REVIEW

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Optically active 1,5-benzothiazepines

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Dedicated to the late Prof. Dr. Márton Kajtár on the occasion of his 70th birthday

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1. Introduction

Benzothiazepines are the benzocondensed derivatives of the three isomeric thiazepine parent compounds, 1,2-thiazepine, 1,3-thiazepine and 1,4-thiazepine. From the latter isomer three basic benzothiazepine structures can be derived which are 1,4-, 4,1- and 1,5-benzothiazepines. None of these basic structures has hitherto been described as appropriate substance in the literature. However, the derivatives of all these isomeric benzothiazepines are known compounds [1]. The most frequently studied 1,4-thiazepine derivatives are the 1,5-benzothiazepines. This may be due to their easy availability and the wide variety of their bioactivities. Optically active benzothiazepines have hitherto been synthesized only as 1,5-benzothiazepine derivatives. Owing to their important and useful bioactivities, these compounds received a special interest among the seven-membered heterocyclic compounds. The aim of this review article is to provide examples for the synthesis of the known groups of the optically active 1,5-benzothiazepines together with relevant references for their most important bioactivities.

2. Synthesis and stereochemistry of optically active 2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-ones substituted at position 2

The first representatives of the optically active 1,5-benzothiazepines were prepared by optical resolution of 2-carboxymethyl-2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-one with brucine as early as 1927 [2]. However, this was the sole example for the synthesis of optically active benzothiazepines for four decades. A second example was the optical resolution of the 2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-phenyl-1,5-benzothiazepin-4(5 *H*)-one (thiazesim) with (+)-tartaric acid in 1968 [3]. A common feature of both examples is that the appropriate 1,5-benzothiazepine was synthesized as racemate with a functional group capable of salt formation. Therefore, the optical resolution of the racemates was based on the fractional crystallization of the diastereomeric salts followed by the libration of the optically active 1,5-benzothiazepine enantiomers.

For the preparation of optically active 1,5-benzothiazepines substituted at position 2 a retrosynthetic approach was introduced by Lévai et al. [4]. This procedure made available the first synthesis of optically active 2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-ones without functionalities capable of salt formation (Scheme 1). With the knowledge of the conformation of their seven-membered ring [5], it became possible to determine the absolute configuration of the centre of chirality by a combination of X-ray diffraction analysis and circular dichroism (CD) spectroscopic measurements of the optically active intermediates and the 1,5-benzothiazepine derivatives [6, 7].

A new chemoenzymatic enantioselective synthesis of the 2,3-dihydro-2(*R*)-methyl-1,5-benzothiazepin-4(5 *H*)-one (Scheme 2) has been performed by Dike et al. starting from the Baker's yeast reduction of the ethyl acetoacetate [8]. A key intermediate of this procedure was the 3(*R*)-(phenylmercapto)butyric acid which was cyclized to 2(*R*)-methyl-1-thiochromanone. This 1-thiochromanone was converted into its oxime which afforded the desired optically active 2,3-dihydro-2(*R*)-methyl-1,5-benzothazepin-4(5 *H*)-one on Beckmann rearrangement with polyphosphoric acid.

