder cycloaddition as shown in Scheme 7. Wang resin (**25**) served as the solid-support linker combination. The allyl ester **53** was deprotected to give the benzoic acid **54**, which was reacted with an allyl amine. After the insertion of the olefin function, an intramolecular Ruthenium catalyzed olefin/alkyne metathesis yielded **59**. A Diels–Alder reaction with maleimide gave the resin-bound cycloadducts **60** as single diastereomers. This approach was used to prepare a 4200-membered combinatorial library of isoindoles.



Scheme 7. Solid-phase synthesis of isoindoles and hydroindoles **60** by Heerding et al.[47]

Substituted indoles such as the *N*-arylazoindoles[48] have also been reported. The Pictet–Spengler[49,50] reaction has been used for the preparation of tetrahydro-β-carboline alkaloids **61**,[51] while an efficient solid-phase Tsuge reaction has been employed for the synthesis of maleimide-fused indolizinium carboxylates **62**[46] (Fig. 3).

Employing some reactions previously described, new synthetic routes to indoles have been developed that

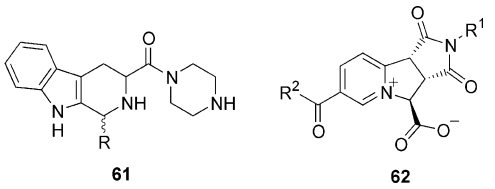


Figure 3. Annelated indole derivatives.

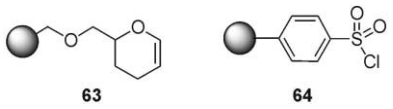


Figure 4. Linkers for indole synthesis.

take advantage of versatile linkers[52] such as the THP linker **63**[41,53] or a sulfonyl linker **64** (Fig. 4).[54–56] The indole NH as a resin attachment point leads to effective linking of indoles.[57,58] Recently, Macleod et al.[59] have developed novel titanium(IV) benzylidene reagents that allow the traceless solid-phase synthesis of indoles in high purity using a chameleon catch approach. A highly efficient method for the solid-phase synthesis of substituted indoline scaffolds, which can be elaborated and cleaved in a traceless manner providing access to members of the medicinally important 1-methyl indoline class, has been described.[43]

Benzimidazoles

The benzimidazole is a crucial heterocyclic skeleton often associated with biological activity. The benzimidazole ring **65** represents an important pharmacophore in drug discovery notable clinical examples being the antihistamine Astemizole (**66**)[60] and the proton pump inhibitor Omeprazole (**67**)[61] (Fig. 5).

In addition, benzimidazole based compounds have shown a broad range of biological activities, including

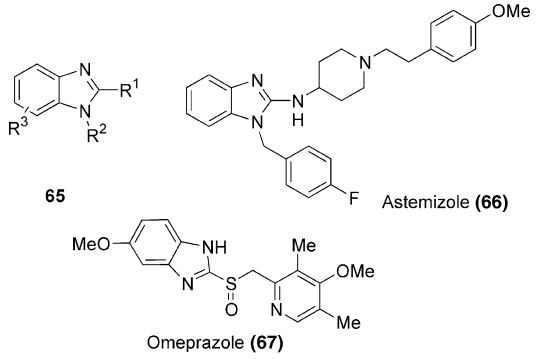


Figure 5. Relevant molecules with a benzimidazole moiety.

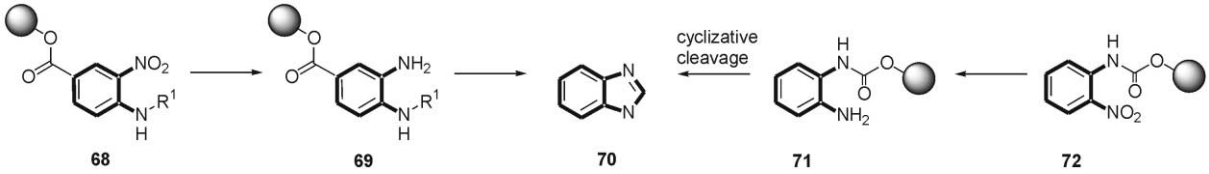
selective inhibition of the platelet-derived growth factor receptor,[62] class III antiarrhythmic activity,[63] neuropeptide Y_1 receptor antagonism,[64] antiproliferative activity,[65,66] angiotensin II receptor antagonism[67] and antiviral properties.[68,69]

Because of their relative ease of synthesis and precedence as bioactive molecules, benzimidazoles have been an obvious target for the development of solid-phase synthesis. Recent reports have described the benzimidazole synthesis.[70–81] As shown in Scheme 8, the key step was the reduction of the nitro group to a primary amine. The benzimidazole unit was then formed by a cyclization reaction.

One example for the solid-supported synthesis of benzimidazoles, wherein the five-membered ring compound was constructed on the site of the solid phase, was described by Huang and Scarborough.[71] As outlined in Scheme 9, the first building blocks, substituted 2-nitroanilines **74** were attached to *p*-nitrophenyl carbonate Wang resin **73**. After alkylation of the carbamate moiety using strong bases as lithium *t*-butoxide, the nitro groups were reduced to the corresponding anilines **77**. The benzimidazoles were formed by treatment with trimethylorthoformate. Using this cyclative cleavage approach, a small library of nine compounds was synthesized.

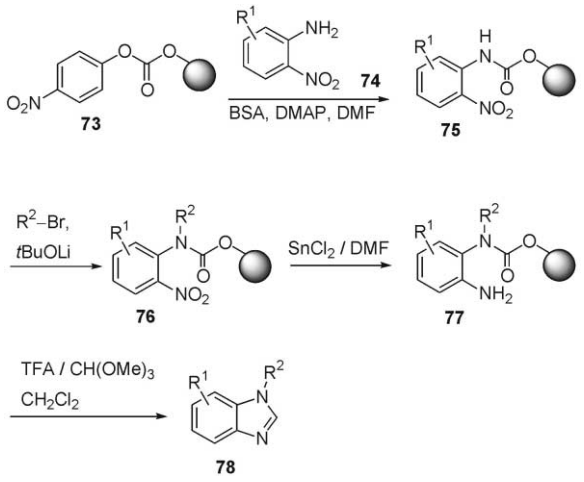
An example of cyclization on the other site was demonstrated by Tumelty et al. in 1998.[80] As shown in Scheme 10, fluoronitrobenzoic acid **80** was connected to the deprotected ArgoGel™ Rink Fmoc resin **79**. Nucleophilic aromatic substitution was followed by reduction to give the diamines **84**. The next step was a reaction with bromoacetic acid anhydride. After displacement of the bromide with a nucleophilic monomer, the benzimidazoles were formed and the products **87** were cleaved from the solid support in good yields (65–95%) and high purities (>95%).

A publication of Pan and Sun described the combinatorial synthesis of oxobenzimidazoles.[82] As described in Scheme 11, the fluoro group was displaced by several primary amines in the first step. The nitroanilines **89** were then reduced to the diamines **90**. In the third step, the oxobenzimidazole building block was formed by a cyclization with triphosgene. The products **92** were obtained in good yields and purities after cleavage. Smith et al.[83] reported a synthesis of 2-arylaminobenzimidazoles on SynPhase™ Crowns, which involved *o*-nitroaniline intermediates. It is also possible to synthesize thiobenzimidazoles in a very analogous synthetic pathway.[84]

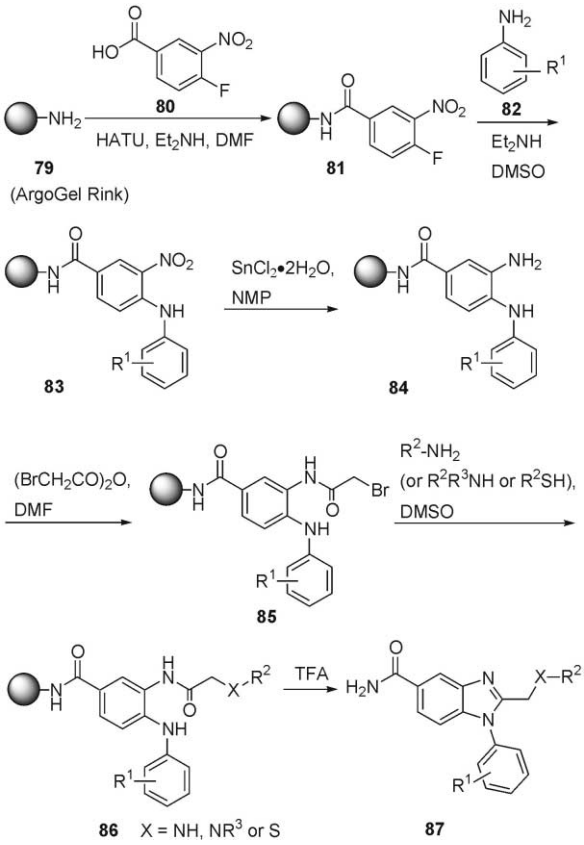


Scheme 8. Synthetic pathways for benzimidazoles.

Several other groups have reported the 'traceless' synthesis of benzimidazoles with three points of diversity.[75,77,85,86] All of these traceless methods allow the attachment of the solid support through the anilinic nitrogen of the ring precursor.



