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Synthesis of the 1,5-Benzothiazepane Scaffold – Established Methods and New Developments

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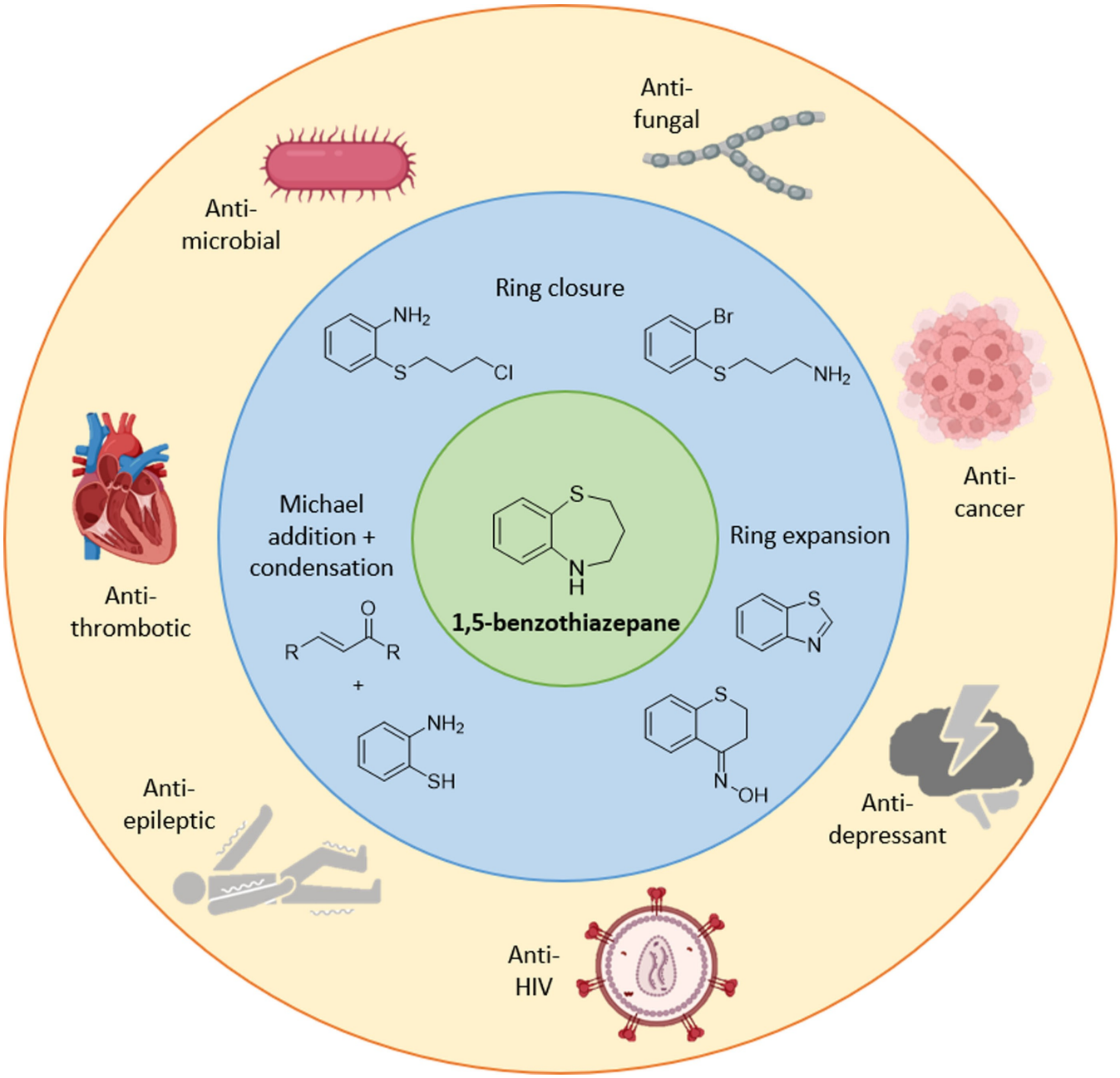


The 1,5-benzothiazepane structure is an important heterocyclic moiety present in a variety of commercial drugs and pharmaceuticals. This privileged scaffold exhibits a diversity of biological activities, including antimicrobial, antibacterial, anti-epileptic, anti-HIV, antidepressant, antithrombotic and anti-cancer properties. Its important pharmacological potential renders research into the development of new and efficient synthetic methods of high relevance. In the first part of this review, an overview of different synthetic approaches toward 1,5-benzothiazepane and its derivatives is provided, ranging from established protocols to recent (enantioselective) methods that promote sustainability. In the second part, several structural characteristics influencing biological activity are briefly explored, providing a few insights into the structure-activity relationships of these compounds.

1. Introduction

Heterocycles constitute important building blocks in natural products and pharmaceuticals, as more than 85% of bioactive compounds are based on a heterocyclic scaffold or contain a heterocyclic ring in their structure.[1] The introduction of such ring systems often has a positive impact on the physicochemical properties of the concerned molecules through modulation of for example their lipophilicity and solubility, resulting in an easier uptake and improved bioavailability.[2] One of these privileged heterocycles is the benzothiazepine scaffold, which consists of an unsaturated seven-membered thia-aza-ring, termed as a thiazepine, fused to a benzene. When the seven-membered ring is completely saturated, the corresponding system is denoted as a benzothiazepane. Depending on the position of the heteroatoms, three isomeric benzothiazepane structures can be identified, namely 1,3-benzothiazepane **1**, 1,4-benzothiazepane **2** and 1,5-benzothiazepane **3** (Figure 1).[3,4]

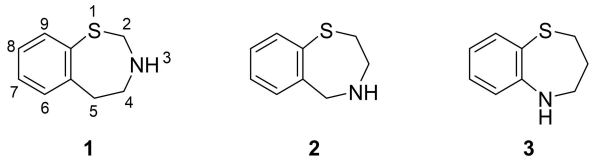
Compared to its flat thiazepine counterpart, the benzothiazepane system introduces a degree of three-dimensionality within the overall structure due the presence of sp^3 atoms. Research has shown that the elevated sp^3 fraction cannot only improve the solubility of the compound, but can also lead to higher success rates in clinical testing.[5] Furthermore, 'bioisosteric replacement' is known to be a valuable approach in drug discovery to improve upon pharmacokinetic properties or to diminish unwanted side effects. As (saturated) benzothiazepines are considered bioisosteres of benzodiazepines, which contain an additional nitrogen atom instead of a sulfur atom, they can be relevant from that point of view as well.[6] Because of their easy accessibility in particular, 1,5-benzothiazepane derivatives have received a great amount of attention, and an array of drugs based on this structural system has already been FDA-approved (Figure 2). Examples of 1,5-benzothiazepane-based cardiovascular agents are Diltiazem **4**, Clentiazem **5** and Siratiazem **6**. Thiazesim **7** and Quetiapine fumarate **8**, containing the 1,5-dibenzothiazepine scaffold, are drugs used for the treatment of central nervous system (CNS) disorders,[3,7,8] interacting with the lateral amygdaloid nucleus and the Serotonin 2a and Dopamine D2 receptors, respectively.[9] This is only the tip of the iceberg regarding the diverse biological activities of these structures. Other possible applications of 1,5-benzothiazepane-derived pharmaceuticals include their use as antimicrobials[10,11] and antifungals,[12] anti-epileptic agents,[13] anti-HIV medicines,[14] antidepressants,[15,16] antithrombotic drugs,[17] and anticancer agents.[18]

Due to the broad applicability of these promising thia-aza-heterocycles, there is a continued interest in developing new and more efficient methods for their synthesis. In recent years, these methods have shifted toward greener alternatives that can reduce waste, shorten reaction times and avoid the use of harmful chemicals.[19] In this mini-review, an overview of different synthetic methods for the construction of 1,5-(di)benzothiazepane derivatives will be discussed, ranging from established methods to recent (green) developments. In addition, a few examples regarding the possible interactions of these scaffolds with their target and some structure-activity relationship studies will be briefly explored to gain insight into their diverse biological activity.

2. Synthetic Methods

2.1. Synthesis of 1,5-benzothiazepanes through ring expansion

A first method, known in the literature since the 1980s, concerns the expansion of a thiopyran-4-one-derived oxime to a benzothiazepane ring.[20] Cho et al. used this approach to synthesize 1,5-benzothiazepane **3**, and are the first to have proposed a reaction mechanism.[21,22] In the standard protocol,



1 **2** **3**

Figure 1. Three isomeric benzothiazepane structures.

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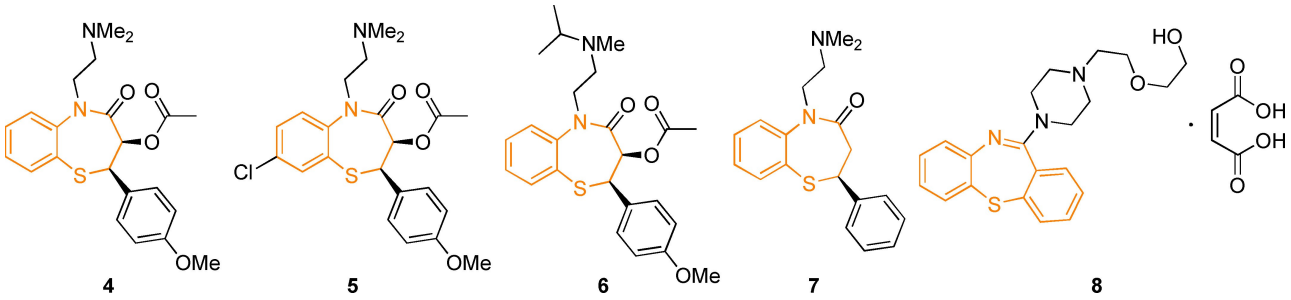

Figure 2. Examples of drugs containing the 1,5-benzothiazepane scaffold. From left to right: Diltiazem **4**, Clentiazem **5**, Siratiazem **6**, Thiazesim **7** and Quetiapine fumarate **8**.

thiochroman-4-one **9** was treated with hydroxylamine, affording thiochroman-4-one oxime **10** through nucleophilic addition of the hydroxylamine across the carbonyl function and subsequent elimination of water. After purification by extraction and column chromatography, thiochroman-4-one oxime **10** was redissolved and diisobutylaluminum hydride (DIBALH) was added to achieve C=N reduction, followed by N–O bond cleavage, which led to the rearrangement toward the ring-expansion product. Lastly, work-up and purification of the reaction mixture through column chromatography furnished 1,5-benzothiazepane **3** (Figure 3).[21,23] This method uses dangerous and harmful chemicals and requires cooling, rendering it unattractive from a green chemistry point of view.

Cho et al. further explored the ring expansion of oximes by means of different aluminum reagents, such as $LiAlH_4$, $(MeOCH_2CH_2O)_2AlH_2Na$, $LiAlH(tOBu)_3$, AlH_3 and $AlHCl_2$. Some of these experiments, however, led to the formation of the undesired primary amine **15** as a side product (Figure 3). Fortunately, this issue was resolved by using dichloroaluminum hydride ($AlHCl_2$) as the reagent in combination with cyclopentyl methyl ether (CPME) as the solvent. This reaction was carried out in a similar way as the one described above.[22]

Another ring expansion-based approach toward benzothiazepanes has been described in 1980 by Federsel et al., consisting of ring enlargement of quaternized benzothiazole **17** (Figure 4). Once the benzothiazolium salt **17** was isolated, it was brought into an alkaline environment in order for the rearrangement to take place. Nucleophilic attack of the hydroxide anion opened the C=N double bond, which led to 3-(3-chloropropyl)-2,3-dihydrobenzo[*d*]thiazol-2-ol **18**. Subsequent carbonyl formation cleaved the C–S bond, enabling the sulfur atom to perform an intramolecular nucleophilic substitution reaction in structure

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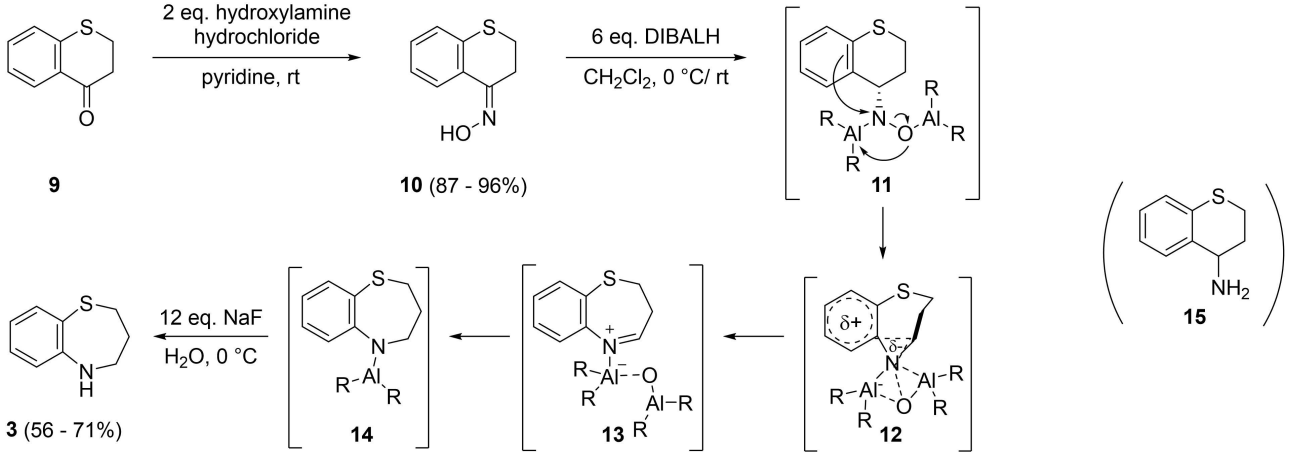


Figure 3. Ring expansion of oximes toward 1,5-benzothiazepane **3** using hydroxylamine hydrochloride and DIBALH with primary amine **15** as undesired side product.