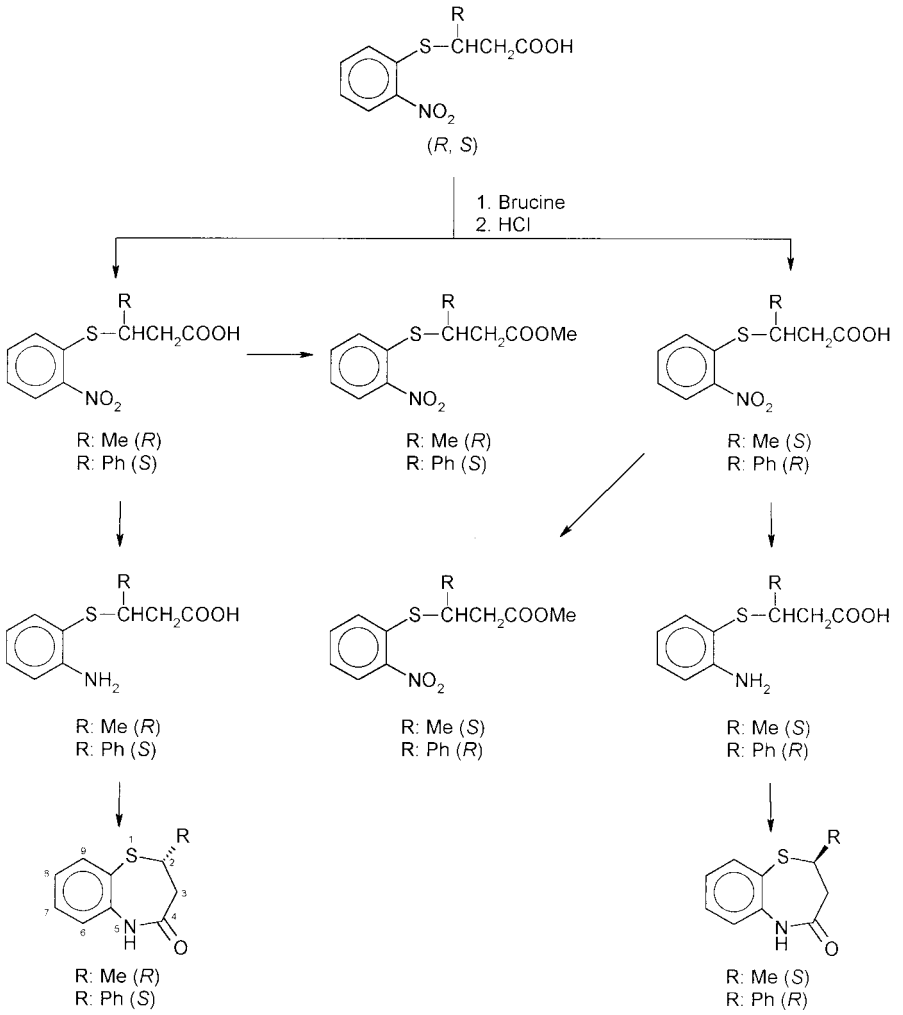
Dike et al. also managed to work out a chemoenzymatic enantioselective synthesis of the *R*-thiazesim [9]. This procedure starts with a Baker's yeast reduction of the ethyl benzoyl acetate which provides the highly optically pure (95% e.e.) 3(*R*)-phenylmercapto-3-phenylpropionic acid via several reaction steps. Ring closure of this optically active carboxylic acid afforded 1(*R*)-thioflavanone oxime which gave 2,3-dihydro-2(*R*)-phenyl-1,5-benzothiazepin-4(5*H*)-one on Beckmann rearrangement with polyphosphoric acid (Scheme 3). *N*-Alkylation of this optically active 1,5-benzothiazepine provided the *R*-thiazesim in high optical purity (95% e.e.). Thiazesim is the first optically active 1,5-benzothiazepine with known bioactivity since it was found to exhibit central nervous system activity [3].

For the preparation of an optically active 2,3-dihydro-2-methyl-1,5-benzothiazepine-4(5 *H*)-one a one-pot procedure was described by Breitschuh and Seebach [10]. (*S*)-β-Butyrolactone was allowed to react with *o*-(*N*-methylamino)thiophenol to afford 2,3-dihydro-2(*R*),5-dimethyl-1,5-benzothiazepin-4(5 *H*)-one without the isolation of the appropriate carboxylic acid intermediate (Scheme 4). However, to our knowledge, this procedure has not hitherto been used for the synthesis of any other related optically active 1,5-benzothiazepines.

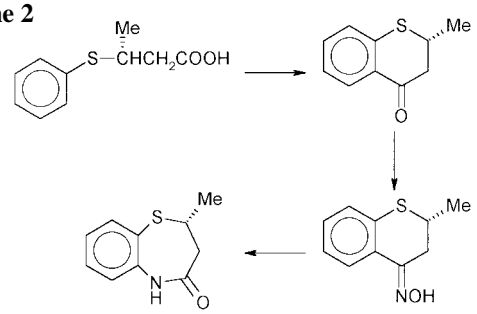
3. Synthesis of optically active 3-amino-2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-ones

The angiotensin converting enzyme (ACE) is a dipeptidyl carboxypeptidase catalyzing the hydrolysis of the decapep-