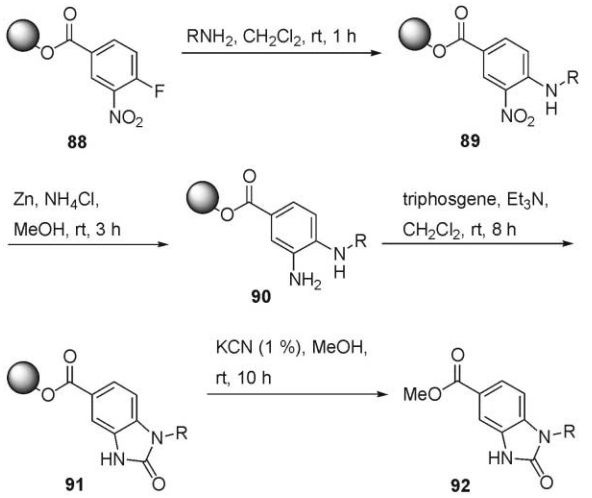
Scheme 9. Solid-supported synthesis of benzimidazoles **78** by Huang and Scarborough.[71]



Scheme 10. Synthesis of benzimidazoles **87** by Tumelty et al.[80]

Benzotriazoles

Recently, a novel series of benzotriazoles derivatives has been synthesized and has been screened as anti-inflammatory,[87] antitumoral and anti-HIV agents.[88] The



Scheme 11. Solid-phase synthesis of oxobenzimidazoles **92** by Pan and Sun.[82]

antiemetic Alizapride (**93**) is a benzotriazole that is used for the treatment of side effects of chemotherapy caused by Cisplatin[89] (Fig. 6).

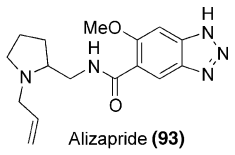
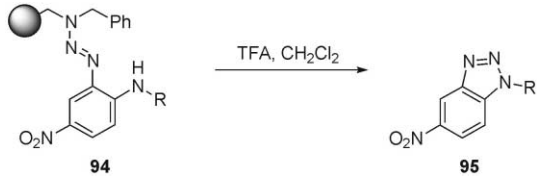


Figure 6. Structure of Alizapride (**93**).

The only solid-supported synthetic pathway to benzotriazoles was described by Bräse et al.[90] as shown in Scheme 12. The polymer-bound α-aminotriazenes **94**, readily available by substitution of a nitrofluoro resin,



Scheme 12. Synthetic pathway to benzotriazoles **95** by Bräse et al.[90]

were converted to the benzotriazoles **95**. Cleavage from the solid support and cyclization of the α-aminodiazonium salt with trifluoroacetic acid in dichloromethane gave the products **95** in good yields and excellent purities.

The unsubstituted benzotriazole core has been used as polymeric support for the synthesis of organic molecules libraries.[91–96]

Indazoles

The indazole moiety is present in the marketed anti-inflammatory drugs Bendazac (**96**)[97] and Benzydamine (**97**).[98] Apart from this, the range of pharmacological effects of the indazole derivatives include DNA intercalating as the benzothiopyranoindazoles CI-958,[99] acti-

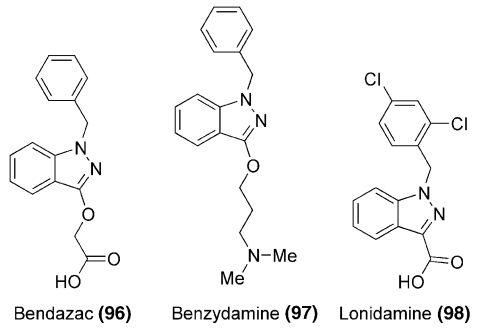
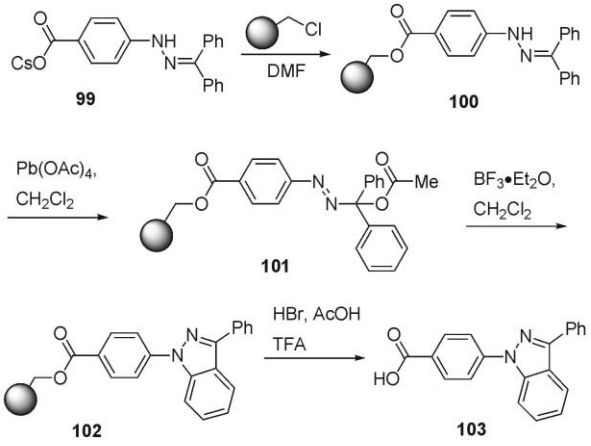


Figure 7. Relevant molecules with an indazole moiety.

vators of the nitric oxide receptor,[100] DY-9760 calmodulin antagonist,[101] immunosuppresive effects of Bindarit,[102] and the anticancer activity of Lonidamine (**98**)[103] (Fig. 7).

So far, only one synthetic pathway for indazoles on solid phase has been reported. Yan and Gstach described the synthesis shown in Scheme 13 in 1996.[104] Therefore, the hydrazone **99** was coupled to unmodified Merrifield resin. Subsequently, the immobilized hydrazone **100** was oxidized to the ester **101**. The indazole unit was formed by a Lewis catalyzed cyclization. The indazole **103** cleaved from the solid support in a final yield of 79% and purity >95%. All the reaction steps were monitored by single-bead IR.



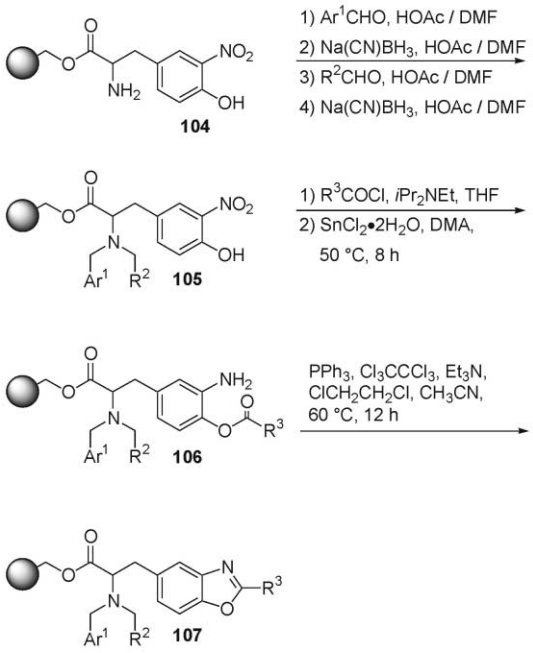
Scheme 13. Synthetic pathway for a indazole **103** on solid support by Yan and Gstach.[104]

In addition, as numerous natural and non-natural guanidine-containing compounds have had a significant impact on medicinal chemistry,[105,106] López-Cremades el al.[107] developed a simple method for the preparation of fused indazolobis(guanidines) on solid support via an Aza–Wittig intramolecular cyclization.

Benzoxazoles and benzisoxazoles

Until now, few papers have reported the solid-phase synthesis of benzoxazoles, although these heterocycles are present in biologically active compounds,[108] and have been described as 5-HT_3 partial agonists,[109] antibacterials,[110] as well as inhibitors of thrombin,[111] human cytomegalovirus protease,[112] and chymase.[113] Besides this, the benzisoxazoles Risperidone[114] and Zonisamide[115] have been approved for the treatment of schizophrenia and epilepsy, respectively.

Beebe et al. described a new strategy for synthesizing benzoxazoles in 2001.[116] A modified Wang resin was used as the solid support. As formulated in Scheme 14, in the first two steps, the primary amine **104** was converted into a tertiary amine **105**. Subsequently, the phenol was esterified and the nitro group was reduced to the diamino ester **106**. The final step was a dehydrative cyclization to the benzoxazoles **107**.



Scheme 14. Synthesis of benzoxazoles **107** by Beebe et al.[116]

Lepore et al. described a synthetic pathway to isoxazoles[117] (Scheme 15). The Boc-protected amine **109** was loaded on the Kaiser resin **108** and treated with trifluoroacetic acid to give **111**. This resin was treated with different electrophiles to give oximes **112**, which were cyclized by cleavage from the solid support to give the isoxazoles **113** in good yields and high purities (>93%).

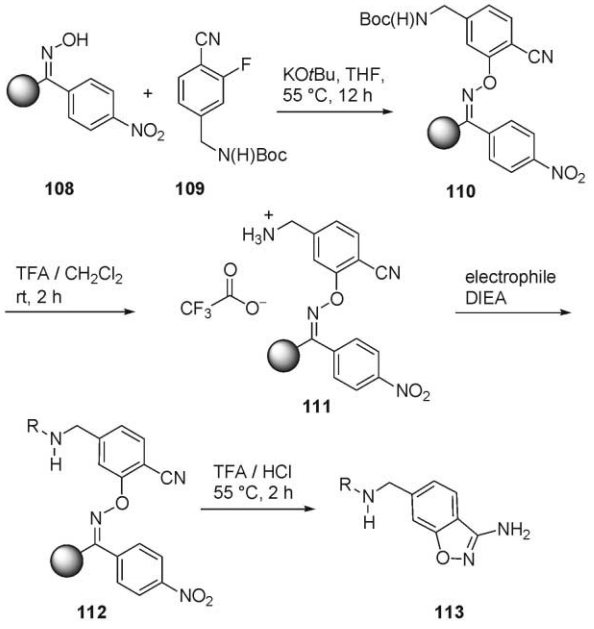
Stephensen and Zaragoza used the partial reduction of nitro groups to hydroxylamines and subsequent cyclization with ketones as the synthesis strategy[118] (Scheme 16). In the first step, the fluoride ion of **114** was substituted by the arylacetonitrile **115**. Reductive cyclization and cleavage of the solid support resulted in the benzisoxazole **117**.