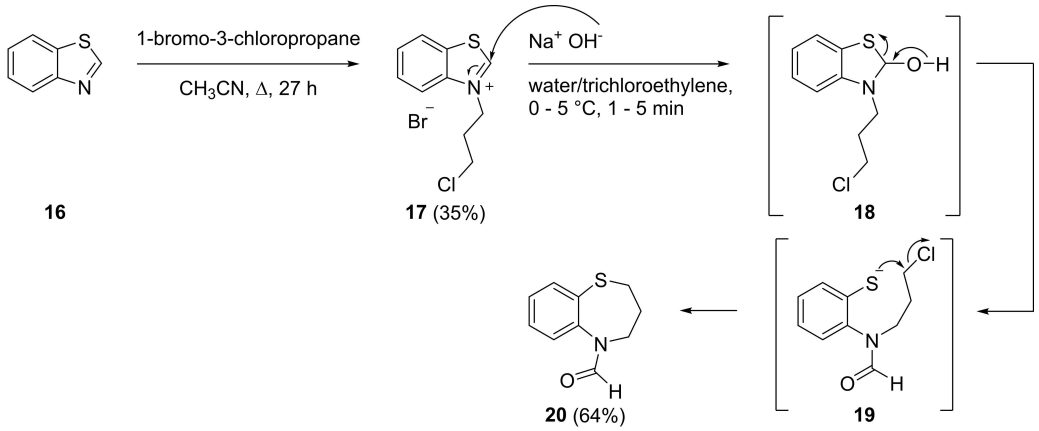


Figure 4. Synthesis of quaternized benzothiazole **17** and ring expansion toward 1,5-benzothiazepane **20**.

19, which ultimately gave rise to heterocycle **20**. The rearrangement reaction was shown to have a short reaction time. Removal of the solvent and recrystallization afforded the pure product *N*-formyl-2,3,4,5-tetrahydro-1,5-benzothiazepine **20**.[24]

However, this method is rarely mentioned in the literature to create new benzothiazepane compounds. Possible explanations are the relatively low yield and harsh reaction conditions (reflux for >24 h) of the quaternization reaction on the one hand, or the use of trichloroethylene on the other hand, as the latter is suspected of causing genetical damage and cancer.[25] As a result, a risk analysis was performed, which led to the decision in the Commission Regulation (EU) No 348/2013 that an authorization requirement is needed for the use of this solvent.[26]

2.2. Synthesis of 1,5-benzothiazepanes through ring closure

The second general approach toward 1,5-benzothiazepanes encompasses a ring-closing reaction starting from amino- or bromo-substituted thiophenols. After alkylation of the thiol, the ring closure proceeds via a nucleophilic substitution reaction in which the amino group attacks the carbon atom connected to a leaving group.[27–29]

Ueyama et al. treated thiophenol **21a**–**b** with 1-bromo-3-chloropropane in basic conditions to allow the sulfur atom to attack 1-bromo-3-chloropropane through nucleophilic substitution, forming 2-[(3-chloropropyl)thio]aniline **22a** or 4-chloro-2-[(3-chloropropyl)thio]aniline **22b** (Figure 5). After purification by extraction and column chromatography, chlorides **22a**,**b** were re-dissolved and brought into basic conditions by adding tripropylamine,[27] which is toxic and flammable.[25] This led to a nucleophilic substitution reaction, where the amino group attacked the chlorinated carbon atom at high reaction temperatures with expulsion of chlorine. The reaction mixture was purified by column chromatography and 1,5-benzothiazepane **3** and 7-chloro-1,5-benzothiazepane **23** were isolated.[27]

Mukherjee et al. used 2-bromothiophenol **24** as starting compound and brought this substrate into contact with 3-bromopropan-1-amine in basic medium, which allowed for nucleophilic substitution to occur, producing 3-[(2-bromophenyl)thio]propan-1-amine **25** (Figure 6). The product **25** was then re-dissolved and lithium diisopropylamide (LDA) was added as a strong base to induce the ring closure.[28] The

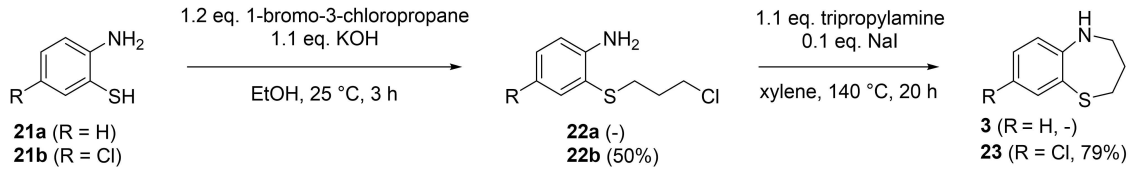


Figure 5. Ring closure starting from 2-aminothiophenol **21 a**–**b**.

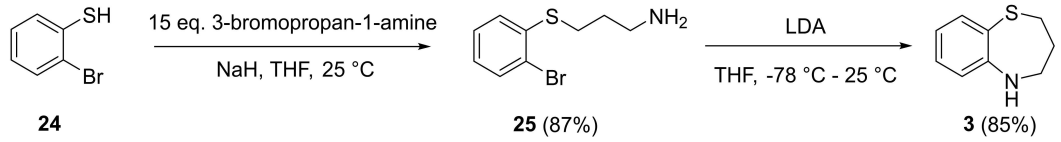


Figure 6. Ring closure starting from 2-bromothiophenol **24**.

notably low stability of LDA in THF above 0 °C imposed a sub-zero temperature for this reaction.[30] The ring closure most likely proceeds via the elimination-addition (benzyne) mechanism. In this mechanism, the strong base removes a proton from the benzene ring with the elimination of bromide, which produces a reactive benzyne intermediate.[31] The benzyne molecule then rapidly undergoes addition of the amino group, leading to the formation of 1,5-benzothiazepane **3**.[28] This method required a large excess of 3-bromopropan-1-amine, a highly flammable base and low reaction temperatures in the second step, yet it resulted in higher yields than the aforementioned method.

Lastly, the regio- and stereo-controlled synthesis of 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines **27** has been discussed by Karikomi et al.[29] These compounds were obtained by reacting *trans*-2,3-disubstituted aziridines **26 a**–**c** with 2-aminothiophenol **21 a** in a basic environment (Figure 7). It is a fairly efficient method to access *trans*-2- or *trans*-4-substituted 3-aminobenzothiazepanes (**28** or **27 a**–**b**), depending on the leaving group of the aziridine. Indeed, when the leaving group is more reactive (tosyl vs. mesyl), the aziridine experiences a nucleophilic substitution reaction where the leaving group is replaced by the mercapto group of 2-aminothiophenol **21 a** (instead of initial aziridine ring opening at the carbon atom linked to R^1), followed by cyclization to 4-substituted benzothiazepane derivatives **27**. A benefit of this method is that the aziridines can easily be synthesized starting from allylic sulfonamides or allylic alcohols.[29]

A similar approach was successfully used to achieve the synthesis of 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines **31 a-c** starting from 2-(bromomethyl)aziridines **29 a**–**c**. In this case, the sulfur atom of 2-aminothiophenol **21 a** attacked the less sterically hindered carbon atom of the reactive aziridine, opening up the latter structure. The resulting nitrogen anion then attacks the brominated carbon atom, leading to the smooth formation of the final 1,5-benzothiazepanes **31 a**–**c** (Figure 8). However, also initial bromide displacement by the mercapto group, followed by amino group-induced aziridine ring opening could be considered as a mechanism to explain the formation of structure **31**. [29]

2.3. Synthesis of 1,5-benzothiazepanes through reaction of α,β-unsaturated carbonyl compounds with 2-aminothiophenol

The first report of the reaction between 2-aminothiophenols and α,β-unsaturated carboxylic acids was made in 1927 by Mills et al. They observed that the thiol group associates with the ethylenic group through a (thia-)Michael addition, and that the amino group of 2-aminothiophenol **21 a** condenses with the

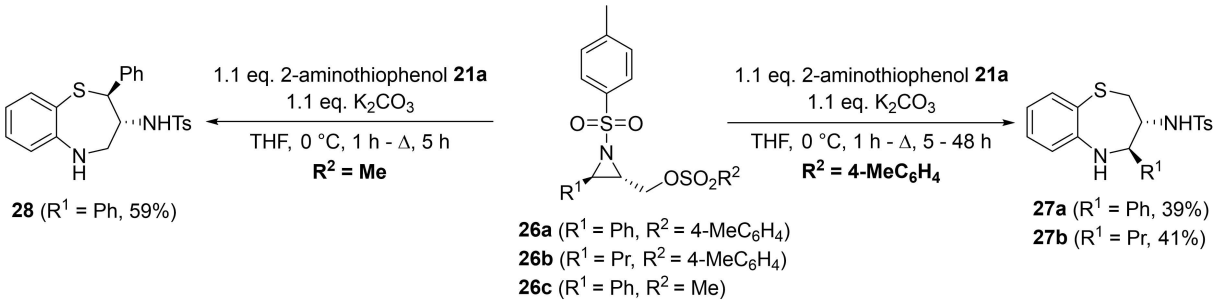


Figure 7. Synthesis of 3-sulfonamido-1,5-benzothiazepanes **27 a**–**b** and **28** starting from *trans*-2,3-disubstituted aziridines **26 a**–**c**. When the tosyl group is used as the leaving group (R^2=4-MeC_6H_4), 4-substituted 1,5-benzothiazepanes **27 a**–**b** are formed. In contrast, 2-substituted 1,5-benzothiazepanes **28** are formed when the leaving group is a mesyl group (R^2=Me).

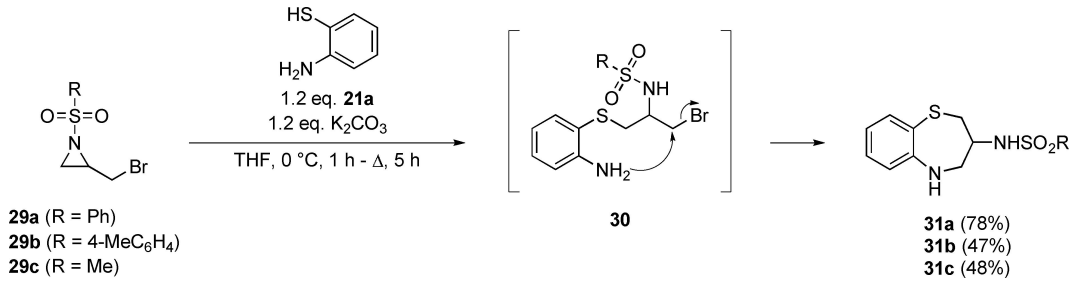


Figure 8. Synthesis of 3-sulfonamide-1,5-benzothiazepane **31 a–c** starting from 2-(bromomethyl)aziridines **29 a–c**.

carbonyl group of the acid with the loss of a water molecule.[32] These two steps formed the basis for the synthesis of 2,4-disubstituted 1,5-benzothiazepanes **34** from 2-aminothiophenol **21 a** and a range of different α,β-unsaturated carbonyl compounds **32** (Figure 9).