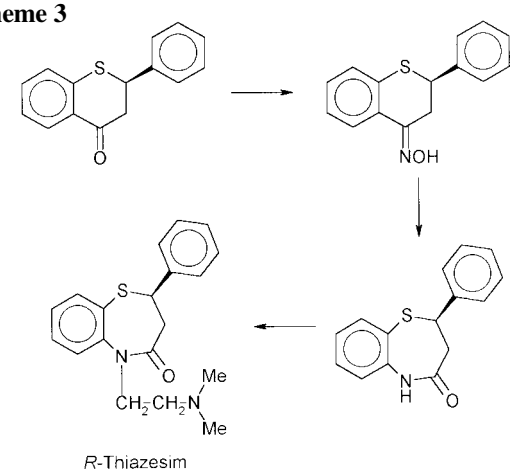
Scheme 1



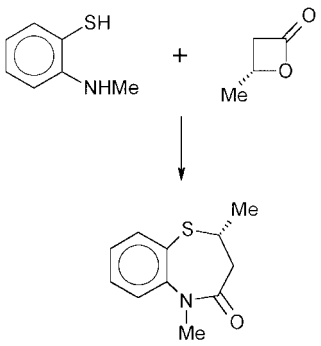
Scheme 2



Scheme 3



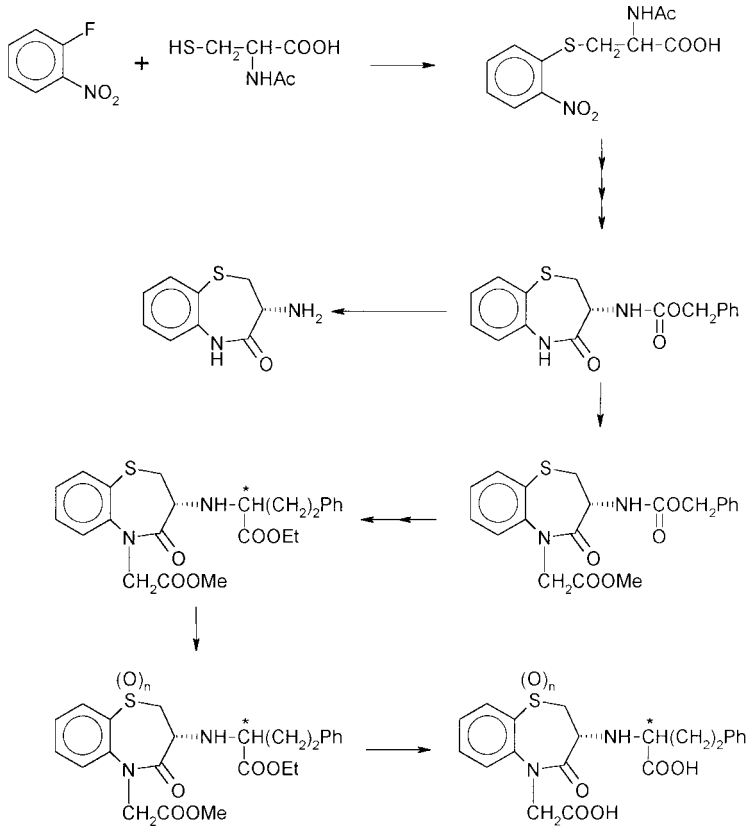
Scheme 4



tide angiotensin I to the octapeptide angiotensin II. This octapeptide is a known vasoconstrictor triggering the release of aldosterone, a sodium-retaining steroid derivative. Thus, the ACE raises the blood pressure and, therefore, various ACE inhibitors received a considerable acceptance in the treatment of hypertension and congestive heart failure [11]. As a result, various types of ACE inhibitors have been synthesized and tested for this purpose. In our present review article we discuss only the synthesis of ACE inhibitors with a 1,5-benzothiazepine skeleton.

A first representative of the optically active 3-amino-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones was synthesized by Slade et al. [12]. Source of the chirality was the L-cysteine as a natural amino acid used as building block. *N*-Acetylcysteine was allowed to react with *o*-fluoronitro-