Benzoannelated Six-Membered Heterocycles

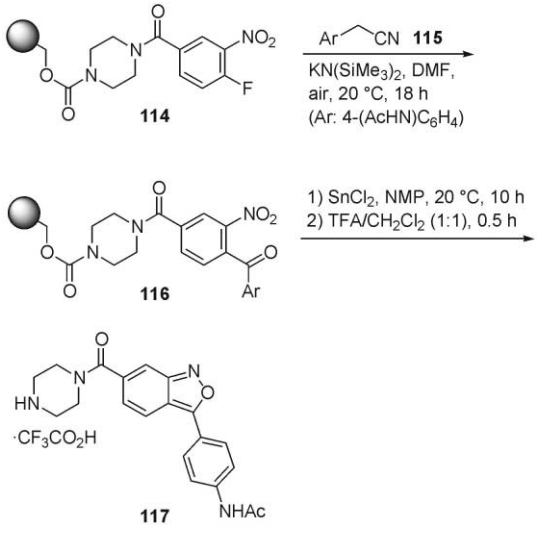
(Tetrahydro)quinolines and (tetrahydro)isoquinolines

Quinoline and isoquinolines as well as their tetrahydro derivatives are part of many biologically interesting

compounds. They appear in natural and synthetic products possessing significant pharmacological properties. In fact, they have been used as HIV protease inhibitors [e.g., Saquinavir (**118**)],[119] antimalarial drugs [e.g., Mefloquine (**119**)],[120] drugs for the treatment of asthma [e.g., Montelukast (**120**)],[121] broad spectrum antibacterial agents [e.g., Ciprofloxacin (**121**), that can be used to treat anthrax],[122] and even as antidepressants [e.g., Nomifensine (**123**)][123] and an inhibitor of angiotensin converting enzyme [e.g., Quinapril (**122**)][124] (Fig. 8). This family of heterocycles have shown potential as ligands for the human glucocorticoid receptor,[125] inhibitors of platelet-derived growth factor receptor tyrosine quinase,[126] inhibitors of potassium ion channels on human T lymphocytes,[127] anti-inflammatory agents,[128] factor Xa inhibitors,[129] antitumorals,[130] phosphodiesterase 5 inhibitors[131] and analgesics.[132]



Scheme 15. Solid-phase synthesis of isoxazoles **113** by Lepore et al.[117]



Scheme 16. Synthetic pathway to benzisoxazoles **117** by Stephensen and Zaragoza.[118]

For these reasons, a general method for the solid-phase synthesis of these molecules would be extremely valuable.

Tetrahydroquinolines have been synthesized in two different ways on the solid support as shown in Scheme 17. Kiselyov et al.[133–136] described different pathways to the tetrahydroquinolines using the Grieco three-component condensation. A 1,4-addition also offers a synthetic pathway to tetrahydroquinolines.

In the first example of the Grieco three-component condensation shown in Scheme 18, Kiselyov connected the 4-nitrophenylalanine **129** to the Wang resin (**25**) by esterification.[133] The amino group was deprotected, acylated and the nitro group reduced to the amine **133**. The Grieco three-component condensation of **133**, the

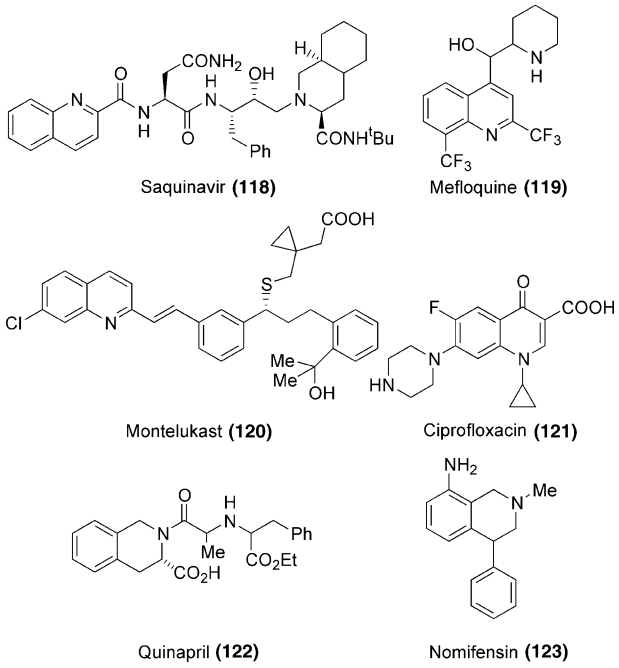
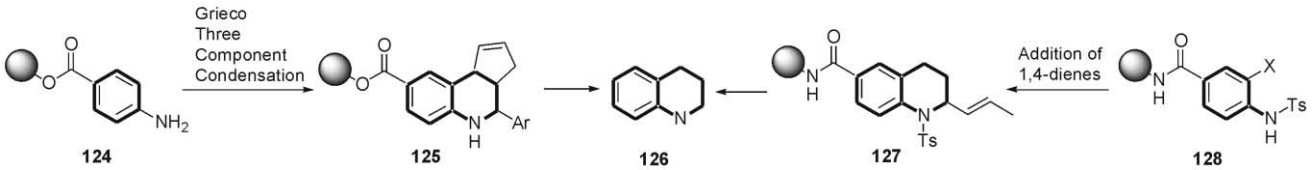
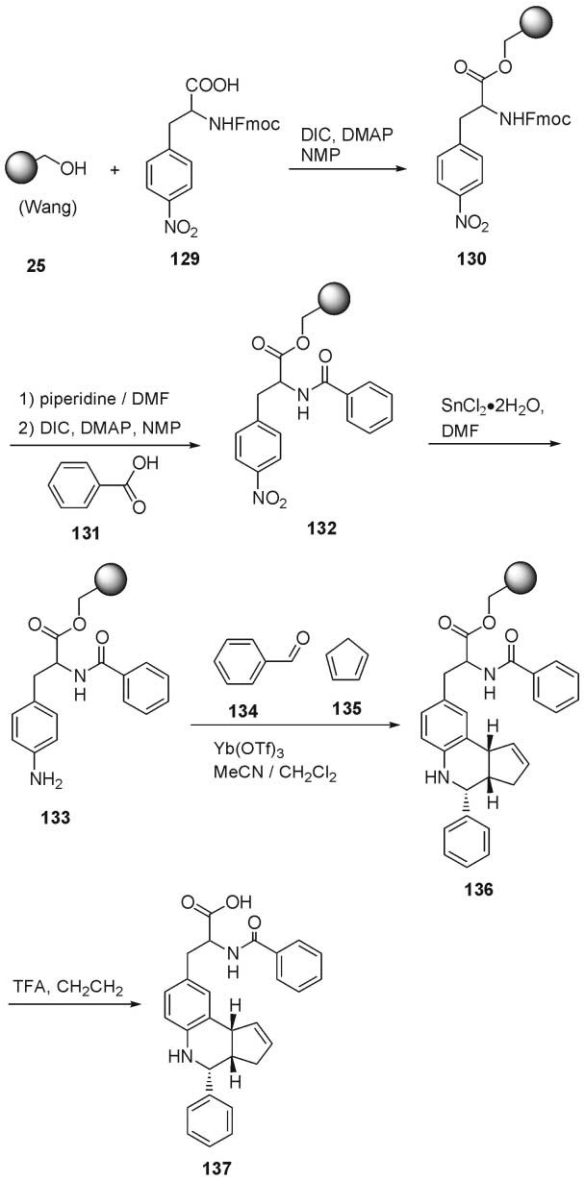


Figure 8. Relevant molecules with quinoline/quinolone and tetrahydroisoquinoline moiety.



Scheme 17. Solid-phase synthesis of tetrahydroquinolines.

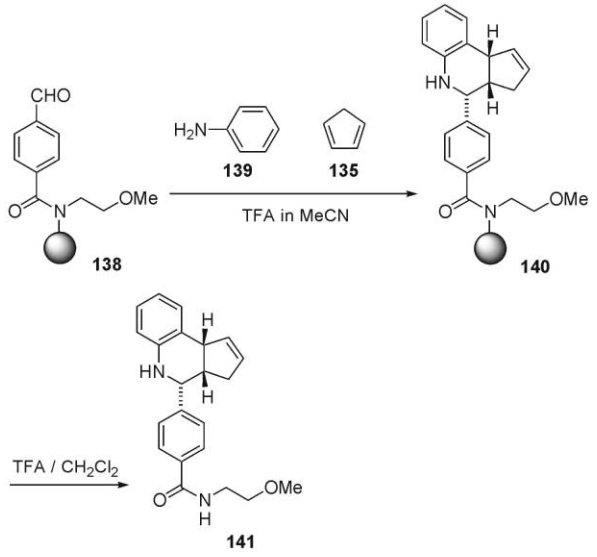


Scheme 18. Three-component condensation catalyzed by $Yb(OTf)_3$ according to Kiselyov et al.[133]

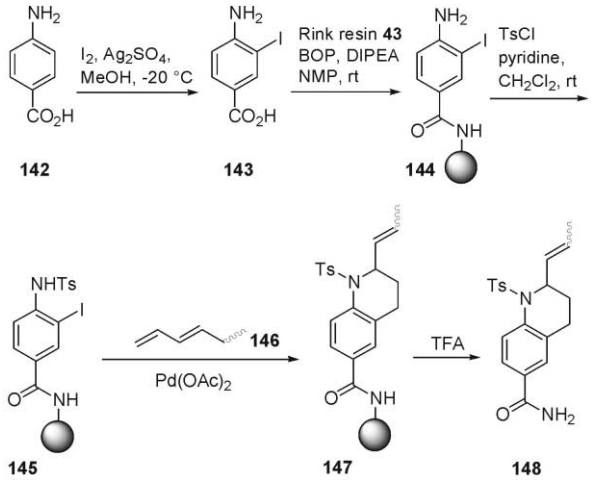
aldehyde **134** and the diene **135** furnished the desired tetrahydroquinoline derivative **137** after cleavage with TFA.

Kiselyov also connected the aldehyde position to the solid support[135] (Scheme 19). Therefore, the aldehyde resin **138** was reacted with aniline (**139**) and cyclopentadiene (**135**) to get the tetrahydroquinolines **140**. After cleavage with TFA, the tetrahydroquinolines **141** were isolated.

The other synthetic pathway to tetrahydroquinolines was described by Wang et al.[42] (Scheme 20). 4-aminobenzoic acid (**142**) was iodinated to the 4-amino-3-iodobenzoic acid (**143**) and coupled to Rink resin (**43**). After tosylation, the palladium-catalyzed annelation of the solid-phase linked *o*-iodoanilines **145** with 1,4-dienes took place. Cleavage from the solid support gave the tetrahydroquinolines **148** in high yield (88%) and good purities (81%).