The reaction is most commonly performed in (anhydrous) methanol or ethanol at reflux temperature with the addition of acetic acid[11,12,33–36] or hydrochloric acid[37,38] to aid the condensation of the amino group. Bases, such as pyridine[39] and piperidine,[40,41] have also been used. As can be seen in the general scheme (Figure 9), product **34** still carries a C=N double bond. This bond can be converted to a single bond by adding a reductive agent, such as lithium aluminum hydride ($LiAlH_4$) or sodium cyanoborohydride ($NaBH_3CN$), to the reaction.[37,42] This method is widely used as it is simple, does not require expensive catalysts or solvents, and the product **34** is generally easily purified as it tends to precipitate from the reaction mixture and can be obtained in pure form after filtration and recrystallization.[12,18,34,37,38] In some cases, however, the reaction mixture is concentrated and subsequently recrystallized or purified by column chromatography.[33,35] Drawbacks of this method are that it requires high temperature and often takes multiple hours to complete, which is not in line with the principles of green chemistry.[18]

The reaction can also be performed using cyclic α,β-unsaturated carbonyl compounds, as demonstrated by the group of Urbanski et al. 5,6-Dihydropyran-2-one **35** was added to 2-aminothiophenol **21 a** in a solvent mixture and was then heated under reflux to encourage cyclization (Figure 10). The reaction mechanism is fairly similar to the one described before, with the exception that no water molecule is eliminated. Instead, the carbonyl function is restored as an amide and the lactone is opened to produce the thiazepane ring, substituted on the C2-position with a 2-hydroxyethyl fragment (see structure **36**). The amide carbonyl function was then reduced using a borane-tetrahydrofuran complex, giving rise to 2-hydroxyethyl-substituted benzothiazepane **37** as the product.[43]

Although it leads to an all-sp^2 benzothiazepine system, the following, recently developed method, in which α,β-unsaturated ynones **38** have been treated with 2-aminothiophenols **21** in order to obtain 2,4-disubstituted 1,5-benzothiazepines **40**, is worth mentioning as well. To that end, a zirconocene catalyst was complexed with a suitable ligand to increase the transformation rate. Multiple ligands were screened, and that study revealed that the highest yield was obtained using the amino acid L-phenylalanine **39**. Unlike the classical method, it was not necessary to heat up to reflux temperature, and the reaction was completed after five hours. It can be noted that there is considerable variation concerning the yield. The lowest yields of 41% and 50% were ascribed to steric hindrance caused by 2-OMe-substituted ynones (Figure 11).[44]

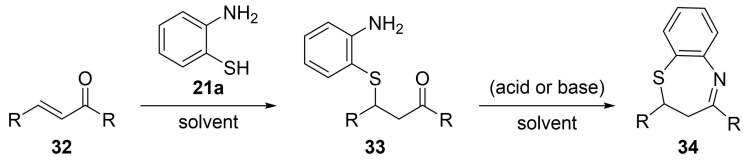


Figure 9. General scheme for the reaction of α,β-unsaturated carbonyl compounds **32** with 2-aminothiophenol **21 a**.

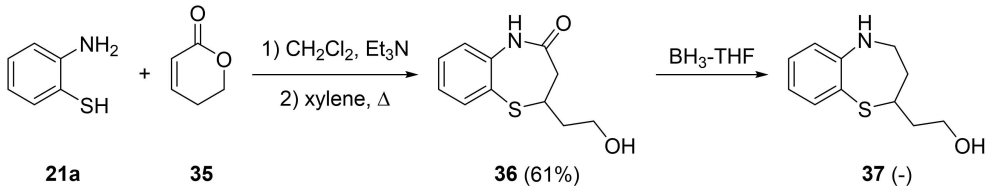


Figure 10. Synthetic method starting from cyclic α,β-unsaturated compound **35**. The 1,5-benzothiazepinone **36** was reduced with BH_3-THF to form the 2-hydroxyethyl-substituted benzothiazepane **37**.

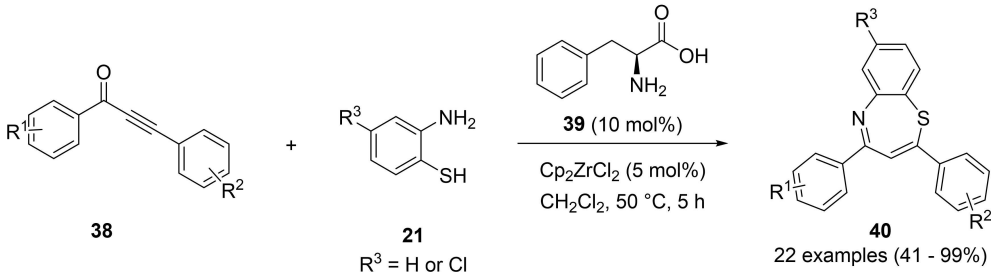


Figure 11. Reaction of α,β-unsaturated ynones **38** with 2-aminothiophenols **21** to form 2,4-disubstituted 1,5-benzothiazepines **40** using a zirconium catalyst.

In recent years, the focus has shifted increasingly toward the implementation of green chemistry principles within all areas of organic synthesis, including benzothiazepane synthesis.[19] One way to achieve this is by looking at alternative catalysts that can be re-used (e.g., Co_3O_4 nanosheets[45] or H-Fer zeolites),[46] are non-toxic and cheaper (e.g., saturated ammonium chloride solution in water[10] or mango juice),[47] can be used in one-pot tandem reactions (e.g., nanocrystalline ZSM-5)[48] or either do not require the use of any solvent, or can be used with water as the solvent (e.g., tetra-*n*-butylammonium fluoride (TBAF)[49] or Na_2CO_3/tetrahexylammonium chloride (THAC) in water).[47] Another way to pursue greener approaches is to employ a different solvent that can be recycled and that allows for mild reaction conditions, such as hexafluoropropan-2-ol[50] and polyethylene glycol in combination with ultrasound irradiation,[51] or a biodegradable and non-toxic solvent, such as glycerol.[52] Lastly, ionic liquids can be considered as another green alternative as they can be re-used, can reduce the reaction time and can help to reduce the need of harmful catalysts. Examples that have been employed for the synthesis of 1,5-benzothiazepine derivates are [1-butyl-3-methylimidazolium]ClO_4 ([Bmim]ClO_4),[53] [1-methyl-3-octylimidazolium]SCN ([Omim]SCN) and [Omim]Cl.[54]

Very recently, Pinate et al. reported on the use of 1,4-diazabicyclo[2.2.2]octane-based acidic ionic liquids as a medium for the reaction of different chalcones **41** with 2-aminothiophenol **21 a** (Figure 12, route a). From the ionic liquids that were tested, [C_4H_{10}-1,4-diazabicyclo[2.2.2]octane][HSO_4]$_2$ ([C_4H_{10}-DABCO][HSO_4]$_2$) led to the highest yield of derivatives **42** in the shortest amount of time. According to the authors, this method is easy to perform, generally applicable, allows for cleaner reaction conditions than other methods, avoids the use of harmful organic solvents and catalysts, uses a green solvent medium, reduces reaction times, and facilitates the isolation with moderate to excellent yields.[55] Nevertheless, using ionic liquids is also associated with some drawbacks such as their high price, high viscosity and low vapor pressure.[56] Starting from similar substrate compounds, a new method using ferrous sulphate as a catalyst in combination with sonification has been reported by Pawar et al. (Figure 12, route b). Benefits of this protocol are that it allows working under mild reaction conditions, has relatively short reaction times, uses a recyclable catalyst and leads to good yields and high purity.[57] It does, however, require the use of morpholine, which is flammable, toxic and suspected of damaging fertility and causing harm to the unborn child.[25]

Phippen et al. have developed another method focusing on less harsh conditions and taking further steps toward green chemistry by using water as a solvent and reducing the reaction temperature and time. This method started from *N*-acryloyl-2,5-dimethylpyrrole **43**, which reacted with iodobenzene in an aqueous Heck reaction. Sonication was used to improve contact between pyrrole **43** and iodobenzene. After work-up and purification by column chromatography, (*E*)-*N*-cinnamoyl-2,5-dimethylpyrrole **44** was added to 2-aminothiophenol **21 a** in water and was strongly mixed in order to effect the desired Michael addition. After work-up and purification using column chromatography, *p*-toluenesulfonic acid was added to thioether **45** to induce addition of the amino group across the amide with elimination of dimethylpyrrole (Figure 13).[58] However, although water is a greener solvent, it can also cause solubility issues and can thus result in reactions with lower efficiency.

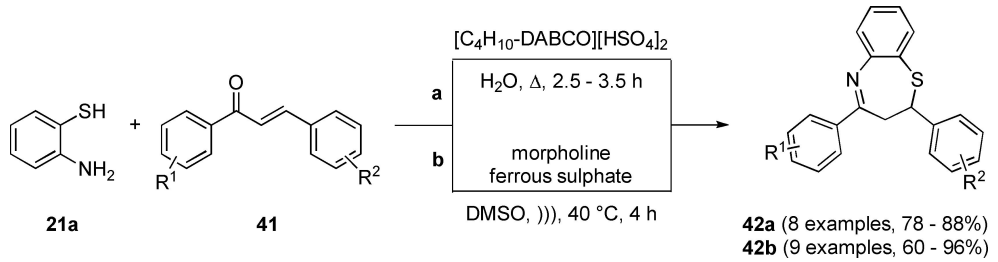


Figure 12. Two approaches toward the green synthesis of 1,5-benzothiazepines **42**; Entry **a** uses an ionic liquid and entry **b** uses sonification and a recyclable catalyst.

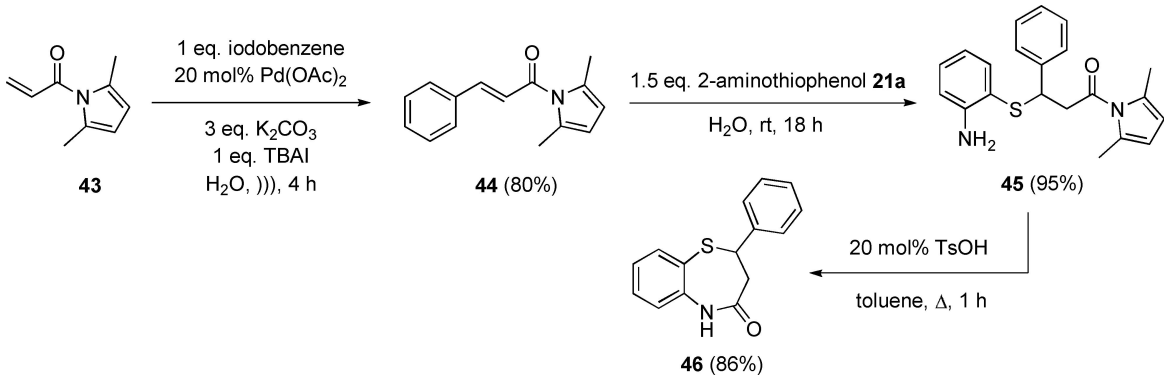


Figure 13. Green synthesis method starting from N-acryloyl-2,5-dimethylpyrrole **43** using water as the solvent.

The green synthesis of 1,5-benzothiazepines can also be achieved through multicomponent reactions (MCRs). Multicomponent reactions are defined as reactions in which three or more components are combined in one pot to form a product that contains structural features of all the components.[59,60] It not only allows to synthesize a library of structurally complex compounds, but it also is selective, minimizes the number of consecutive reaction steps and increases atom efficiency.[60,61] A first approach was developed by Willy et al. and combined the Sonogashira coupling of an acid chloride **47** and an alkyne **48** with a Michael addition and subsequent condensation (Figure 14). Mild reaction conditions were used and, apart from two benzothiazepines **49** with a trimethylsilyl substituent, all yields were above 57%. Purification was achieved using column chromatography,[62] which can lead to a lot of solvent waste.[63] However, by using this one-pot approach, an additional purification step after the Sonogashira coupling was circumvented.[63]

3-Substituted 1,5-benzothiazepine-2,4-diones **52a–c** could be accessed by the three-component reaction of coumarin-3-carboxylic acid **50**, an isocyanide **51** and 2-aminothiophenol **21a** (Figure 15). The reaction conditions were optimized by Akbarzadeh et al., who proposed a reaction mechanism as well. First, an addition of the isocyanide **51** to coumarin-3-carboxylic acid **50** occurred, which led to the formation of an iminolactone intermediate **54**. Attack of the mercapto group of 2-aminothiophenol **21a** on the activated carbonyl moiety of the iminolactone opens up the latter structure and 1,5-benzothiazepine-2,4-dione **52** is then formed by intramolecular nucleophilic attack of the NH_2 group.[64] The reaction is efficient and sustainable, as it was performed at room temperature, used ethanol, which is recommended to be used according to CHEM21,[65] was purified by simply filtering and washing the precipitated product, and led to good yields.[64]

Some less conventional methods have also been developed, such as protocols making use of microwave irradiation in combination with inorganic solid support systems or solvent-free systems.[15,18] For example, Ameta et al. compared the conventional approach for the reaction of chalcones **56** with 2-aminothiophenol **21a** to a solid phase methodology (Figure 16). In the solid phase method, a minimum amount of DMF was used to achieve a homogeneous mixture of chalcone **56**, 2-aminothiophenol **21a** and basic alumina, after which the solvent was left to evaporate and the solid material was irradiated inside a microwave oven. The product **57** was purified through recrystallization and was obtained in yields higher than those obtained with the conventional method (64–72%).[18]

A similar approach has been explored by Nikalje et al. They prepared a mixture of 1,3-substituted 1-arylprop-2-en-1-one **58**, 2-aminothiophenol **21a** and a catalytic amount of zinc acetate dihydrate in a clean beaker and subjected it to microwave radiation. The product **59** was filtered, dried and recrystallized from ethanol (Figure 17).[15,16] Compared to the aforementioned method, the price of this catalyst is considerably lower, yet the yield is not as high.