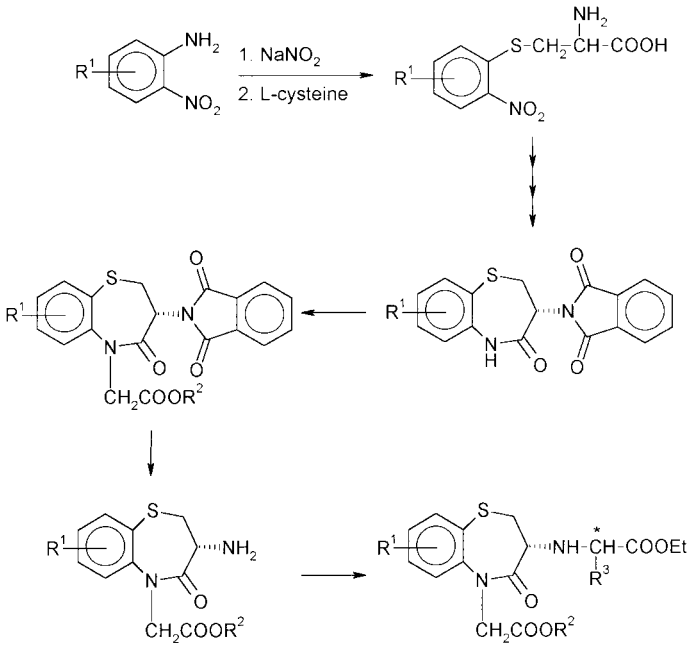
Scheme 5



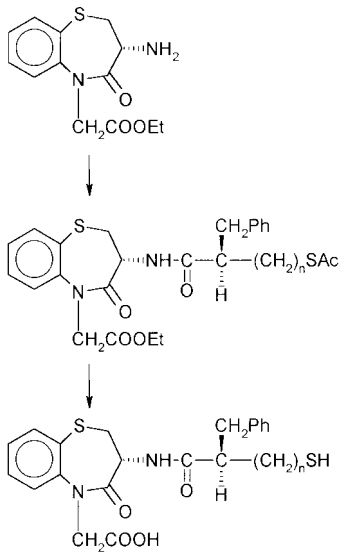
benzene to afford a nitrocarboxylic acid which then gave 3(*R*)-amino-2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-one on several reaction steps (Scheme 5). Various *N*-alkylated derivatives, sulfoxides and sulfones have also been synthesized (cf. Scheme 5) to improve the bioactivities of these aminobenzothiazepine derivatives. By ACE inhibition, one of the carboxylic acid derivatives lowered the blood pressure in the spontaneous hypertensive rat as well [12].

A wide variety of ACE inhibitory 3(*R*)-amino-5-carboxymethyl-2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-ones have also been synthesized by Itoh et al. [13–15] using L-cysteine as enantiopure chiral building block (Scheme 6). Further chemical transformations of the initially synthesized optically active aminobenzothiazepines provided numerous substances to study the structure-activity relationship as well. Both *in vitro* and *in vivo* ACE inhibitory

Scheme 6



Scheme 7



n: 0,1

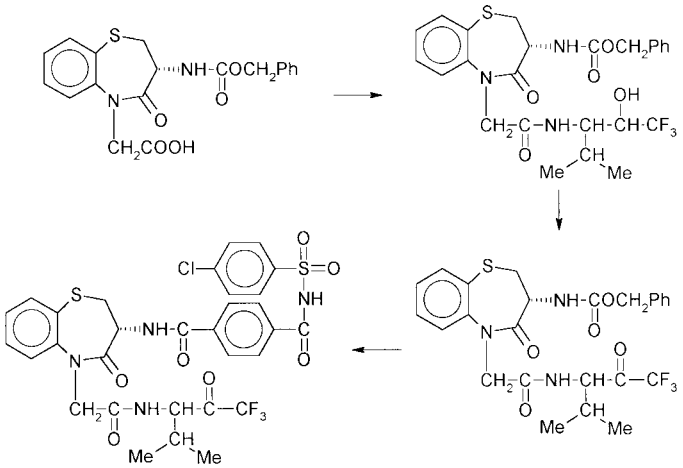
activities were investigated in comparison with other types of compounds to get informations on the structural units responsible for the ACE inhibitory activity.

Robl et al. [16, 17] synthesized optically active 3-amino-1,5-benzothiazepine derivatives (Scheme 7) possessing high inhibitory activity against ACE and neutral endopeptidase (NEP) both *in vitro* and *in vivo*. These benzothiazepines have a mercapto group beside the carboxylic acid and amide functionalities.