Scheme 19. Three-component condensation with the aldehyde connected to the solid support according to Kiselyov et al.[135]

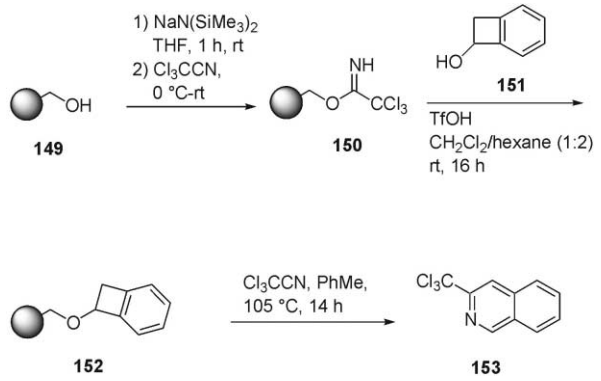


Scheme 20. Synthesis of a tetrahydroquinoline **148** by Wang et al.[42]

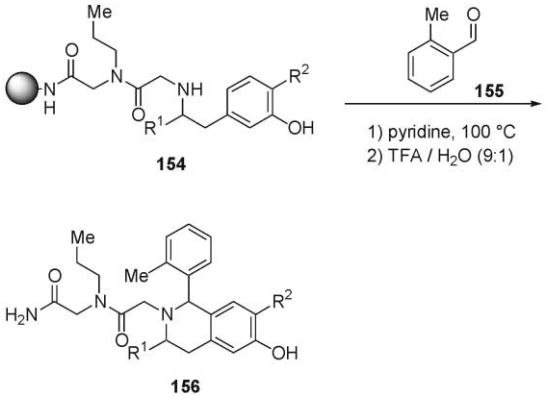
Various synthetic pathways offer the accessibility to isoquinolines. The first one was described by Craig et al. and shown in Scheme 21.[137] Hydroxymethylpolystyrene resin (**149**) was used as the solid support. Reaction with trichloroacetonitrile delivered the functionalized resin **150**. The benzocyclobutanole **151** was connected to the solid support and resulted in the *o*-quinodimethane precursor **152**. A Diels–Alder reaction with trichloroacetonitrile yielded 3-(trichlormethyl)isoquinoline (**153**) with concomitant cleavage from the solid support.

Another pathway was described by Hutchins et al.[138] As demonstrated in Scheme 22, they used a cyclization reaction for the preparation of tetrahydroisoquinolines **156**. The reactive intermediate was a resin-bound imine, which reacted at very mild conditions upon cleavage to the heterocycle.

Meutermans et al. and Röfling et al. exploited the Bischler–Napieralski reaction on solid support for the synthesis of tetrahydroisoquinolines.[139,140]



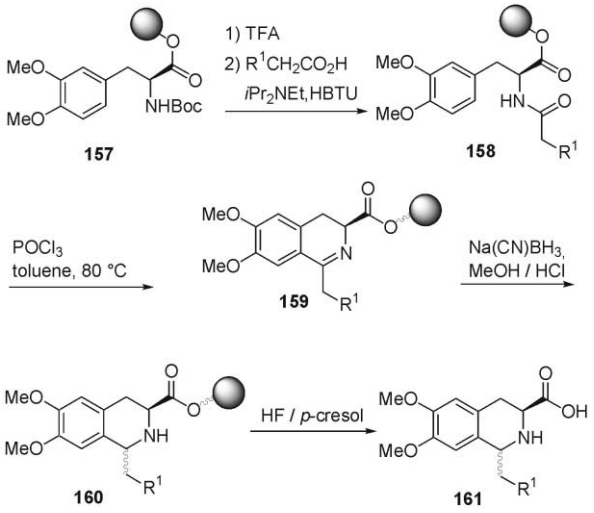
Scheme 21. Traceless solid-phase synthesis of isoquinoline **153** by Diels-Alder reaction according to Craig et al.[137]



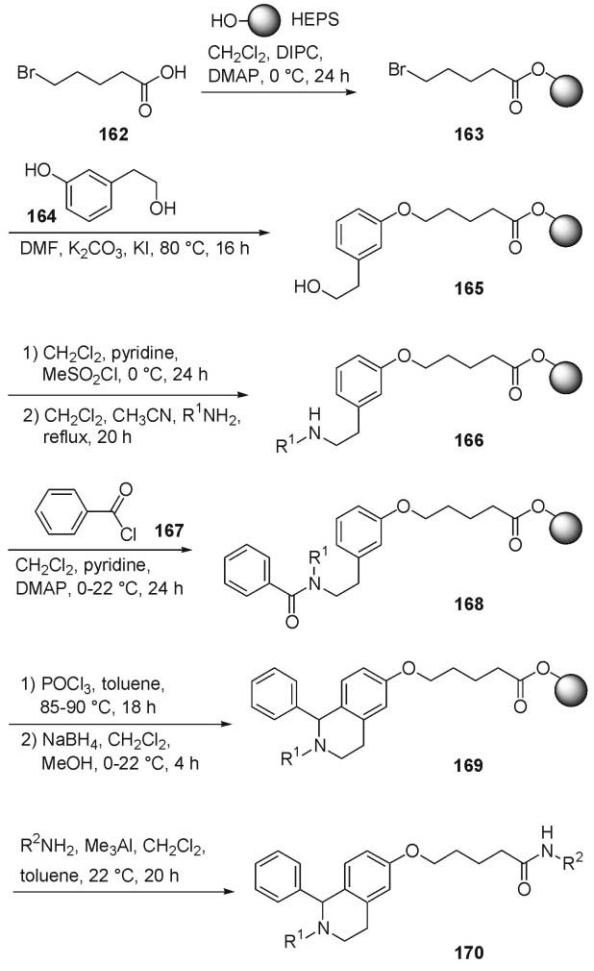
Scheme 22. Solid-phase synthesis of tetrahydroisoquinolines **156** by Hutchins et al.[138]

Meutermans et al. deprotected the linked Boc-protected *L*-3,4-dimethoxyphenylalanine **157** and acylated it to yield **158** (Scheme 23). The cyclization took place by a Bischler–Napieralski reaction and gave the imine **159**. The reduction of the imine **159** and cleavage from the solid support yielded the tetrahydroisoquinolines **161** in high yield and good purities.

Röfling et al. started with bromocarboxylic acid **162**, which was connected to 2-hydroxyethylpolystyrene resin by esterification (Scheme 24). After a nucleophilic substitution **165**, the system was activated, so that the phenethylamine could be elaborated. The amine was connected to chlorobenzoic acid. Parallel Bischler–Napieralski type ring closure and iminium ion reduction furnished the isoquinoline skeleton. Cleavage of the solid support resulted the tetrahydroisoquinoline amide **170**. Röfling et al. produced a library of 24 tetrahydroisoquinoline amides by this synthetic pathway.[140]



Scheme 23. Solid-supported Bischler–Napieralski reaction by Meutermans et al.[139]



Scheme 24. Solid-supported Bischler–Napieralski reaction by Röfling et al.[140]

Quinazolines

Quinazolines are widely used as antitumorals, for example **171**,[141–143] although they exhibit also a wide range of biological properties as potent non-nucleoside reverse transcriptase inhibitors of HIV-1,[144] antibacterial agents **172**,[145] phosphodiesterase 5 inhibitors[146] and antagonist for the human adenosine A(3) receptor[147] with potential action as anti-inflammatory, anti-asthmatic or anti-ischemic agents. This heterocycle is present also in the agent for the treatment of *Pneumocystis carinii* pneumonia Trimetrexate (**173**),[148] in Anagrelide[149] that can be used for the treatment of thrombocythaemia,[150] in Prazosin (**174**)[151] (Fig. 9) used in benign

prostatic hyperplasia, and in the antihypertensive agent Ketanserin.[152] There are three different pathways described for the synthesis of quinazolines. Cobb et al., Zhang et al. and Makino et al. took a cyclocondensation as the key step.[153–157] As shown in Scheme 25, Makino also used a cycloaddition for the construction of the quinazoline skeleton.[158]

Cobb et al. described a two-step reaction for quinazolines.[153] In the first step, hydroxymethylpolystyrene (**149**) was reacted with ethyl oxalylchloride to the ethyloxalate linkage **182**, as shown in Scheme 26. The cyclocondensation with the benzamide resulted in the linked quinazoline **184**, which was cleaved from the solid support by treatment with trimethylsilyliodide and finally descarboxylated hydrochloric acid.

Makino et al. synthesized various quinazolines by cycloaddition of anthranilamides with orthoformates.[158] As shown in Scheme 27, the solid-support **186** was treated with *p*-nitrobenzoic acid (**187**) to give **188**. The nitro group was reduced to the amine and transformed with the acid chloride **190** to the amide **191**. After cyclocondensation and cleavage of the solid support, the quinazolines **193** were produced in very high purities (>95%).