The same group developed a method for the synthesis of 2-indolyl-1,5-benzothiazepanes **62** as well. Starting from indole

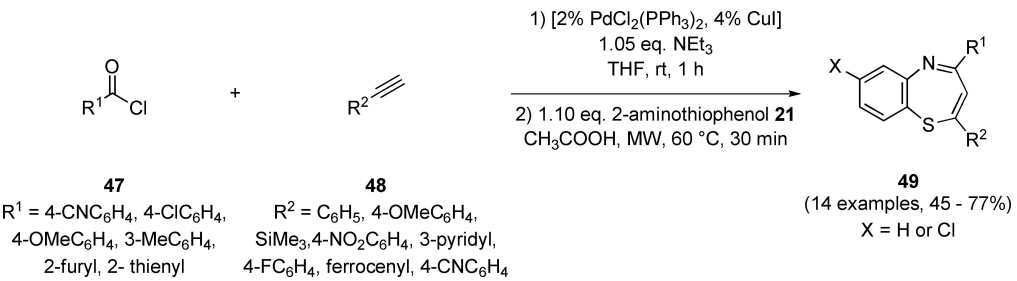


Figure 14. Multicomponent reaction combining a Sonogashira coupling and a Michael addition and subsequent condensation in a one-pot approach.

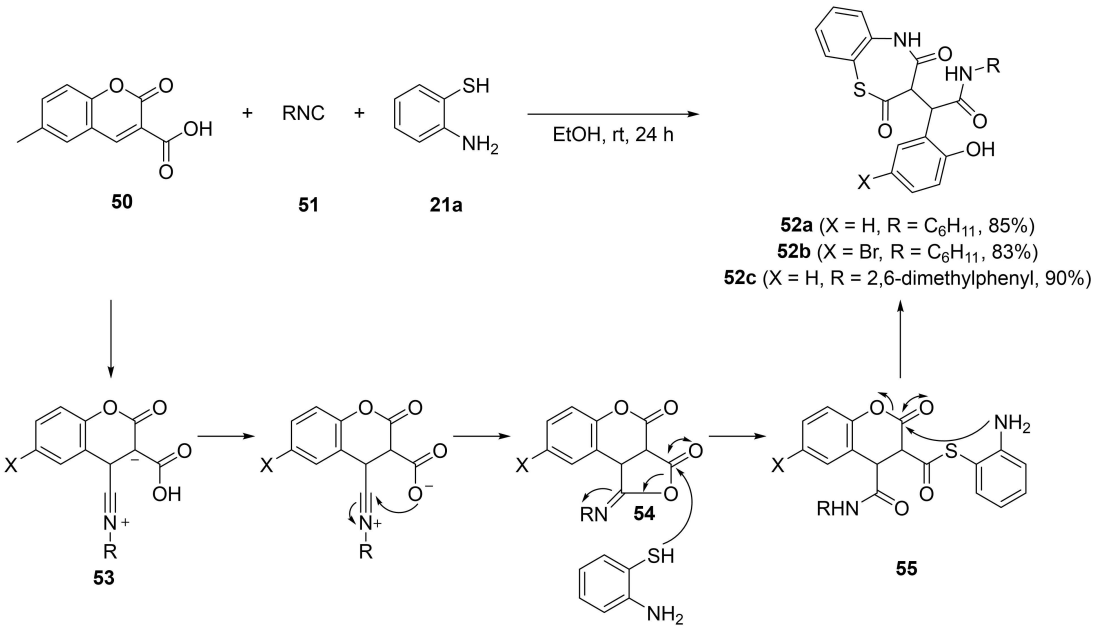


Figure 15. Multicomponent reaction and proposed mechanism for the synthesis of 3-substituted 1,5-benzothiazepine-2,4-diones **52a–c**.

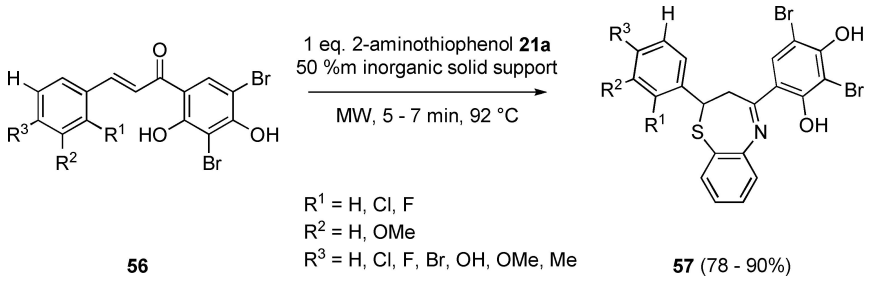


Figure 16. Solid-phase method toward the synthesis of 2,4-disubstituted 1,5-benzothiazepines **57**.

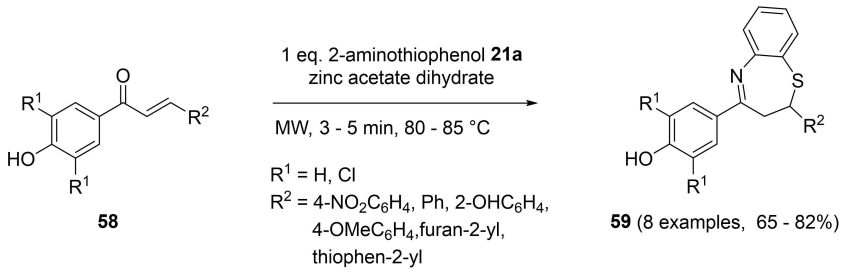


Figure 17. Microwave synthesis of 2,4-disubstituted benzothiazepines using zinc acetate dihydrate.

60, a formyl substituent was first introduced, after which a Claisen–Schmidt condensation ensured the introduction of the α,β-unsaturated carbonyl side chain. Enone compound **61** was then mixed with 2-aminothiophenol **21a** and a pinch of zirconium oxychloride catalyst. This solvent-free mixture was irradiated inside a microwave oven for a significantly shorter time than the conventional method (minutes vs. hours). As the catalyst was water-soluble, it could easily be removed and product **62** was purified by recrystallization from ethanol (Figure 18).[66]

In the next example, the benefits of microwave irradiation and the solvent polyethylene glycol (PEG-400) have been combined. This green solvent is inexpensive, non-halogenated, degradable and shows low toxicity, making it an excellent candidate as a substitute for volatile organic solvents in sustainable chemistry approaches. Product **64** was easily isolated and purification was accomplished by recrystallization from ethanol (Figure 19).[67]

Similarly, Kotalwar et al. used glycerol as a green reaction medium. Glycerol displays many beneficial properties, such as

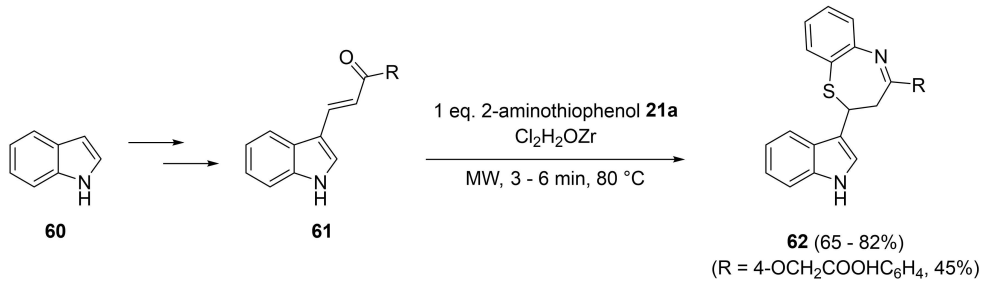


Figure 18. Solvent-free microwave synthesis starting from indole **60** using a zirconium catalyst.

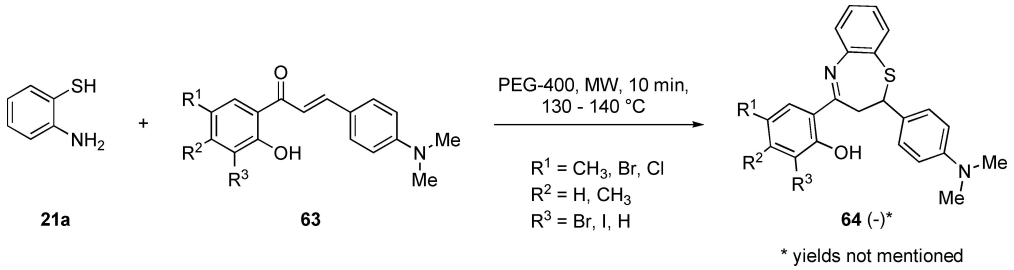


Figure 19. Green synthetic method making use of microwave irradiation and polyethylene glycol.

non-toxicity, biodegradability and recyclability, and it can be manufactured from renewable resources. For the synthesis of 1,5-benzothiazepane derivatives **66**, chalcones **65**, 2-aminothiophenol **21 a** and glacial acetic acid were dissolved in glycerol and exposed to microwave irradiation. After isolation through extraction, the pure product **66** was obtained by recrystallization (Figure 20).[68]

In a last microwave-promoted example, an approach using water as the solvent has been described by Kendre et al. 1,3-Diketone **67**, 2-aminothiophenol **21 a** and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) **68** were stirred in an acidic environment. DMFDMA reacted with the methylene group of the 1,3-diketone, introducing an enamine moiety. 2-Aminothiophenol **21 a** then condensed with the intermediate, resulting in the expulsion of dimethylamine and water. The product **69** was isolated by extraction with ethyl acetate and was purified via recrystallization from ethanol (Figure 21).[69]

These microwave-assisted reactions certainly contribute to green chemistry, because they use little to no solvent, proceed quickly and generally lead to better yields as compared to conventional alternatives. However, the costliness of a microwave apparatus, and difficult sampling, thus follow-up of the reaction, can be considered as disadvantages.[70] In addition, scale-up of microwave reactions often proves to be challenging,

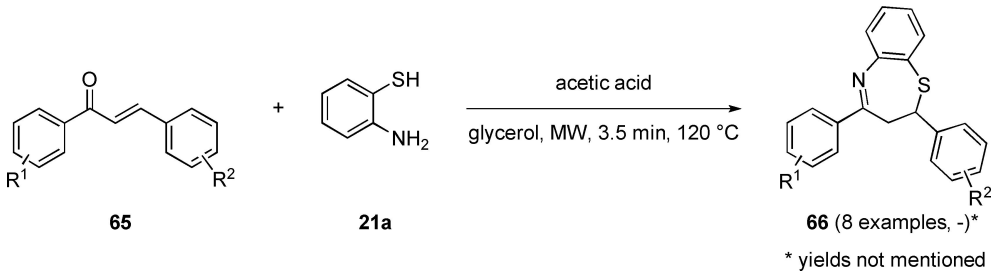


Figure 20. Microwave synthesis of 1,5-benzothiazepanes **66** using glycerol as a green solvent.