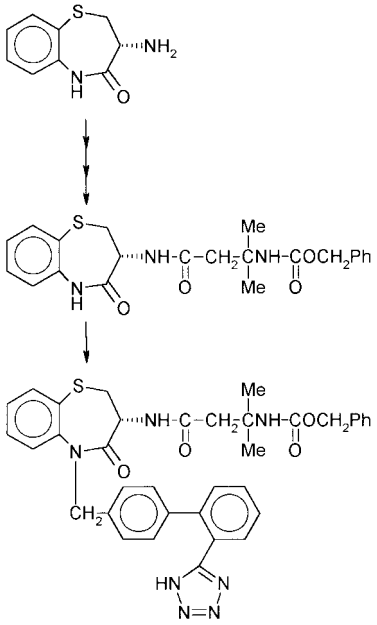
Among the optically active 3-amino-2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-ones human leukocyte elastase (HLE) inhibitors have also been found. Skiles et al. [18] synthesized 1,5-benzothiazepine derivatives bearing a trifluoromethyl ketone moiety (Scheme 8) and these compounds were found to possess good HLE inhibitory activity both *in vitro* and *in vivo*.

Similar optically active 3-amino-2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-ones proved to be non-peptidic growth hormone secretagogues [19]. Synthesis of such 1,5-benzothiazepine derivatives is based on the chemical transformation of 3(*S*)-amino-2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-one (cf. Scheme 5) as outlined in Scheme 9 [19].

Scheme 8



Scheme 9

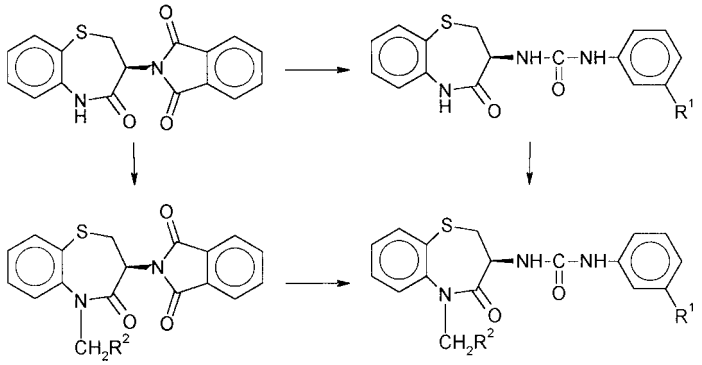


Dual histamine H_2 and gastrin receptor antagonistic, optically active 3(*S*)-amino-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones have been synthesized by Kawanishi et al. [20] starting with the reaction of 2-nitroaniline and D-cysteine. Further chemical transformations of the initially formed 1,5-benzothiazepine provided various *N*-substituted derivatives (Scheme 10) used for biological trials.

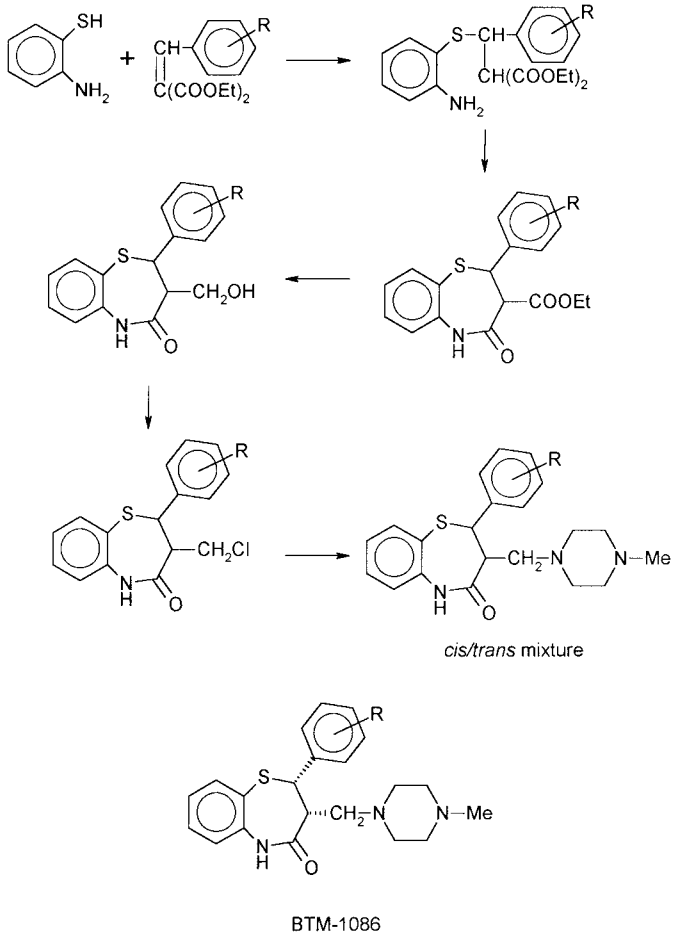
4. Synthesis of optically active 2-aryl-2,3-dihydro-3-[(4-methylpiperazinyl)methyl]-1,5-benzothiazepin-4(5 *H*)-ones