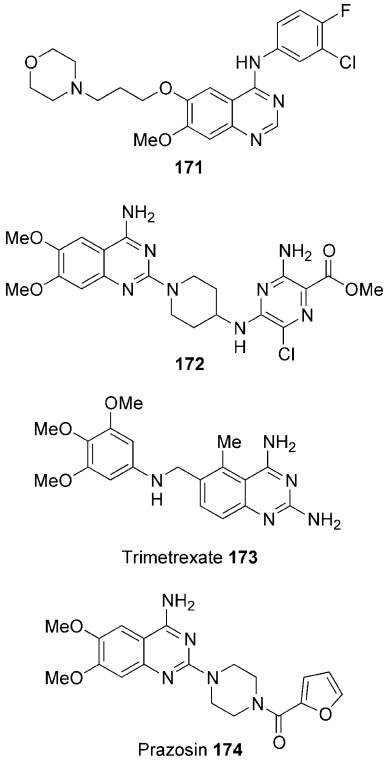
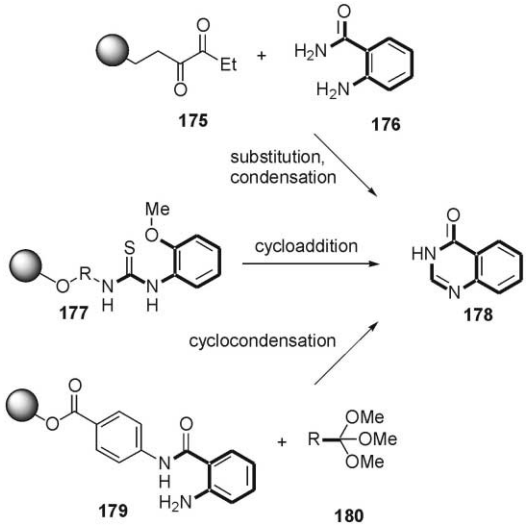
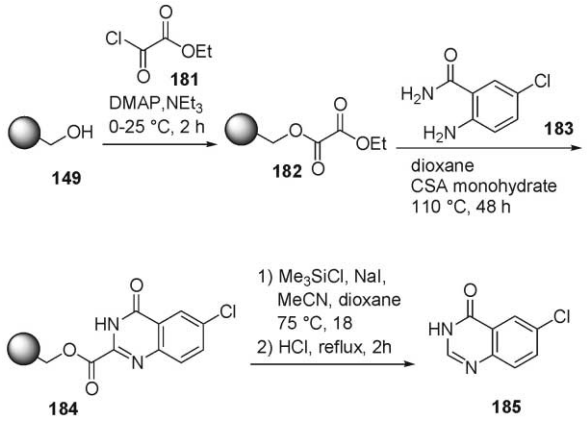


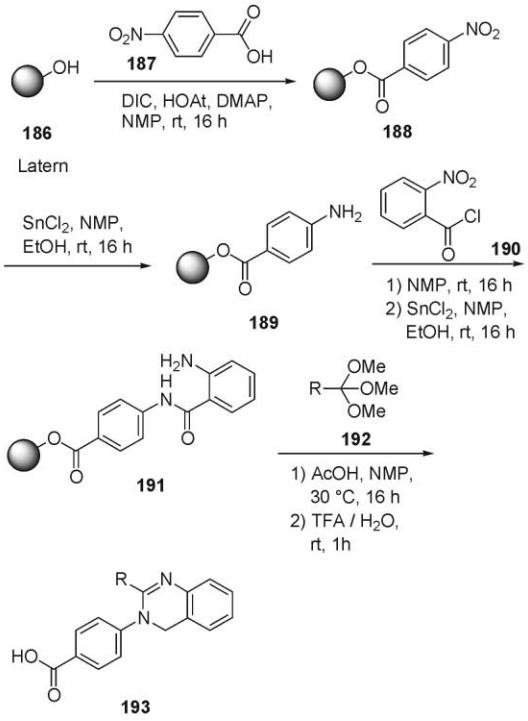
Figure 9. Relevant molecules with quinazoline moiety.



Scheme 25. Pathways to quinazolines.

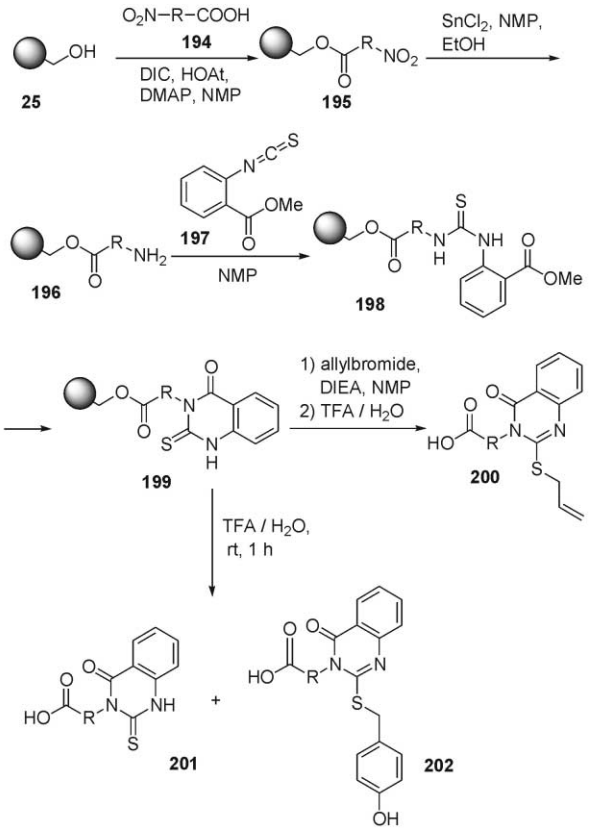


Scheme 26. Synthetic pathway to quinazolines **185** described by Cobb et al.[153]



Scheme 27. Solid-phase synthesis of quinazolines **193** using a cyclocondensation by Makino et al.[158]

Makino et al. also described a pathway to quinazolines using a cyclocondensation[155] (Scheme 28). The first step in this synthesis was the connection of nitro acids **194** by etherification onto Wang resin (**25**). After reduction to the corresponding amine, a cycloaddition with the 2-methoxycarbonyl phenylisothiocyanate (**197**) took place. Cleavage of the resin **199** with trifluoroacetic acid yielded a mixture of the products **201** and **202** depending of the acid concentration, which is due to fragmentation of the linker. However, after *S*-allylation of the quinazoline **199**, a clean synthesis of the *S*-allyl quinazoline **200** was achieved.

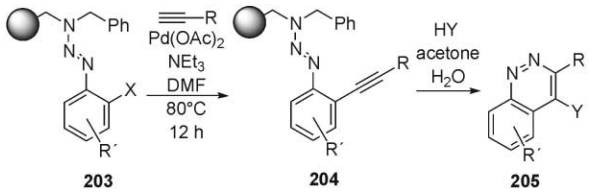


Scheme 28. Solid-phase synthesis of quinazolines **202** using a cyclocondensation by Makino et al.[155]

Cinnolines

Recently, the synthesis and biological activity of indolo[3,2-*c*]cinnolines with antiproliferative, antifungal, and antibacterial activity have been described.[159] Before this, some cinnoline derivatives were screened for their effect on the Central Nervous System,[160] and it was found that some of them had sedative action at low doses.[161]

Cinnolines were synthesized by a Richter type solid-phase reaction by Bräse et al.[162] (Scheme 29). Starting from benzylaminomethyl polystyrene, the required diverse *o*-haloaryl resins **203** were prepared from substituted *o*-haloanilines. The following cross-coupling reaction with the alkynes was catalyzed by palladium. The Richter cleavage reaction with hydrobromic or hydrochloric acid yielded the cinnolines **205** in 47–95% yield and 60–95% purity.



Scheme 29. Synthetic pathway to cinnolines **205** by Bräse et al.[162]

Quinoxalines

Examples of biologically active quinoxalines include antitrypanosomal drugs,[163] partial agonist of the γ-aminobutyric acid A/benzodiazepine receptor complex **207/208**,[164] angiotensin II receptor antagonist,[165] adenosine receptor antagonist,[166] and broadly active antitumoral agents as XK 469 (**206**)[167] (Fig. 10).

The solid-phase synthesis of benzopiperazinones (1,2,3,4-tetrahydroquinoxalin-2-ones) was described.[168–171] Morales et al.[169] (Scheme 30), began the synthesis with esterification of 4-fluoro-3-nitrobenzoic-acid **80** on to Wang resin **25** or bromo Wang resin **209**. *ipso*-Fluoride displacement of the resulting fluoronitro resin **210** yielded aniline resin **211**, which was reduced to the diamine **212**. Direct cyclization of the amine assembled the benzopiperazinones skeleton. Cleavage of the solid support yielded the products **214**.

A similar pathway to tetrahydroquinoxaline-diones was described by Nefzi et al.[172]

The solid-phase traceless synthesis of tetrahydroquinoxalines has been reported, too.[173–175]

The solid-phase synthesis of Quinoxalines on SynPhase™ Laterns was described for the first time by Wu et al.[176]