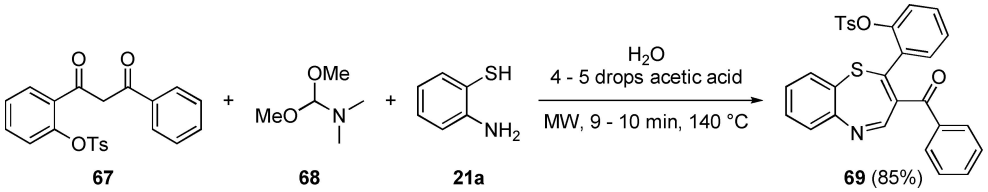


Figure 21. Green synthetic procedure toward a 2,3-disubstituted 1,5-benzothiazepine using water as the solvent.

because of limited penetration depth of the microwave radiation into the reaction medium, although continuous flow microwave systems could be a solution to this problem.[71]

The ability to synthesize compounds in an enantioselective manner is of particular importance to the pharmaceutical industry. For that reason, extensive research has been performed with respect to the enantioselective synthesis of 1,5-benzothiazepanes,[72] and selected recent methods will be discussed here. For more detailed information on asymmetric catalysis approaches, we refer the reader to the appropriate literature mentioned in the reference section.[19,72]

Meninno et al. have demonstrated that the conversion of a pyrazole-substituted α,β-unsaturated carbonyl compound **70** to 2-substituted 1,5-benzothiazepinone **73 a** can be achieved by using a hydroquinone-derived squaramide (Figure 22, route a). The protocol worked well for different alkyl- and (bi)aryl-substituted substrates and provided good to excellent yields and good enantioselectivities, while using mild reaction conditions and readily available reagents and catalysts. In general, the use of substituted aminothiophenols led to lower isolated yields.[73] Fang et al., on the other hand, started from α-bromo-enals **71** with an *N*-heterocyclic carbene precursor as the catalyst (Figure 22, route b). While this method can be performed at room temperature and delivers excellent enantioselectivities, it still requires the use of a base and molecular sieves (MS) and results in lower yields than the previous method.[74] A third method to generate 2-substituted 1,5-benzothiazepinones **73** commenced with a 3,5-dimethylpyrazole-substituted α,β-unsaturated carbonyl compound **72**. Wang et al. optimized the reaction conditions and observed that an L-RaPr$_2$/Yb(OTf)$_3$ complex led to the highest yield with the best enantioselectivities (Figure 14, route c). The reaction was shown to be applicable toward a large range of substrates with good to excellent yields, with 2,4-diene-1-amides leading to the lowest and cycloalkyls to the highest yields.[75]

Whereas the previous methods led to the synthesis of 2-substituted 1,5-benzothiazepinones **76**, Fukata et al. have developed an enantioselective reaction that can be used to access 2-mono-, 3-mono- and 2,3-disubstituted 1,5-benzothiazepinones with minimal adaptations of the reaction conditions (change of solvent and addition of molecular sieves). As an example, the reaction scheme for the preparation of 3-substituted benzothiazepinones **73** is presented in Figure 23. In this method, substituted acrylic pivalic anhydrides **74** were reacted with (substituted) *N*-tosyl-2-aminothiophenol **75** in the presence of an isothiourea catalyst. Although the enantioselec-

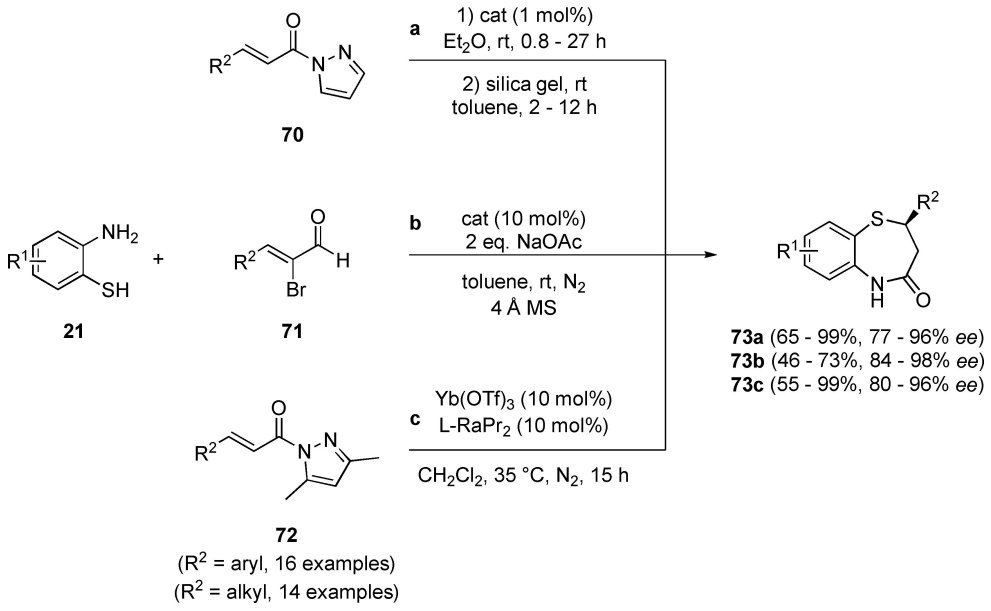


Figure 22. Three methods toward the enantioselective synthesis of 2-substituted 1,5-benzothiazepinones. Route **a** starts from a pyrazole-substituted α,β-unsaturated carbonyl compound, route **b** from an α-bromo-enal and route **c** from a 3,5-dimethylpyrazole-substituted α,β-unsaturated carbonyl compound.

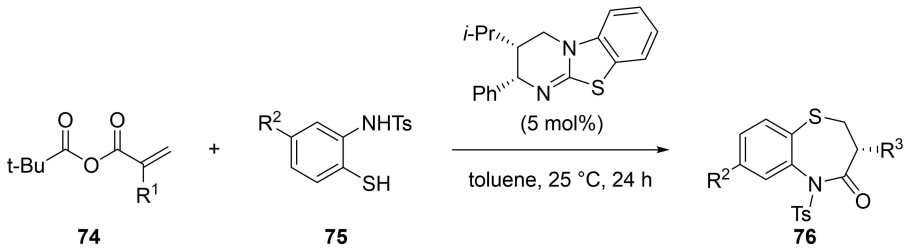


Figure 23. Enantioselective method for the synthesis of 3-substituted benzothiazepinones **53**.

tivity of this method was good to excellent (57–98% *ee*), the NH group is protected in the resulting product, making an additional deprotection step necessary.[76]

Lastly, Corti et al. have developed a two-step approach to synthesize *trans*-2,4-disubstituted benzothiazepanes **78** starting from *E*-chalcones **77**. In the first step, substrate **77** was reacted with a (substituted) 2-aminothiophenol **21** in the presence of the catalyst, a sulfonamide derived from 9-amino-(9-deoxy)epicinchonidine. This allowed for the enantioselective addition of the sulfur group across the β-carbon atom of the α,β-unsaturated carbonyl compound. In the second step, a reductive amination was performed in order to achieve cyclization (Figure 24). All of the enantiomeric excess values were around 80%, except for those resulting from the reaction of chalcones **77** with 2-MeC_6H_4 or 1-naphthyl as Ar^1. This suggests that steric hindrance in the chalcone **77** negatively affects the stereoselectivity of the Michael addition.[42]

2.4. Synthesis of 1,5-dibenzothiazepines

By fusing a second ring to the 1,5-benzothiazepane structure, the conformational inversion of the seven-membered ring is limited which ameliorates the thermodynamic profile of the scaffold.[3] The 1,5-dibenzothiazepine scaffold can be found as a core structure in a number of biologically active compounds, such as quetiapine (fumarate),[77] metiapine[78] and clotiapine.[79] Sharma et al. developed a three-step approach for the synthesis of 1,5-dibenzothiazepinones **83**. In a first step, an aromatic nucleophilic substitution takes place between 2-mercaptobenzoic acid **79** and 1-(4-chloro-3-nitrophenyl)ethan-1-one **80**. Then the nitro group is reduced followed by cyclization, leading to the 1,5-dibenzothiazepinone scaffold (Figure 25).[80] Some disadvantages of this method are the multi-step process, the long reaction time, the need for high temperatures and an overall yield lower than 50%.

A one-pot approach concerns the reaction between 2-aminothiophenol **21a** and a 2-fluorobenzaldehyde **84** (X=F) in the presence of a base (Figure 26, entry **a**). The amino group first condenses with the aldehyde group to form a Schiff base, after which aromatic nucleophilic substitution causes the formation of the 1,5-dibenzothiazepine **85a**. This simple method could be performed without the need for expensive equipment or reagents. It does, however, require a relatively long reaction time and reflux temperature.[81] These issues could be resolved by employing microwave irradiation (Figure 26, entry **b**) which proved to be efficient and applicable to all four 2-halobenzaldehydes as well as substituted 2-chloro- or 2-fluorobenzaldehydes **84**. The reactivity seemed to decrease in the following order: F > Cl > Br > I, which could be explained by increasing size of the atom and decreasing electronegativity.[82]

A different approach toward microwave synthesis was developed by Saha et al. Even though this method requires the use of an additional catalyst and ligand, it is an attractive approach as it can provide access to several substituted 1,5-dibenzothiazepines **87**. The authors explored further diversification of the 1,5-dibenzothiazepine scaffold by using, for example, multicomponent reactions (MCR).[83,84] The first method (Fig-

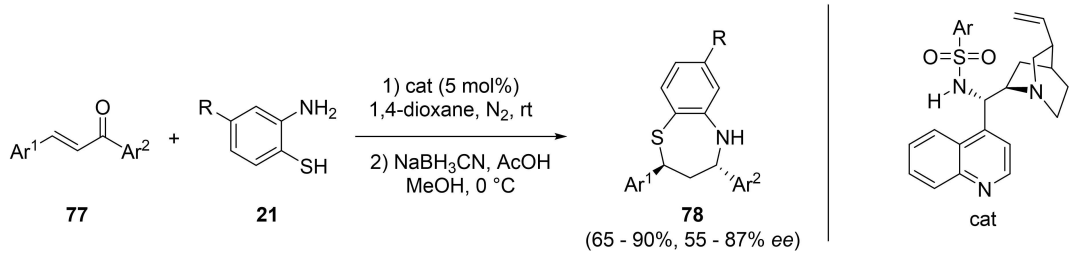


Figure 24. Synthesis of *trans*-2,4-disubstituted benzothiazepanes from *E*-chalcones.

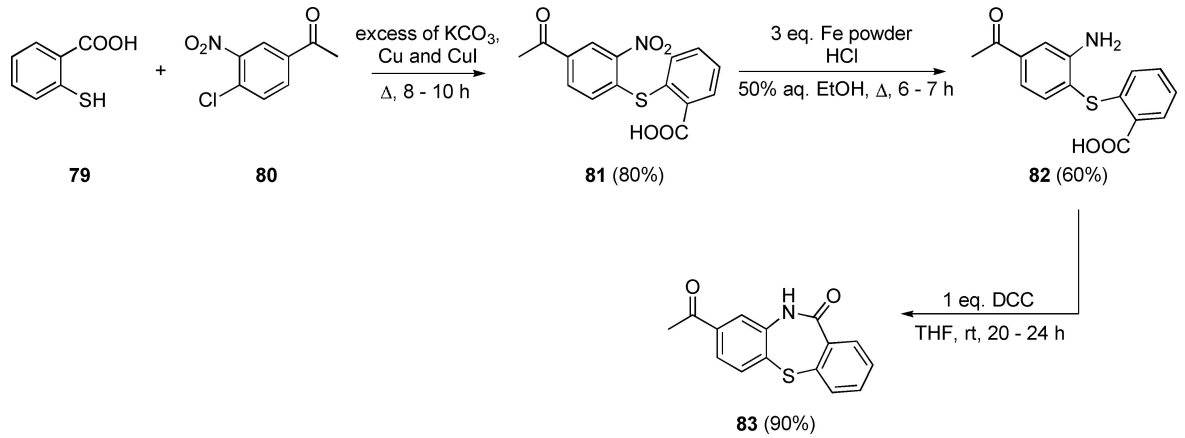


Figure 25. A multi-step process toward the synthesis of 1,5-dibenzothiazepine **83**.