The first optically active 2,3-disubstituted 2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-ones were synthesized in 1983 by Ohno et al. [21]. Reaction of diethyl arylidenemalonates with 2-aminothiophenol afforded an aminocarboxylic acid derivative ring closure which provided 2-aryl-2,3-dihydro-3-(ethoxycarbonyl)-1,5-benzothiazepin-4(5 *H*)-ones (Scheme 11). These benzothiazepines were then converted into 3-hydroxymethyl derivatives on reduction with $LiAlH_4$. The hydroxy group was replaced by a chlorine atom and these intermediates were allowed to react with *N*-methylpiperazine to yield a *cis*/*trans* mixture of 2-aryl-2,3-dihydro-3-[(4-methylpiperazinyl)methyl]-1,5-benzothiazepin-4(5 *H*)-ones (Scheme 11). The diastereomers were then separated

Scheme 10



Scheme 11

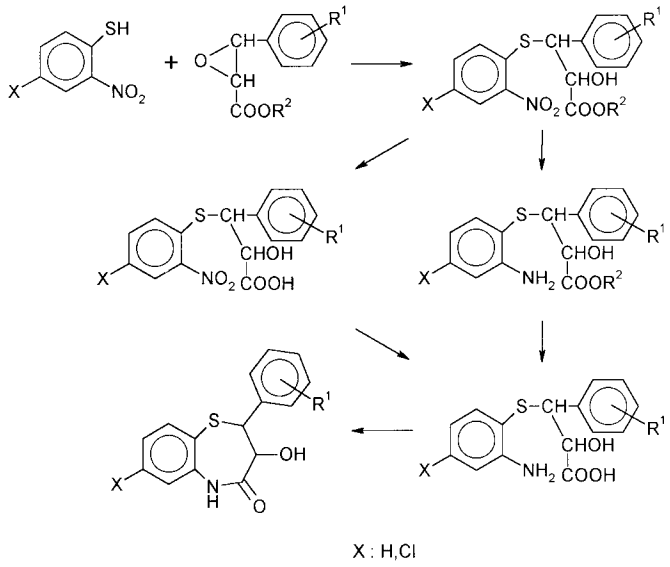


and the *cis*-2-aryl-2,3-dihydro-3-[(4-methylpiperazinyl)methyl]-1,5-benzothiazepin-4(5 *H*)-ones were optically resolved with tartaric acid in methanol. As a result, the (−)-*cis*-2,3-dihydro-3-[4-(methylpiperazinyl)methyl]-2-phenyl-1,5-benzothiazepin-4(5 *H*)-one was obtained. Its hydrochloride (BTM-1086) (Scheme 11) proved to be a potent anti-ulcer and gastric secretory inhibitory agent [21–24]. However, to our knowledge, no other representatives of these 2,3-disubstituted 1,5-benzothiazepines have hitherto been synthesized and tested for their bioactivities. It should also be mentioned that no data are available in the literature concerning the determination of the absolute configuration of the centres of chirality of these optically active 1,5-benzothiazepines.

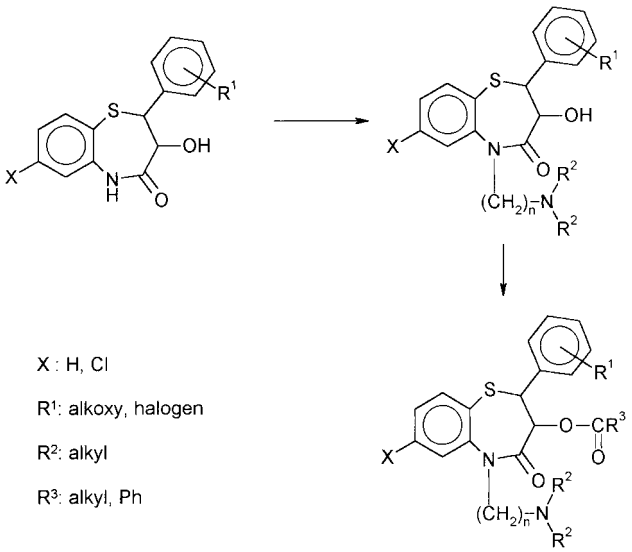
5. Synthesis and bioactivities of optically active 2-aryl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5 *H*)-ones