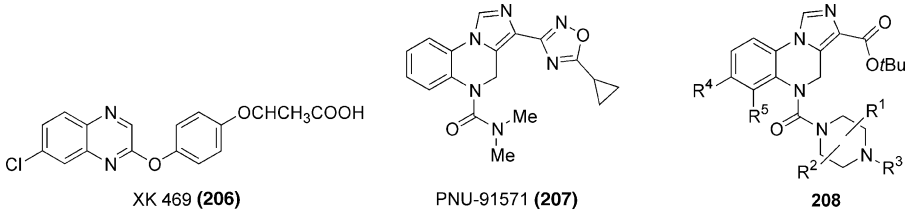
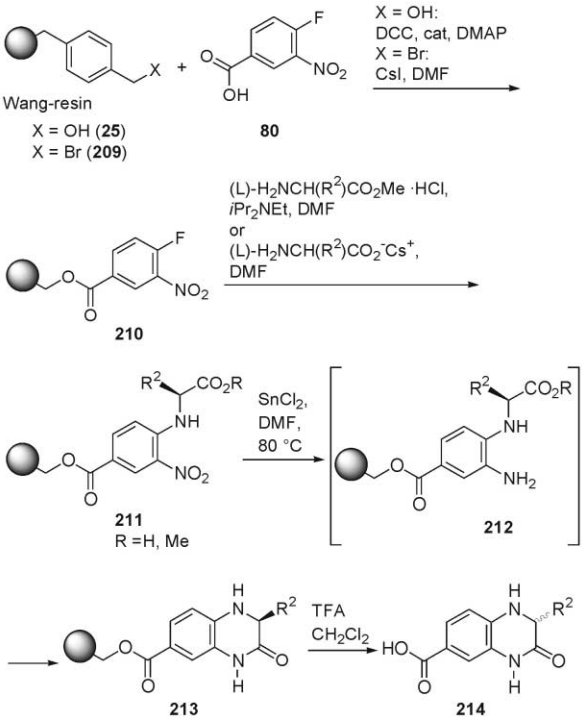
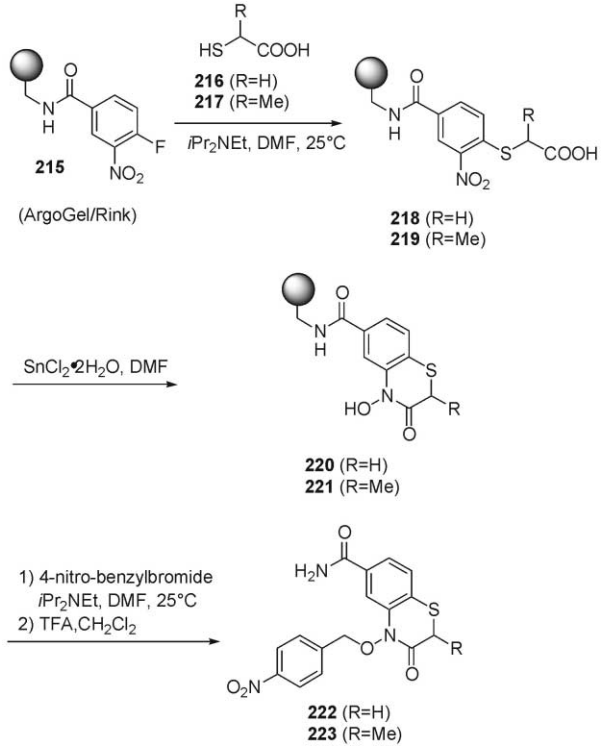


Figure 10. Structure of biologically active quinoxalines.



Scheme 30. Solid-phase synthesis of benzopiperazinones **214** by Morales et al.[169]



Scheme 31. Solid-phase synthesis of benzothiazines **222**, **223** by Schwarz and Gallop.[179]

Benzothiazines

Some benzothiazine derivatives have proven to be potent candidates to be new antiallergic[177] or antirheumatic[178] agents.

Schwarz and Gallop[179] described a synthesis (Scheme 31) in which the fluoronitro resin **215** was reacted with solutions of thiocarboxylic acids **216** or **217,** respectively. The solid-phase nucleophilic aromatic substitution reaction again proved reliable and afforded the corresponding *o*-nitroethers **218** or **219**, respectively. Exposure of these to standard nitro group reduction conditions, however, did not furnish the expected *o*-alkylthioanilines or the corresponding 1,4-benzothiazin-3-ones. Another set of products was obtained in purities exceeding 90%. These were the corresponding cyclic hydroxamic acids **220** and **221**. Thus, treatment of these with *p*-nitrobenzyl bromide at room temperature and subsequent cleavage resulted in smooth conversion to the corresponding **222** and **223**, respectively.

Using a similar procedure Lee et al.[180] reported the solid-phase synthesis of 1,4-benzoxazin-3(4*H*)-one and 1,4-benzothiazin-3(4*H*)-one derivatives.

Benzoannelated Seven-Membered Heterocycles

Benzazepines

Various benzazepines have been reported as potentially antitumoral agents, as the paullones **224**,[181] and the related darpones **225**[182] (Fig. 11). Another compounds having this nucleus have shown biological activity as

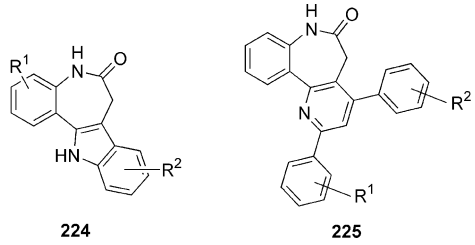


Figure 11. Relevant molecules with benzazepine moiety.

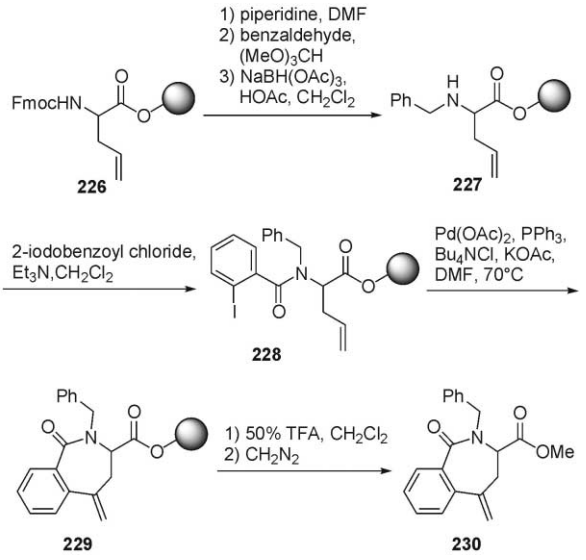
central selective acetylcholinesterase inhibitors,[183] vasopressin receptor antagonist[184] and specific bradycardiac agent as Zatebradine, whose solid-phase synthesis has been recently described.[185]

Bolton and Hodges[186] described the synthesis of benzazepines via intramolecular Heck cyclization as shown in Scheme 32. Following deprotection of immobilized allylglycine ester **226**, reductive amination with benzaldehyde cleanly produced the secondary amine **227**. Subsequent acylation with 2-iodobenzoyl chloride provided **228**, which underwent efficient Heck cyclization to bicyclic lactam **229** following acidic cleavage and esterification. This new class of bicyclic amino acid scaffold can be efficiently functionalized at various sites.

Benzoxazepines

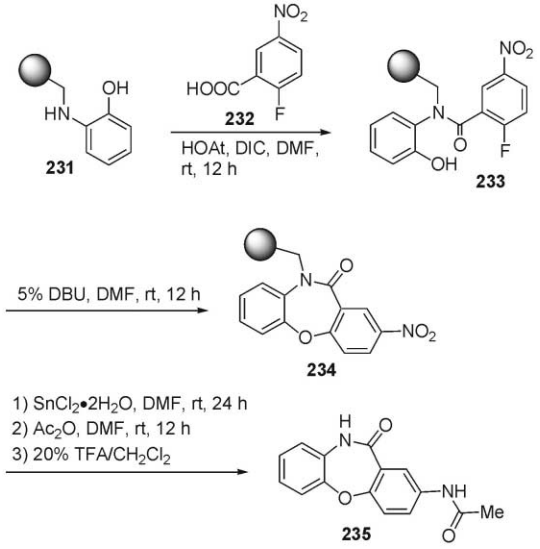
A series of new benzoxazepine derivatives has recently described as 5-HT_1 receptor agonists[187] with remarkable neuroprotective activity. Other derivatives exhibit suitable

properties as anticancer agents[188] or HIV-1 non-nucleoside reverse transcriptase inhibitors.[189]



Scheme 32. Synthesis of benzazepines **230** via intramolecular Heck cyclization by Bolton and Hodges.[186]

Ouyang et al.[190] reported a synthetic strategy toward the benzoxazepine ring (Scheme 33). The resin **231** was prepared by the reductive amination of *o*-aminophenol on AMEBA polystyrene resin. This resin was further modified to afford the immobilized substrate **233**, which was ready for the assembly of the desired derivative **234**. Cleavage of the solid support amounts the benzoxazepine **235** in quantitative yield.



Scheme 33. Synthesis of a benzoxazepine **235** by Ouyang et al.[190]

Benzothiazepines

Diltiazem (**236**) is a well-known 1,5-benzothiazepin-4-one that is among the most widely used drugs in the treatment of cardiovascular disorders, due of its role as calcium channel blocker.[191] Recently, a new family of potent and selective bradykinin receptor antagonist have been reported as JMV 1645 (**237**)[192] and **238**[193] (Fig. 12). Schwarz et al. described a synthetic pathway to benzothiazepines[194] (Scheme 34). They started with a nucleophilic aromatic substitution of the benzoic acid **80** after immobilization. The nitro group was reduced by tin (II)chloride. Reductive alkylation of **240** gave the secondary anilines **242**. Intramolecular cyclization formed the 3,5-disubstituted 2,3-dihydro-1,5-benzothiaepin-4(5*H*)-ones **243**. Using the same procedure, the same group also synthesized benzothiazocine derivatives.[179]

A similar pathway to benzothiazepines was described by Nefzi et al.[195] (Scheme 35) Therefore, *N*-α-Fmoc-*S*-trityl-L-cysteine was coupled to *p*-methylbenzhydrylamine resin, the trityl group was cleaved and the benzoic acid **80** was connected. The protected amine **245** was deprotected and reductively alkylated. Cyclization of **246** resulted in the benzothiazepine skeleton **247**. The nitro group was reduced and coupled to the carboxylic acid.