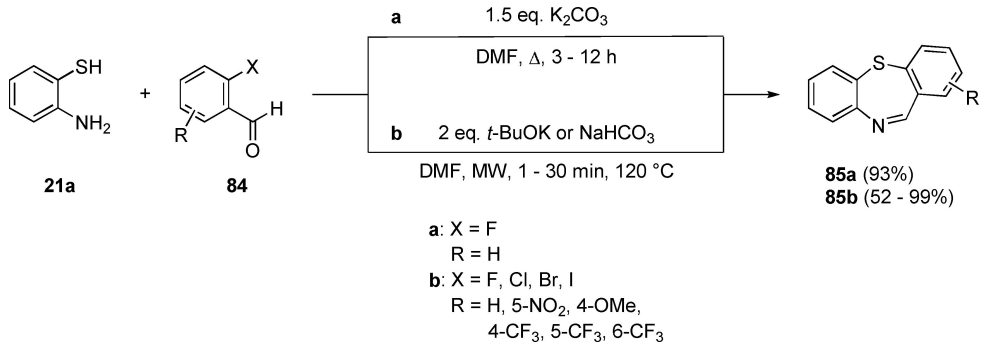


Figure 26. Two synthetic one-pot approaches toward 1,5-dibenzothiazepines **85**; a conventional method (route **a**) and a method using microwave irradiation (route **b**).

ure 27, entry **a**) used the Ugi–Joullié protocol to access novel 1,5-dibenzothiazepine carboxamides **90**. Some advantages are that it can be performed at room temperature, results in good yields and allows for the introduction of four (different) R groups.[84] The second method (Figure 27, route **b**) involved cycloaddition of an α-acidic isocyanide via the Van Leusen protocol with the formation of dihydrodibenzo[*b,f*]imidazo[1,5-*d*][1,4]thiazepines **92**. The reaction was easy to perform, used environmentally friendly reaction conditions, only took ten minutes and proved easy to purify.[83] Other possible strategies for diversification, including MCRs, encompass the Ugi tetrazole,[81] Castagnoli–Cushman,[81] Mannich,[85] aza-Henry,[86] Strecker[87] and Pudovic reaction.[88] More detailed information on the various synthetic methods for 1,5-dibenzothiazepines can be found in the literature.[3,89]

3. Study of Biological Activity

1,5-Benzothiazepane derivatives can interact in various ways with their target, as illustrated by the co-crystal structures in Figure 28. In the case of Diltiazem (Figure 28a), the compound is surrounded by a large number of hydrophobic residues, of which three, highlighted in transparent orange, were defined to be responsible for the specificity of L-type Calcium channels for Diltiazem.[90] Besides hydrophobic interactions of the dibenzothiazepinone ring system with nearby residues, compound **93** (Figure 28b) also forms hydrogen bonds via the thiazepinone carbonyl group.[91] The biological activity is influenced by the strength of these interactions and the way the compounds fit inside the target enzyme, which in its turn depends on factors such as stereochemistry, nature of functional groups, and size of substituents. These factors will be briefly explored in what follows, based on structure-activity relationship (SAR) studies of different 1,5-benzothiazepane-containing compounds. For more detailed information on the diverse biological activities, we

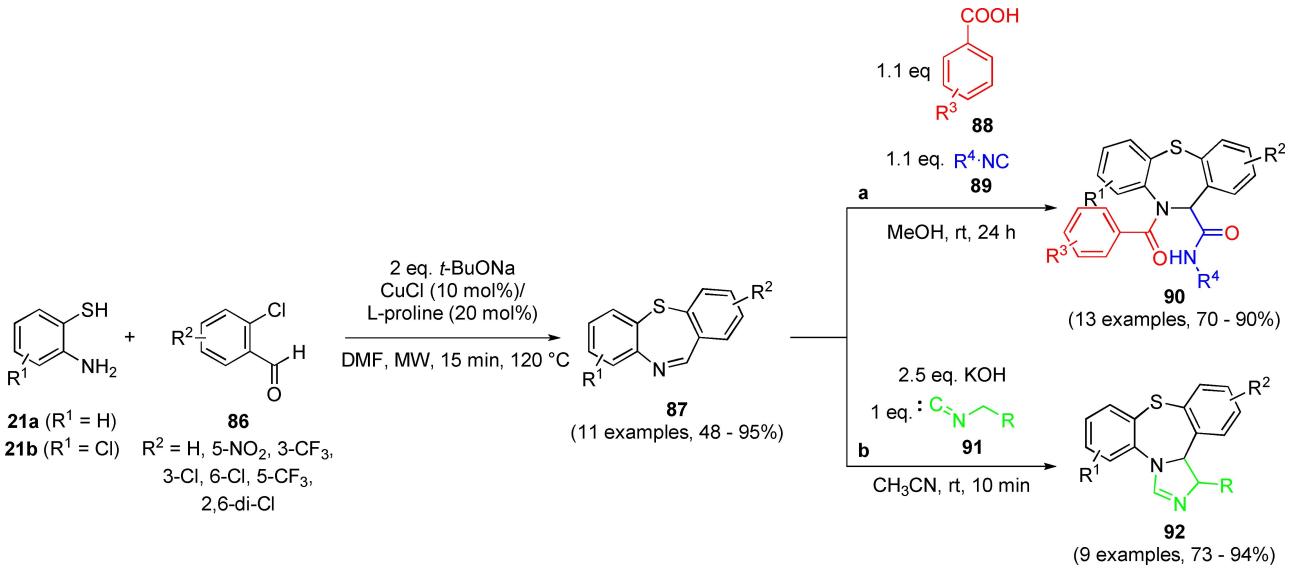


Figure 27. A second approach toward the microwave synthesis of 1,5-dibenzothiazepines **87** with further diversification via the Ugi–Joullié protocol (entry **a**) or the Van Leusen method (entry **b**).

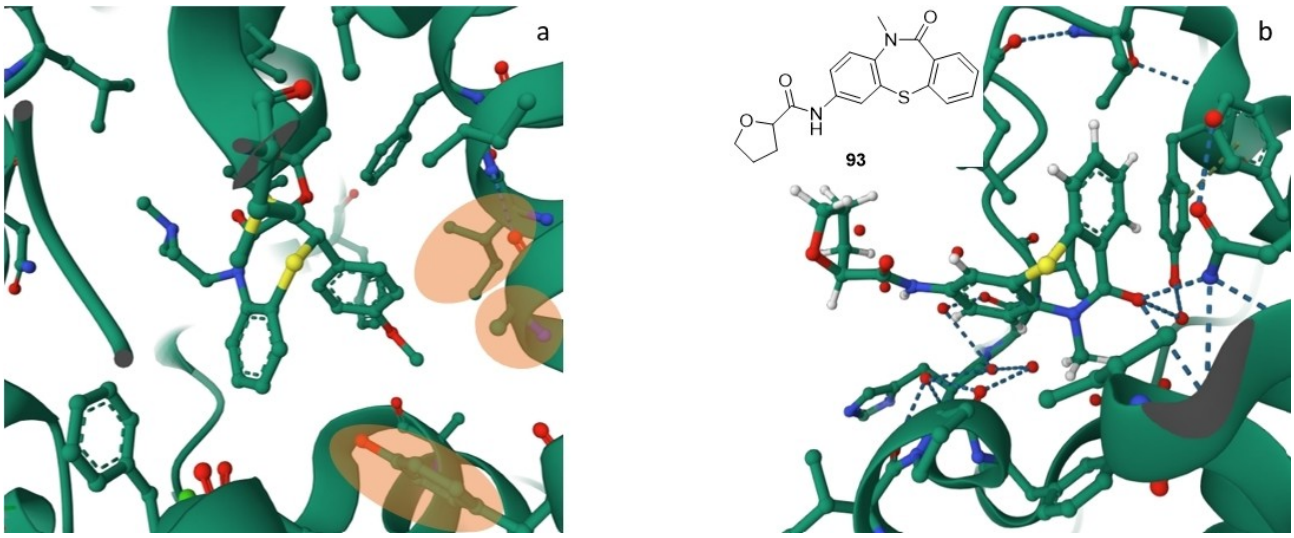


Figure 28. a) Co-crystal structure of Diltiazem **4** and L-type calcium channel with the residues responsible for Dilitiazem **4** sensitivity highlighted in transparent orange. Image from the RCSB PDB (rcsb.org) of PD ID 6JPB.[90] b) Co-crystal structure of carboxamide-substituted 1,5-dibenzothiazepine **93** and bromodomain-containing factor 1 on the right. Image from the RCSB PDB (rcsb.org) of PD ID 5N17.[91]

refer to the appropriate literature sources mentioned in the reference section.[7,92]

Nagao et al. have compared the biological potency of *cis* and *trans* isomers in the context of their coronary vasodilating activity, which is the ability of the compound to dilate blood vessels. They synthesized four pairs of benzothiazepane derivatives **94a**–**d**, that had a 2,3-*cis* or 2,3-*trans* configuration, and compared their effectiveness as a coronary vasodilator (Figure 29).[93]

The potency of the compounds was expressed relative to papaverine, a compound that is known to relax the smooth muscle of the small arteries and thus to cause vasodilation,[94]

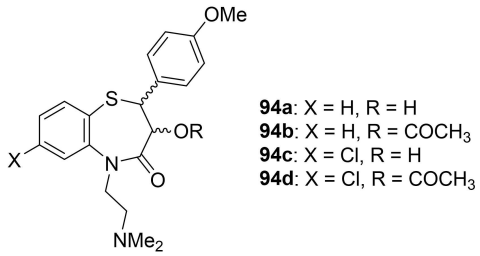


Figure 29. Structure of the compounds studied by Nagao et al.

Table 1. Potency of compounds **94**; expressed relative to papaverine (potency = 1).[93]

Compound	Stereochemistry	Potency
94a	*cis*	1.9
	trans	< 0.1
94b	*cis*	3.5
	trans	< 0.1
94c	*cis*	0.8
	trans	< 0.1
94d	*cis*	3.3
	trans	0.1

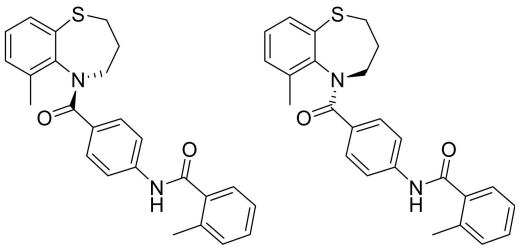
although they later discovered that papaverine and Diltiazem **94b** display their effects through different modes of action.[95] Table 1 shows that the potency of the *cis* isomers ranged from 0.8 to 3.5, while for the *trans* isomers values of < 0.1 to 0.1 were noted. This indicated that there was a clear difference in favor of the *cis* isomer.[93]

Comparable results regarding the differential activity of *cis* vs. *trans* isomers were obtained in the research of Campiani et al. and Yoneda et al., showing that the active compounds often display a *cis* configuration.[96,97] Yoneda et al. went a step further and looked at the influence of axial chirality. This term is used to describe isomers that are the result of the arrangement of four groups on a non-planar molecule along an axis of chirality (in this case the Ar–N(CO) axis).[97] An example of their findings can be derived from Table 2. These compounds were synthesized to act as vasopressin receptor ligands, which play a role in for example the treatment of hyponatremia and congestive heart failure. The results showed that the chirality impacted the inhibition ability of the compounds for the two human vasopressin receptors, as an approximately 10-fold increase in inhibition potency was observed in both cases in favor of the *aS*-enantiomer (Figure 30).[97]

In some cases, the presence of specific functional groups on the benzothiazepane structure can induce a significant increase in biological activity. Urbanski et al., for example, synthesized a number of 2,5-disubstituted benzothiazepane derivatives **96**

Table 2. K_i = Inhibition constants: the concentration of **95** needed to produce 50 % of the maximum inhibition, for two human vasopressin receptors.[97]

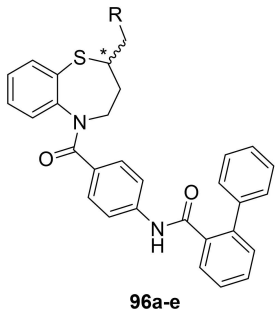
Compound	K_i [μM] hV_{1a}	K_i [μM] hV_2
Racemate	0.037	0.360
95a (+)-(*aS*)	0.019	0.184
95b (−)-(*aR*)	0.147	1.800



95a (+)-(*aS*) **95b** (-)-(*aR*)

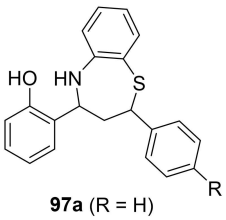
Figure 30. Two enantiomers of compound **95** displaying axial chirality.

(Figure 31) to function as V_2 arginine vasopressin receptor antagonists.[43] These compounds promote the excretion of water without electrolytes and are used for the treatment of hyponatremia, which means that the sodium levels in the blood are too low.[99] The side chain, featuring a substituted *p*-amidobenzoyl group and linked via *N*-1 to the benzothiazepane scaffold, is considered to be a key pharmacophore. Table 3 shows some of the results of an *in vitro* binding assay carried out with different benzothiazepane analogs. Firstly, it was noticed that a carboxylic acid on position 2 (R=COOH) greatly improved the selectivity toward the V_2 arginine vasopressin receptor. When looking at compound **96b** for example, the dosage to achieve equal inhibition in V_{1a} and V_2 was 104.1 times less for the latter, whereas for molecule **96d**, a dosage of only 2.8 times less was necessary to achieve equal inhibition. Secondly, it was observed that the stereochemistry only impacted the biological effect on the V_{1a} receptor. When comparing compound **96a** with compound **96c**, the *R*-enantiomer seemed to be preferable, while this time, no preference for a certain stereochemistry in case of the V_2 receptor was observed.[43]



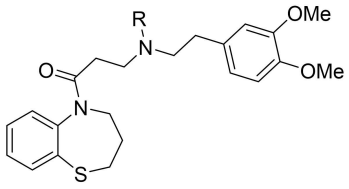
96a-e

Figure 31. Structure of the compounds studied by Urbanski et al.



97a (R = H)
97b (R = F)
97c (R = CH_3)

Figure 32. Structure of the compounds studied by Nawaz et al.



98a-f

Figure 33. Structure of the compounds studied by Ueyama et al.