The first synthesis of 2-aryl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5 *H*)-ones has been performed by Kugita et al. [25–27] about three decades ago. 2-Nitrothiophenol was allowed to react with phenylglycidic esters to afford the appropriate nitrocarboxylic acids which gave then diastereomeric mixtures of 2-aryl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5 *H*)-ones (Scheme 12). As a further development, depending on the reaction conditions of the ring opening of the phenylglycidic esters, both *cis* and *trans*-2-aryl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-ones were prepared as single diastereomers.

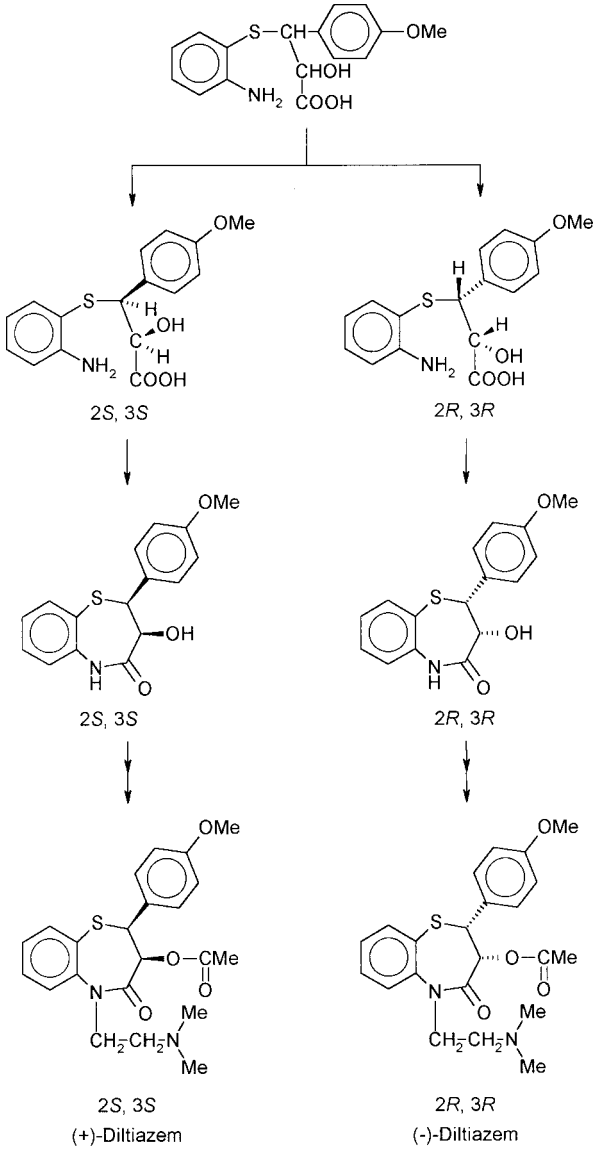
Scheme 12



Scheme 13



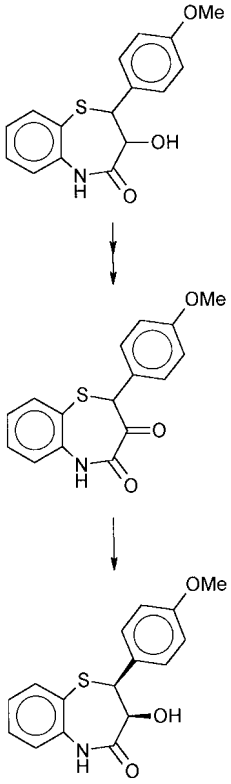
Scheme 14



It has also turned out that these 2,3-disubstituted 2,3-dihydro-1,5-benzothiazepin-4(5 *H*)-ones are useful seven-membered heterocyclic compounds in the drug research. To obtain new derivatives with beneficial bioactivities, many of their *N*-alkylated derivatives were prepared and tested in the early stage of the research and development of these benzothiazepines [27–34] (Scheme 13). The 3-acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5 *H*)-one (diltiazem) proved to be the most active substance with its coronary vasodilator [29–31], antiarrhytmic [32] and haemodynamic [33] effects. It has also turned out that the four optically active stereoisomers of diltiazem, the (+)-*cis*-enantiomer, viz. the 3(*S*)-acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2(*S*)-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one is the most effective.