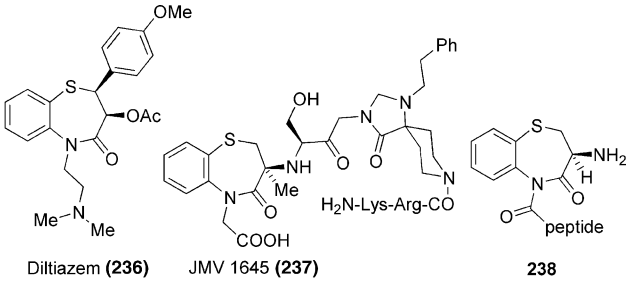
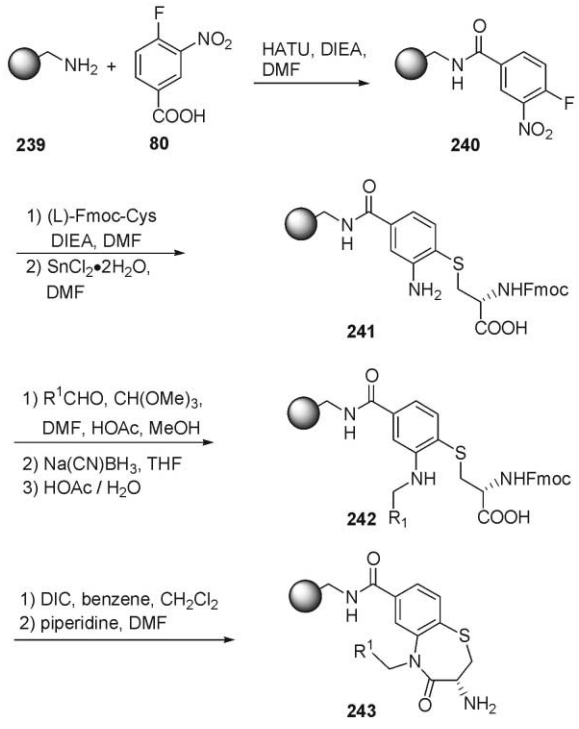


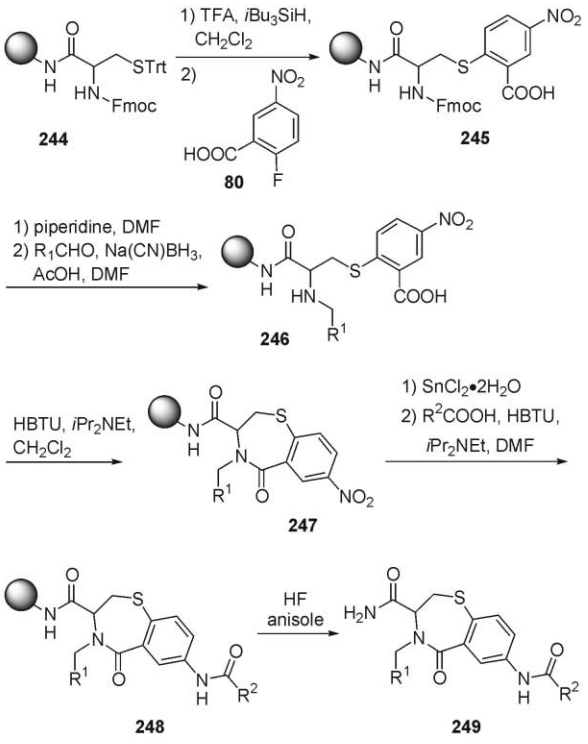
Figure 12. Structure of biologically active benzothiazepines.



Scheme 34. Solid-phase synthesis of 3,5-disubstituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones 243 by Schwarz et al.[194]

Cleavage of the solid support yielded the 1,4-benzothiazepine-5-ones **249** in very high purity.

Another routes for the synthesis of [1,5]-benzothiazepine derivatives, have been reported by Lee et al.[196] and by Micheli et al.[197]



Scheme 35. Solid-phase synthesis of 1,4-benzothiazepine-5-ones **249** by Nefzi et al.[195]

Benzodiazepines

Often the search for new drugs is initiated by modifications of well known drug; this has proven to be a common and reliable route to a new product. One such example has been the azepine class of drugs. Benzodiazepines are an important group of bioavailable therapeutic agents with widespread biological activities. The therapeutic applications of benzodiazepines such as Diazepam (**250**), Triazolam (**251**), Midazolam (**252**) (Fig. 13) are well-known anxiolytic,[198] sedative,[199] and anticonvulsant properties.[200] They have also shown promising activities as antithrombotics[201] and fibrinogen receptor antagonists.[202] As well related structures have experimental applications as ethanol-intoxication antagonists.[203] Members of this family also possess applications as antiarrhytmics,[204] vasopressin antagonists,[205] HIV reverse transcriptase inhibitors,[206] and cholecystokinin antagonists.[207] In addition, the 1,4-benzodiazepine-2,5-dione core appears in a number of natural products.[208,209]

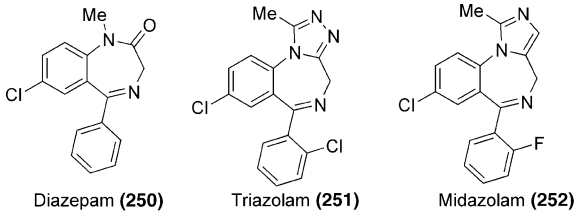
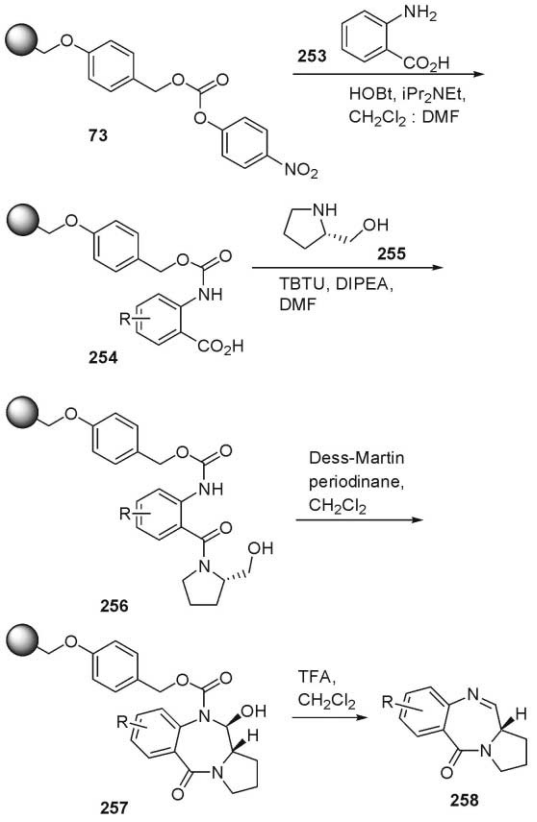


Figure 13. Structure of relevant molecules with benzodiazepine moiety.

Due to their widespread biological activities and favorable pharmacokinetical properties,[210] benzodiazepines were among the first classes of small molecules to be synthesized on solid support.[14,211] Since then, there have been numerous reports on the synthesis of similar skeletons, the first efforts to prepare libraries of this type were focused on 1,4-benzodiazepin-2-ones and 1,4-benzodiazepin-2,5-diones. There are also examples for the solid supported synthesis of 2,3-benzodiazepine-4-ones[212] and 1,4-benzodiazepine-2,3-diones.[213]

There are many pathway examples to synthesize benzodiazepines using cyclocondensation approaches.[214–218] For example, the synthesis by Berry et al. is described in Scheme 36.[214] In the first step, they coupled anthranilic acid (**253**) to the *p*-nitrophenyl carbonate Wang resin **73**. After this, pyrrolidinemethanol (**255**) was added to the immobilized A-ring. The closure of the B-ring was achieved by an oxidation to give the benzodiazepine **257**. Cleavage from the solid support gave the product **258** in good yield.

The solid-phase synthesis of pyrrolo[2,1-*c*][1,4] benzodiazepine-5,11-diones using Wang resin trough amide



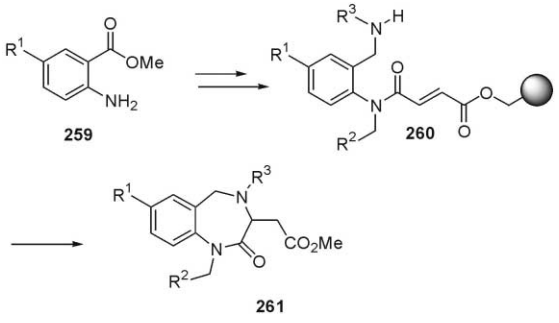
Scheme 36. Synthetic pathway to benzodiazepines **258** using a cyclocondensation by Berry et al.[214]

formation and reductive cyclization procedures was described by Kamal et al.[219,220]

Bhalay et al. described a synthesis of benzodiazepines by an exo 1,4-addition[221] (Scheme 37). An anthranilic ester was coupled to the solid support. The ester group was displaced by an amine. Subsequent to the cyclization by a 1,4-addition, cleavage of the solid support yielded the benzodiazepin-2-ones **261**. Using this pathway, they designed a 120 compound library with three points of diversity.

Boojamra et al. used a different synthetic strategy to 1,4-benzodiazepine-2,5-diones[222] (Scheme 38). Therefore, Merrifield resin (**263**) was derivatized with the sodium salt of the phenol **262**. The α-amino ester **265** was loaded this then formed BAL linker **264** by reductive amination. Acylation of the resulting secondary amine **266** with unprotected anthranilic acides **267** provides the support-bound tertiary amide **268**. After cyclization and introduction of R^2, the 1,4-benzodiazepine-2,5-diones **272** were cleaved off the solid support.

The Aza–Wittig reaction was used for the cyclization in the synthetic pathway of Goff and Zuckermann.[223] In the first step, they connected the Rink amide resin **43** with the bromoacetic acid. Then, the bromide was displaced by isobutylamine to give **274**. Bromoacetylation and displacement with amino acid esters affected the intermediates **275**, which were directly acylated with *o*-azidobenzoyl chloride (**276**) to **277**. Cleavage of the solid support yielded the 1,4-benzodiazepine-2,5-iones (Scheme 39).