In a second example, Nawaz et al. studied the interactions of three benzothiazepane **97a–c** derivatives (Figure 32) in the active site of acetylcholinesterase (AchE), which is an enzyme believed to be an important target for the treatment of Alzheimer's disease. The main interactions were identified as hydrophobic contacts, π-π interactions and hydrogen bonding. The study showed that the substitution of the aromatic ring with a halogen or methyl moiety could decrease the affinity of these compounds toward AChE, which may be caused by repulsion of these groups with amino acid residues in the active site. Benzothiazepine **97a**, however, is fitted differently inside the active side, which allowed it to form an extra hydrogen bond with the target leading to increased affinity.[101] Lastly, for benzothiazepanes intended to elicit anti-epileptic action, introduction of a halogen atom can improve the biological activity. Studies have been disclosed in which C2-substituted benzothiazepanes containing a 2-chlorophenyl or a 2-bromophenyl group exhibited the highest activity compared to other substitution patterns, such as hydroxy or methoxy groups.[13,102]

Ueyama et al. have studied the effects of different alkyl groups, ranging from one to six carbon atoms, on the vasoconstrictive ability of compound **98** (Figure 33). Table 4 shows an overview of the relevant compounds and their maximal contractile force as a measurement for the contractile activity on the arteries. Going from the methyl group (**98a**) to

Table 3. IC_{50} values for in vitro binding assay performed with compounds **96**, tested both for V_{1a} and V_2 receptor;[43] IC_{50} = half-maximal inhibitory concentration: concentration needed to inhibit 50% of a biological or biochemical function.[100]

Compound	R	Stereochemistry (*)	IC_{50} V_{1a} [μM]	IC_{50} V_2 [μM]
96a	CO_2H	*S*	1.14	0.008
96b	CO_2H	*R/S*	0.729	0.007
96c	CO_2H	*R*	0.44	0.007
96d	$N(CH_3)_2$	*R/S*	1.2	0.43
96e	CH_2F	*R/S*	0.18	0.085

Table 4. Max(%): maximal contractile force (reference: 40 mM KCl = 100 %) of benzothiazepane derivatives **98**.[27]

Compound	R	Max [%]
98 a	Methyl (CH_3)	65.6
98 b	Ethyl (C_2H_5)	101.9
98 c	*n*-propyl (C_3H_7)	102.3
98 d	*n*-butyl (C_4H_9)	21.7
98 e	Cyclopentyl (C_5H_9)	12.9
98 f	Cyclohexyl (C_6H_{11})	0

the *n*-propyl group (**98 c**), a clear increase in activity was observed. However, when the number of carbon atoms was further increased (**98 d**–**f**), there was a decline in activity. This implies that an optimum exists for the length of the alkyl chain, and in this case, a chain length of three carbon atoms should not be exceeded.[27]

The last factor that will be discussed is the influence of substituents with electron-donating or electron-withdrawing properties. Shaik et al. have synthesized chloropyrazine-conjugated benzothiazepanes **100** starting from 5-chloropyrazine-derived chalcones **99** and 2-aminothiophenol **21 a** (Figure 34). When testing the resulting compounds for their antibacterial and antifungal activities (Table 5), derivatives bearing electron-donating groups on the phenyl ring, such as hydroxy **100 d**, methyl **100 e**, methoxy **100 f** and dimethylamino **100 g**, exhibited poor to no activity. When compounds were, on the other hand, decorated with electron-withdrawing groups, such as chlorine **100 a**, fluorine **100 b** or a nitro group **100 c**, an improvement in the activity was noticed.[40]

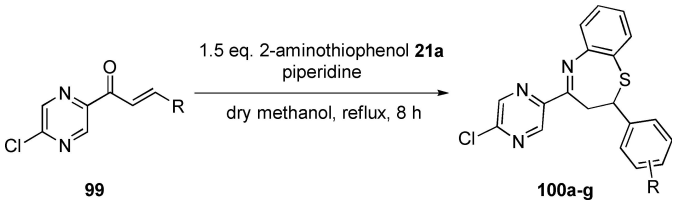


Figure 34. Structure of the compounds studied by Shaik et al.

Table 5. Minimum inhibitory concentration (MIC) of compound **100 a**–**d** for *B. subtilis*.[40]

Compound	R	MIC (μM)
100 a	4-chloro	82.83
100 b	4-fluoro	86.52
100 c	4-nitro	80.63
100 d	4-hydroxy	> 200
100 e	4-methyl	> 200
100 f	4-methoxy	> 200
100 g	4-dimethylamino	162.05

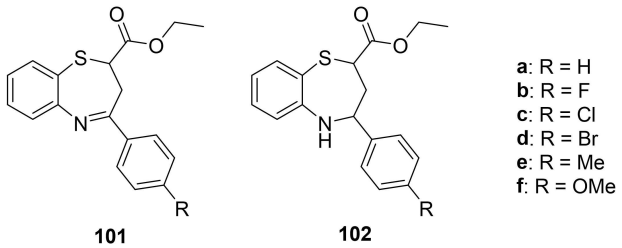


Figure 35. Structure of the compounds studied by Kang et al.

However, in other cases, no specific trend or correlation between the presence of certain substituents and the biological activity of the resulting molecules could be identified. For example, Kang et al. have tested 2-ester-substituted 2,3-dihydro-1,5-benzothiazepines **101** and 1,5-benzothiazepanes **102** for their antifungal activities (Figure 35). All the benzothiazepane derivatives **102** were as good as inactive, while the phenyl-substituted benzothiazepine **101 a** and the fluorophenyl-substituted benzothiazepine **101 b** both showed good antifungal activity, although the chloro- and bromophenyl-substituted benzothiazepines **101 c**,**d** did not exhibit improved activity.[33]

4. Conclusion

In this mini-review, an overview of selected methods for the synthesis of 1,5-benzothiazepane and its derivatives is presented. The 1,5-benzothiazepane system has a long-standing tradition as pharmaceutically relevant heterocycle, which has led to extensive research with respect to its synthesis and biological activities. Synthetic approaches toward 1,5-benzothiazepanes can roughly be divided into three groups: preparations through ring expansions, protocols based on ring closure, and reactions of α,β-unsaturated carbonyl compounds with 2-aminothiophenol. This review does not provide a comprehensive overview of all methods described in the literature, but instead focusses on the most commonly used strategies and on recently developed, more sustainable approaches. The reaction between unsaturated carbonyl compounds and 2-aminothiophenol stands out as the most frequently applied method due to the easy and convenient practical procedures to realize these transformations. Nonetheless, alternative methods have been developed recently, focusing on ionic liquids, recyclable solvents and catalysts, multicomponent reactions and microwave irradiation. Moreover, new approaches for the enantioselective synthesis of 1,5-benzothiazepanes are also discussed in this work, which can be relevant from a drug development perspective. Lastly, the synthesis of 1,5-dibenzothiazepines was briefly touched upon, where the reaction of 2-aminothiophenol with 2-halobenzaldehydes proved to be an easy and efficient methods that could be performed under green reaction conditions. With regard to drug development, it is important to know which factors can have an effect on the biological activity as well, and this aspect is explored in the second part of this review. To that end, several SAR studies are briefly discussed, as well as a few specific examples of compound-target interactions. In conclusion, the 1,5-(di)benzothiazepane system still deserves to be considered as a privileged scaffold in the context of bioactive compound development, and novel, often more sustainable, approaches for their preparation have given a new impetus to the further advancement of this field of research.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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[1] M. M. Heravi, V. Zadsirjan, *RSC Adv.* **2020**, *10*, 44247–44311.
[2] C. Lamberth, J. Dinges, *Bioactive Heterocyclic Compound Classes: Agrochemicals*, Wiley-VCH, Weinheim, **2012**, p. 1–20.
[3] D. Saha, G. Jain, A. Sharma, *RSC Adv.* **2015**, *5*, 70619–70639.
[4] K. Ajay Kumar, V. Kumar Govindappa, R. Nagamallu, *Int. J. Basic Appl. Chem. Sci.* **2015**, *5*, 2277–2073.
[5] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.
[6] S. R. Langdon, P. Ertl, N. Brown, *Mol. Inf.* **2010**, *29*, 366–385.
[7] J. B. Bariwal, K. D. Upadhyay, A. T. Manvar, J. C. Trivedi, J. S. Singh, K. S. Jain, A. K. Shah, *Eur. J. Med. Chem.* **2008**, *43*, 2279–2290.
[8] National Center for Biotechnology Information, "PubChem Compound Summary for CID 65989, Siratiazem" can be found under https://pubchem.ncbi.nlm.nih.gov/compound/Siratiazem, **2021** (accessed on 18 December 2021).
[9] V. B. Siramshetty, I. Grishagin, D. T. Nguyen, T. Peryea, Y. Skovpen, O. Stroganov, D. Katzel, T. Sheils, A. Jadhav, E. A. Mathé, N. T. Southall, *Nucleic Acids Res.* **2022**, *50*, D1307–D1316.
[10] D. Coşkun, S. Kırbağ, *J. Chem. Soc. Pak.* **2015**, *37*, 769–775.
[11] S. Reddy, P. Reddy, G. Nagaraj, *Chin. J. Chem.* **2009**, *27*, 1345–1352.
[12] L. Wang, P. Zhang, X. Zhang, Y. Zhang, Y. Li, Y. Wang, *Eur. J. Med. Chem.* **2009**, *44*, 2815–2821.
[13] H. Kaur, S. Kumar, A. Chaudhary, A. Kumar, *Arab. J. Chem.* **2012**, *5*, 271–283.
[14] R. di Santo, R. Costi, *Farmaco* **2005**, *60*, 385–392.
[15] A. P. Nikalje, D. Vyawahare, *Afr. J. Pure Appl. Chem.* **2011**, *5*, 422–428.
[16] D. Vyawahare, M. Ghodke, A. P. Nikalje, *Int. J. Pharm. Pharm. Sci.* **2010**, *2*, 27–29.
[17] a) E. Ayral, P. Gloanec, G. Bergé, G. de Nanteuil, P. Mennecier, A. Rupin, T. J. Verbeuren, P. Fulcrand, J. Martinez, J. F. Hernandez, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1386–1391; b) H. Inoue, M. Konda, T. Hishiyama, H. Otsuka, A. Watanabe, M. Gaino, K. Takashi, T. Date, K. Okamura, M. Takeda, H. Narita, S. Murata, A. Odawara, H. Sasaki, T. Nagao, *Chem. Pharm. Bull.* **1997**, *45*, 1008–1026.
[18] K. L. Ameta, N. S. Rathore, B. Kumar, *J. Serb. Chem. Soc.* **2012**, *77*, 725–731.
[19] V. Devi, G. Singh, V. Monga, *J. Heterocycl. Chem.* **2020**, *57*, 3255–3270.
[20] a) J. Fujiwara, H. Sano, K. Maruoka, H. Yamamoto, *Tetrahedron Lett.* **1984**, *25*, 2367–2370; b) H. Cho, K. Murakami, H. Nakanishi, H. Isoshima, K. Hayakawa, I. Uchida, *Heterocycles* **1998**, *48*, 919–927; c) S. Sasatani, T. Miyazaki, K. Maruoka, H. Yamamoto, *Tetrahedron Lett.* **1983**, *24*, 4711–4712.
[21] H. Cho, Y. Iwama, K. Sugimoto, S. Mori, H. Tokuyama, *J. Org. Chem.* **2010**, *75*, 627–636.
[22] H. Cho, Y. Iwama, N. Mitsuhashi, K. Sugimoto, K. Okano, H. Tokuyama, *Molecules* **2012**, *17*, 7348–7355.
[23] Z. Guo, Z. Zhang, Y. Zhang, G. Wang, Z. Huang, Q. Zhang, J. Li, *Eur. J. Med. Chem.* **2021**, *218*, 113383.
[24] H.-J. Federsel, J. Bergman, *Tetrahedron Lett.* **1980**, *21*, 2429–2432.
[25] Sigma–Aldrich, "MSDS fiche", can be found under http://www.sigmaaldrich.com/BE/en, **2020** (accessed on 22 November 2022).
[26] a) European Chemicals Bureau, *European Union Risk Assessment Report Trichloroethylene*, **2004**; b) U. S. Environmental Protection Agency, *Final Risk Evaluation for Trichloroethylene CASRN:79-01-6*, **2020**; c) The European Commission, *Commission Regulation (EU) No 348/2013 of 17 April 2013 Amending Annex XIV to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)*, **2013**.
[27] N. Ueyama, S. Wakabayashi, T. Tomiyama, *Chem. Pharm. Bull.* **1997**, *45*, 1761–1766.
[28] C. Mukherjee, E. Biehl, *Heterocycles* **2004**, *63*, 2309–2318.
[29] M. Karikomi, M. D'hooghe, G. Verniest, N. De Kimpe, *Org. Biomol. Chem.* **2008**, *6*, 1902–1904.
[30] W. I. I. Bakker, L. P. Wong, V. Snieckus, J. M. Warrington, L. Barriault, *Lithium diisopropylamide* in *Encyclopedia of reagents for organic synthesis*, John Wiley & Sons, Hoboken, **2004**, p. 1–17.
[31] R. A. Valiulin, *Organic Chemistry: 100 Must-Know Mechanisms*, Walter de Gruyter GmbH, Berlin, **2020**, p. 44–45.
[32] W. H. Mills, J. B. Whitworth, *J. Chem. Soc.* **1927**, 2738–2753.
[33] W. Kang, X. Du, L. Wang, L. Hu, Y. Dong, Y. Bian, Y. Li, *Chin. J. Chem.* **2013**, *31*, 1305–1314.
[34] G. R. Mhaske, S. S. Bajod, D. M. Ambhore, S. N. Shelke, *Int. J. Innov. Res. Technol. Sci. Eng.* **2014**, *3*, 13208–13215.
[35] A. Theppawong, T. Van de Walle, K. Van Hecke, C. Grootaert, J. Van Camp, M. D'hooghe, *Chem. Eur. J.* **2019**, *25*, 12583–12600.
[36] S. Bhabal, S. Shaikh, I. Yellapurkar, G. Pavale, M. Ramana, *J. Serb. Chem. Soc.* **2022**, *87*, 1109–1116.
[37] F. L. Ansari, S. Umbreen, L. Hussain, T. Makhmoor, S. A. Nawaz, M. A. Lodhi, S. N. Khan, F. Shaheen, M. I. Choudhary, *Chem. Biodiversity* **2005**, *2*, 487–496.
[38] T. Li, J. Zhang, J. Pan, Z. Wu, D. Hu, B. Song, *Eur. J. Med. Chem.* **2017**, *125*, 657–662.
[39] S. Nigam, Y. C. Joshi, *Phosphorus Sulfur Silicon Relat. Elem.* **2003**, *178*, 1583–1586.
[40] A. B. Shaik, R. R. Bhandare, S. Nissankararao, B. V. S. Lokesh, S. Shahanaaz, M. Mukhlesur Rahman, *Arab. J. Chem.* **2021**, *14*, 102915.
[41] a) A. B. Shaik, Y. R. Prasad, S. Nissankararao, S. Shahanaaz, *Anti-Cancer Agents Med. Chem.* **2020**, *20*, 1115–1128; b) S. A. Kumara Prasad, S. H. Chetan, A. R. Shabaraya, *World J. Pharm. Res.* **2022**, *11*, 1760–1768.
[42] V. Corti, P. Camarero Gonzalez, J. Febvay, L. Caruana, A. Mazzanti, M. Fochi, L. Bernardi, *Eur. J. Org. Chem.* **2017**, *2017*, 49–52.
[43] M. J. Urbanski, R. H. Chen, K. T. Demarest, J. Gunnet, R. Look, E. Ericson, W. V. Murray, P. J. Rybczynski, X. Zhang, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4031–4034.
[44] M. Yang, Y. Guo, X. Zhang, H. Sun, Y. Wang, W. Zhang, Y. Wu, Y. Jian, Z. Gao, *Asian J. Org. Chem.* **2022**, *11*, 185–190.
[45] M. Darband, E. Tahanpesar, H. Sanaeishoar, R. Badri, *Russ. J. Appl. Chem.* **2021**, *94*, 1624–1634.
[46] T. A. Farghaly, H. M. E. Hassaneen, *Arab. J. Chem.* **2017**, *10*, S3255–S3262.
[47] S. G. Jagadhani, *Int. J. Nov. Res. Dev.* **2022**, *7*, 982–985.
[48] R. Srivastava, B. Sarmah, B. Satpati, *RSC Adv.* **2015**, *5*, 25998–26006.
[49] P. Zhang, D. Ye, Y. Chu, *Tetrahedron Lett.* **2016**, *57*, 3743–3745.
[50] D. C. M. Albanese, N. Gaggero, M. Fei, *Green Chem.* **2017**, *19*, 5703–5707.
[51] C. G. Devkate, S. S. Kola, D. D. Gaikwad, M. I. M. Siddique, *Int. Res. J. Pharm.* **2018**, *9*, 182–185.
[52] N. Yadav, V. B. Yadav, M. Danish Ansari, H. Sagir, A. Verma, I. R. Siddiqui, *New J. Chem.* **2019**, *43*, 7011–7014.
[53] C. Gawande, G. Deshmukh, S. Mahila Mahavidyalaya, A. Dist Gondia, *Int. Res. J. Mod. Eng. Technol.* **2021**, *3*, 966–971.
[54] A. Sharifi, F. Hosseini, N. Ghonouei, M. S. Abaee, M. Mirzaei, A. W. Mesbah, K. Harms, *J. Sulfur Chem.* **2015**, *36*, 257–269.
[55] P. Pinate, S. Makone, *Catal. Lett.* **2022**, 10.1007/s10562-022-04033-z.
[56] W. Kunz, K. Häckl, *Chem. Phys. Lett.* **2016**, *661*, 6–12.
[57] P. Pawar, V. S. Shivankar, Y. A. Gaikwad, S. S. Patil, G. C. Wadhawa, *J. Biol. Chem. Chron.* **2018**, *4*, 95–98.
[58] C. B. W. Phippen, C. S. P. McErlean, *Tetrahedron Lett.* **2011**, *52*, 1490–1492.
[59] I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994**, *18*, 115–122.
[60] R. W. Armstrong, A. P. Combs, P. A. Tempest, S. David Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123–131.
[61] H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–3329.