The first synthesis of (+)-diltiazem was performed by Inoue et al. [35] who determined the (2 *S*, 3 *S*)-absolute configuration of this compound by X-ray diffraction analysis as well. Diastereomeric salt formation of the *cis*-3-(2-aminophe-

Scheme 15



2*S*, 3*S*

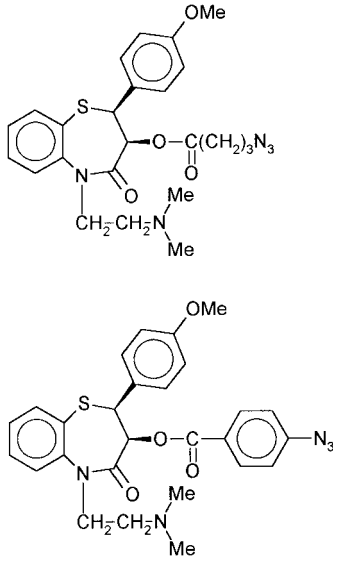
nylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid with various optically active amines has been utilized for the preparation of the optically active intermediate ring closure which provided 2,3-dihydro-3(*S*)-hydroxy-2(*S*)-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [35–38] (Scheme 14). Optical purity, conformation and absolute configuration of these optically active 1,5-benzothiazepines and their intermediates have been elucidated by NMR spectroscopic measurements, X-ray diffraction analysis and circular dichroism (CD) spectroscopy [36, 37, 39–43].

Another opportunity for the preparation of optically active intermediates of diltiazem is the enzyme-catalyzed kinetic resolution of the racemic hydroxycarboxylic acid derivatives [44–46]. Various enantioselective synthetic methods have also been used to obtain optically active intermediates in the synthesis of optically active diltiazem [47–53].

As the latest approach, (±)-*cis*-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one was resolved with 1(*R*)-3-bromocamphor-9-sulfonic acid to afford the desired optically pure (+)-enantiomer which was then acetylated to yield the 3(*S*)-acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2(*S*)-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [54]. 3-Hydroxy-1,5-benzothiazepine derivatives have also been resolved with (2-naphthylsulfonyl)-2(*S*)-pyrrolidinecarbonyl chloride to afford optically active intermediates for the synthesis of diltiazem and related benzothiazepines [55–57].

Asymmetric reduction of 2-(4-methoxyphenyl)-1,5-benzothiazepin-3,4(2*H*,5*H*)-dione with $NaBH_4$ and optically active α-amino acids provided 2,3-dihydro-3(*S*)-hydroxy-2(*S*)-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (Scheme 15) as an optically active intermediate of the diltiazem [58]. These two studies are examples for the preparation of the optically active intermediates of diltiazem

Scheme 16



in the 1,5-benzothiazepine stage of the synthesis. All other procedures are based on the preparation of an optically active carboxylic acid prior to the ring closure to a 1,5-benzothiazepine intermediate.

Since diltiazem proved to be the most effective member of the 3-hydroxy-1,5-benzothiazepines, related substances have also been synthesized. Some azido derivatives (Scheme 16) were found to possess a considerable Ca antagonist effect [59]. Several metabolites of diltiazem have been prepared and showed different bioactivities [34, 60–62]. Biological and pharmacological activities of these benzothiazepines have been investigated by several research groups [63–72]. Their most important effects are antihypertensive, cardiovascular, spasmolytic, calcium channel blocking and antithrombotic activities. For this reason, 3-hydroxy-1,5-benzothiazepines are the most important benzothiazepine type compounds in drug research.

In summary, the present review article discusses the most important synthetic procedures used for the preparation of the four known groups of optically active 1,5-benzothiazepines. Since most of these compounds possess biological or pharmacological activities, some of their most characteristic bioactivities are mentioned as well.

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