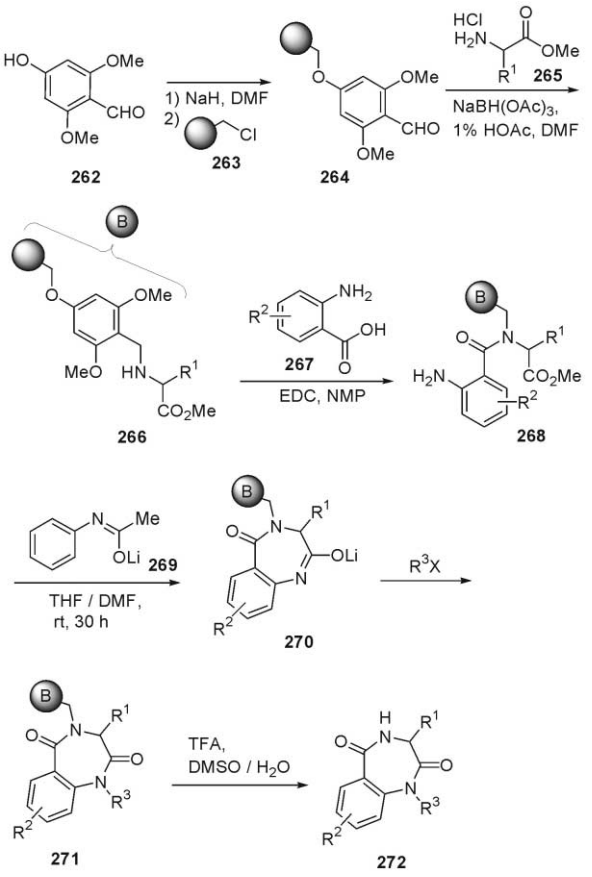
Scheme 37. Synthetic pathway to benzodiazepines **261** by using a 1,4-addition by Bhalay et al.[221]

Benzoannelated Eight-Membered Heterocycles

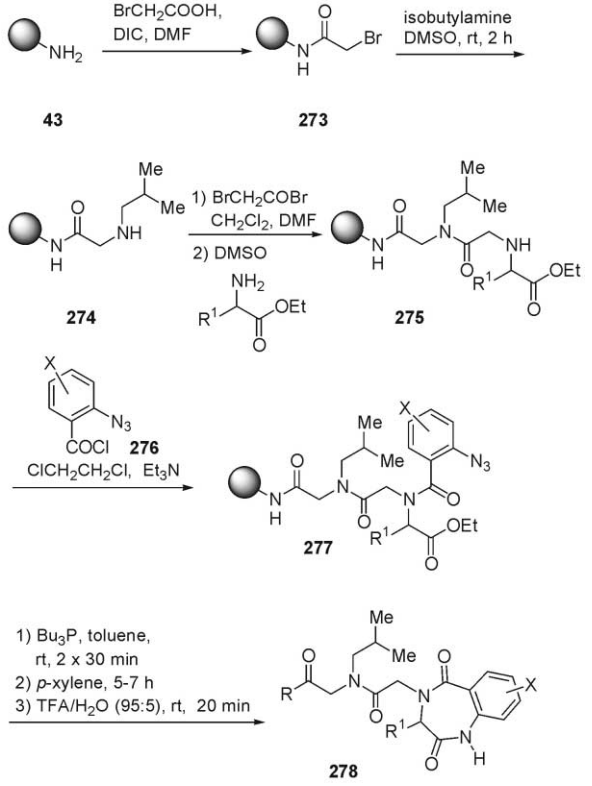
Benzoxazocines

Related heterocycles of the dibenzoxazocine ring have significant anti-inflammatory properties.[224] The benzoxazocine Nefopam (**279**) is a non-narcotic analgesic not structurally related to other analgesic drugs (Fig. 14).[225]

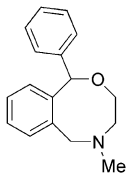
Ouyang and Kiselyov have described an efficient approach to dibenzo[*b*,*g*]1,5-oxazocines on solid support[226,227] (Scheme 40). They modified the Rink amide



Scheme 38. Synthetic pathway to 1,4-benzodiazepine-2,5-diones **272** by Boojamra et al.[222]

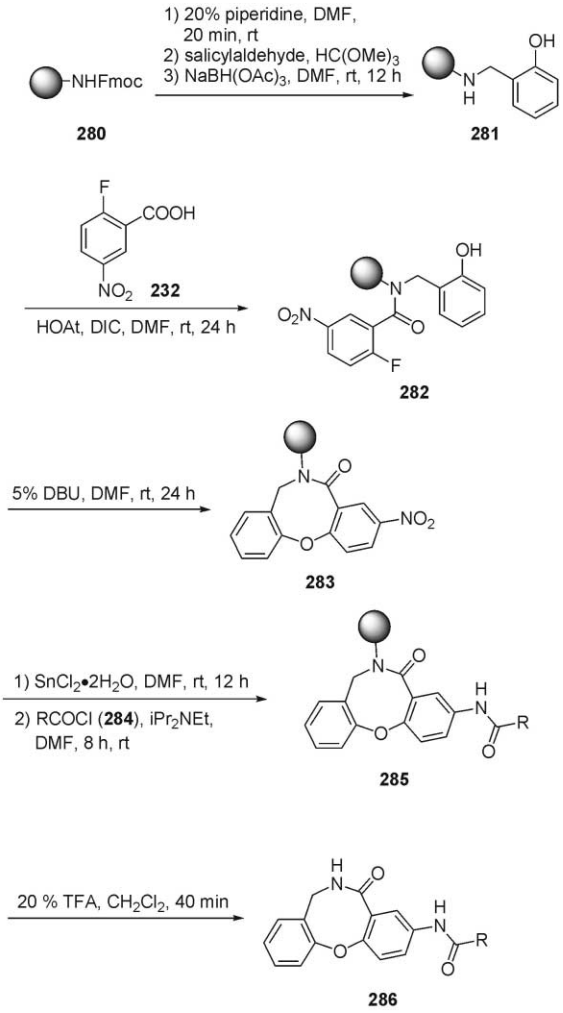


Scheme 39. Synthetic pathway to benzodiazepine-2,5-diones using an Aza–Wittig reaction by Goff and Zuckermann.[223]



Nefopam **(279)**

Figure 14. Structure of Nefopam (**279**).



Scheme 40. Synthesis of benzoxazocines by Ouyang and Kiselyov.[226]

resin with salicylaldehyde. The subsequent attachment of the 2-fluoro-5-nitrobenzoic acid (**232**) to the resulting resin **280** afforded the intermediate **282**. The cyclization took place by nucleophilic aromatic substitution, and the resultant immobilized nitrodibenz[*b*,*f*]oxazocine **283** was reduced to the amino derivative, which was acylated and cleaved to provide **286** in good yields.

Conclusions and Outlook

The solid-phase synthesis of benzoannelated nitrogen heterocycles that have been reported to date, illustrate several different approaches to the challenge of preparing libraries of bioactive products and allows the synthesis of many novel chemical structures.

Due to the impressive pharmacological activities of some heterocycles such as benzodiazepines, benzimidazoles, indoles or (tetrahydro)quinolines for example, these have been targets of intense synthetic efforts, and different synthetic approaches have been reported. Although less extensively investigated, the solid phase synthesis of other interesting benzoannelated heterocycles have been reported also.

Several heterocycles system as benzimidazoles, quinoxalines, benzothiazines, benzothiazepines, benzodiazepines and benzothiazocines have been obtained via nucleophilic aromatic substitution reactions on solid support. Another common procedure for the synthesis of indoles, quinolines, cinnolines and benzazepines is a palladium-catalyzed transformation. However, so far, only one synthetic pathway on solid phase has been reported for the benzotriazoles, indazoles, benzoxazoles or quinoxalines. Therefore, the application of new reactions or well-known name reaction will find also application in solid phase synthesis of heterocycles.

The Grieco reaction is an example of a multicomponent reaction, which was used for the synthesis of quinoline rings. It can be expected that the use of multicomponent reactions will find more applications in the near future. As a traceless strategy[228] for the synthesis of these heterocycles would be highly desirable, it has been developed several synthetic routes for a traceless combinatorial synthesis of indoles, benzimidazoles, quinolines, quinazolines, quinoxalines, benzodiazepines and benzoxazocines. Particularly useful is the cyclative cleavage and it can be expected that this strategy will be employed in various new strategies.

The area of the synthesis of benzoannelated nitrogen rings continues to grow, and the solid-phase chemistry will provide more and better methods for the synthesis of benzoannelated heterocycles, allowing the discovery of new libraries of novel compounds more active, more specific and safer.

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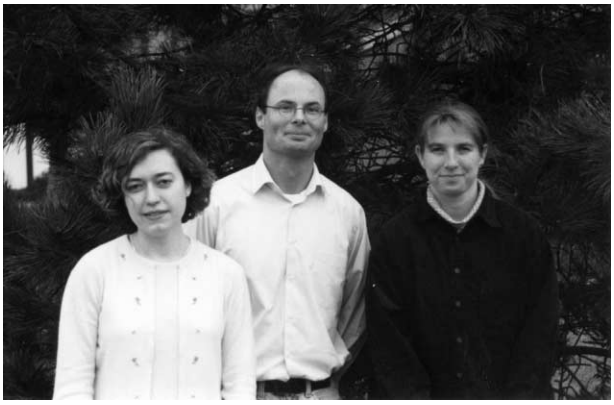

Carmen Gil, Stefan Bräse and Kerstin Knepper are working together in the fascinating area of solid-phase chemistry.

Carmen Gil was born in Talavera de la Reina, Spain in 1972. She studied at the Complutense University of Madrid and received her PhD in 2001, after working with Ana Martínez at Medicinal Chemistry Institute in Madrid. She is currently a Marie-Curie post-doctoral fellow at the University of Bonn with Stefan Bräse.

Kerstin Knepper was born in Dortmund, Germany in 1976 and studied chemistry at the University of Dortmund. In 2001, she obtained her Diploma in chemistry in the group of Prof. Krause. She is currently a PhD student with Stefan Bräse at the University of Bonn. The research interests of both include solid-phase synthesis of new benzoannelated nitrogen heterocycles.

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