[62] B. Willy, T. J. J. Müller, *Mol. Diversity* **2010**, *14*, 443–453.
[63] E. A. Peterson, B. Dillon, I. Raheem, P. Richardson, D. Richter, R. Schmidt, H. F. Sneddon, *Green Chem.* **2014**, *16*, 4060–4075.
[64] R. Akbarzadeh, T. Amanpour, H. R. Khavasi, A. Bazgir, *Tetrahedron* **2014**, *70*, 169–175.
[65] D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada, P. J. Dunn, *Green Chem.* **2016**, *18*, 288–296.
[66] A. P. G. Nikalje, M. S. Ghodke, F. A. K. Khan, J. N. Sangshetti, *Open Pharm. Sci. J.* **2016**, *3*, 117–130.
[67] S. S. Chobe, V. V. Kadam, *Int. J. Res. Anal. Rev.* **2019**, *6*, 492–495.
[68] S. S. Kotalwar, A. D. Kale, R. B. Kohire, V. B. Jagrut, *Asian J. Chem.* **2019**, *31*, 993–996.
[69] B. V. Kendre, M. G. Landge, S. R. Bhusare, *Arab. J. Chem.* **2019**, *12*, 2091–2097.
[70] G. Ambrožič, Z. Crnjak Orel, M. Žigon, *Mater. Tehnol.* **2011**, *45*, 173–177.
[71] Á. Díaz-Ortiz, A. de La Hoz, J. Alcázar, J. R. Carrillo, M. A. Herrero, J. De M. Muñoz, P. Prieto, A. de Cózar, *Microwave Heating*, IntechOpen Ltd., London, **2011**, p. 137–162.
[72] a) K. Asano, S. Matsubara, *ACS Catal.* **2018**, *8*, 6273–6282; b) H. Wang, S. Gu, Q. Yan, L. Ding, F. E. Chen, *Green Synth. Catal.* **2020**, *1*, 12–25.
[73] S. Meninno, C. Volpe, A. Lattanzi, *Chem. Eur. J.* **2017**, *23*, 4547–4550.
[74] C. Fang, T. Lu, J. Zhu, K. Sun, D. Du, *Org. Lett.* **2017**, *19*, 3470–3473.
[75] G. Wang, Y. Tang, Y. Zhang, X. Liu, L. Lin, X. Feng, *Chem. Eur. J.* **2017**, *23*, 554–557.
[76] Y. Fukata, K. Yao, R. Miyaji, K. Asano, S. Matsubara, *J. Org. Chem.* **2017**, *82*, 12655–12668.
[77] M. Srisurapanont, C. Disayavanish, K. Taimkaew, *Cochrane Database Syst. Rev.* **2000**, *2*, 1–11.
[78] M. Zare, A. Bazrafshan, *Cochrane Database Syst. Rev.* **2017**, *3*, 1–41.
[79] M. Berk, J. Rathbone, S. L. Mandriota-Carpenter, *Cochrane Database Syst. Rev.* **2009**, *4*, 1–37.
[80] A. Sharma, D. Kishore, B. Singh, *J. Heterocycl. Chem.* **2018**, *55*, 586–592.
[81] X. Lei, G. Angeli, A. Dömling, C. G. Neochoritis, *Eur. J. Org. Chem.* **2022**, *2022*, e202200220.
[82] Y. C. Lin, N. C. Li, Y. J. Cherng, *J. Heterocycl. Chem.* **2014**, *51*, 808–814.
[83] D. Saha, T. Kaur, A. Sharma, *Asian J. Org. Chem.* **2017**, *6*, 527–533.
[84] D. Saha, P. Wadhwa, A. Sharma, *RSC Adv.* **2015**, *5*, 33067–33076.
[85] Z. F. Deng, B. Huang, H. Xu, F. Shi, Y. Q. Wang, *Asian J. Org. Chem.* **2017**, *6*, 1460–1469.
[86] Y. D. Shao, D. D. Han, X. Y. Yang, D. di Zhou, T. Wang, D. J. Cheng, *Eur. J. Org. Chem.* **2019**, *2019*, 1957–1961.
[87] C. Lluna-Galán, G. Blay, I. Fernández, M. C. Muñoz, J. R. Pedro, C. Vila, *Adv. Synth. Catal.* **2018**, *360*, 3662–3666.
[88] D. Saha, T. Kaur, N. Singh, U. P. Singh, A. Sharma, *Asian J. Org. Chem.* **2016**, *5*, 82–90.
[89] S. S. Pawar, *Int. J. Pharma Bio Sci.* **2013**, *4*, 68–77.
[90] Y. Zhao, G. Huang, J. Wu, Q. Wu, S. Gao, Z. Yan, J. Lei, N. Yan, *Cell* **2019**, *177*, 1495–1506.
[91] F. Mietton, E. Ferri, M. Champleboux, N. Zala, D. Maubon, Y. Zhou, M. Harbut, D. Spittler, C. Garnaud, M. Courçon, M. Chauvel, C. D'Enfert, B. A. Kashemirov, M. Hull, M. Cornet, C. E. McKenna, J. Govin, C. Petosa, *Nat. Commun.* **2017**, *8*, 15482.
[92] a) R. K. Gill, N. Aggarwal, J. Kumari, M. Kumari, P. Kaur, M. Kaur, A. Rani, A. Bansal, A. Shah, J. Bariwal, *Chem. Biol. Interface* **2013**, *3*, 146–163; b) R. Kaur, R. Singh, K. Singh, *Chem. Biol. Lett.* **2016**, *3*, 18–31.
[93] T. Nagao, M. Sato, H. Nakajima, A. Kiyomoto, *Chem. Pharm. Bull.* **1973**, *21*, 92–97.
[94] R. F. Wilson, C. W. White, *Circulation* **1984**, *73*, 444–451.
[95] T. Mukai, E. Yamaguchi, J. Goto, K. Takagi, *Jpn. J. Pharmacol.* **1981**, *31*, 147–157.
[96] G. Campiani, I. Fiorini, M. P. de Filippis, S. M. Ciani, A. Garofalo, V. Nacci, G. Giorgi, A. Sega, M. Botta, A. Chiarini, R. Budriesi, G. Bruni, M. R. Romeo, C. Manzoni, T. Mennini, *J. Med. Chem.* **1996**, *39*, 2922–2938.
[97] T. Yoneda, H. Tabata, T. Tasaka, T. Oshitari, H. Takahashi, H. Natsugari, *J. Med. Chem.* **2015**, *58*, 3268–3273.
[98] IUPAC Gold Book "axial chirality", can be found under https://goldbook.iupac.org/terms/view/A00547, **2014** (accessed 20 March 2022).
[99] D. H. Ellison, C. S. Wilcox, *Therapy in Nephrology & Hypertension*, W. B. Saunders, Philadelphia **2008**, p. 388–411.
[100] G. W. Caldwell, Z. Yan, W. Lang, J. A. Masucci, *Curr. Top. Med. Chem.* **2012**, *12*, 1282–1290.
[101] S. A. Nawaz, S. Umbreen, A. Kahlid, F. L. Ansari, M. I. Choudhary, *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 206–212.
[102] a) V. K. Chaudhri, D. Pathak, Z. Hussain, *J. Appl. Pharmacol.* **2021**, *11*, 16–23; b) N. Garg, T. Chandra, Archana, A. B. Jain, A. Kumar, *Eur. J. Med. Chem.* **2010**, *45*, 1529–1535.

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