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Review

Synthesis and Chemistry of 1,2,3-Benzothiadiazine 1,1-Dioxide Derivatives: A Comprehensive Overview

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Abstract: 1,2,4-Benzothiadiazine 1,1-dioxide derivatives (e.g., chlorothiazide, hydrochlorothiazide) have been long used in the human therapy as diuretic and antihypertensive agents. Marketed drugs containing the structurally related phthalazinone scaffold are applied for the treatment of various diseases ranging from ovarian cancer to diabetes and allergy. 1,2,3-Benzothiadiazine 1,1-dioxides combine the structural features of these two compound families, which led to their more intensive research since the 1960s. In the present review, we summarize the literature of this period of more than half a century, including all scientific papers and patent applications dealing with the synthesis and reactions of this compound family, briefly hinting at their potential therapeutic application as well.

Keywords: 1,2,3-benzothiadiazine 1,1-dioxide; ring closure; alkylation; acylation; reduction; ring contraction

1. Introduction

Several medicaments containing a 1,2,4-benzothiadiazine 1,1-dioxide scaffold (Figure 1) are used as diuretic and antihypertensive agents [1–4].

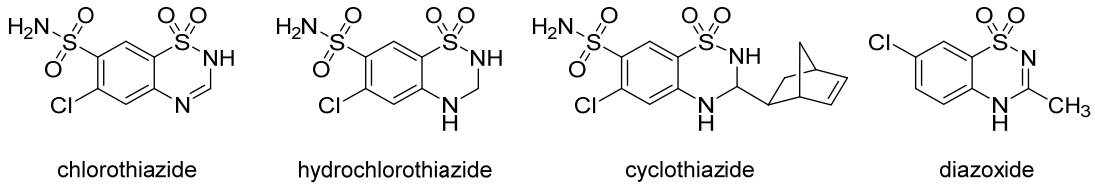


Figure 1. Marketed drugs with a 1,2,4-benzothiadiazine 1,1-dioxide scaffold.

1-Hydrazinophthalazine (hydralazine, Figure 2) is a drug for the treatment of various cardiovascular diseases [5,6], while the structurally related phthalazinone derivatives are applied in a wide range of indications: olaparib as an anticancer agent [7,8], zopolrestat as an antidiabetic [9,10], and azelastine as an antihistamine [11,12].

Nearly 20 years ago, our focus at Egis Pharmaceuticals (Hungary) turned to the chemistry of 2*H*-1,2,3-benzothiadiazine 1,1-dioxides (BTD, see parent compound **1a**, Scheme 1) as relatively scarcely used potential building blocks in medicinal chemistry, which combine the structural features of the abovementioned therapeutically efficient compound families. In this review, we intend to summarize the synthetic strategies that have been employed in the literature to prepare BTDs, briefly mentioning the observed pharmacological activities as well. We seek to specify the reaction conditions and the yields of the discussed reactions in each case if the data are clearly present in the literature sources.

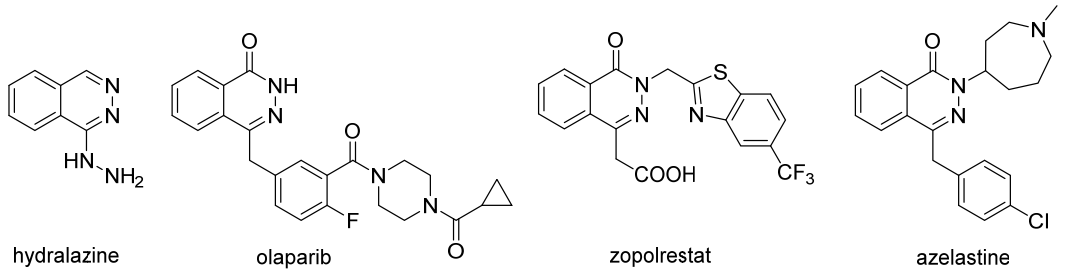
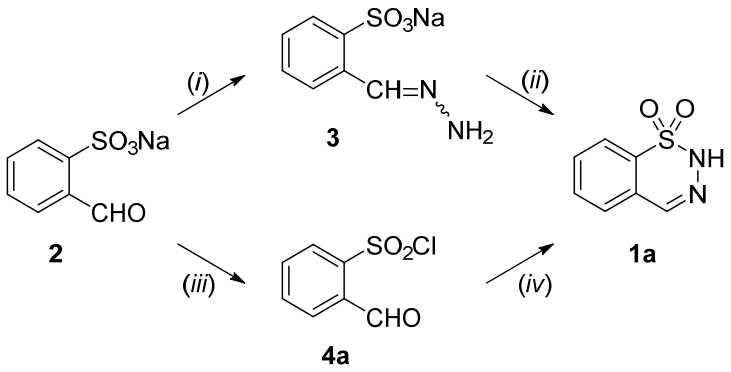


Figure 2. Marketed drugs with a phthalazine or phthalazinone scaffold.



Scheme 1. The first described syntheses of 2*H*-1,2,3-benzothiadiazine 1,1-dioxide (BTD) parent compound **1a.** (*i*) NH_2NH_2 (56%); (*ii*) PCl_5, $POCl_3$, NH_2NH_2 (5–80%); (*iii*) $SOCl_2$, DMF; (*iv*) NH_2NH_2 (50%, two steps).

2. Synthesis and Reactions of 4-Unsubstituted, 4-Aryl and 4-Alkyl Derivatives

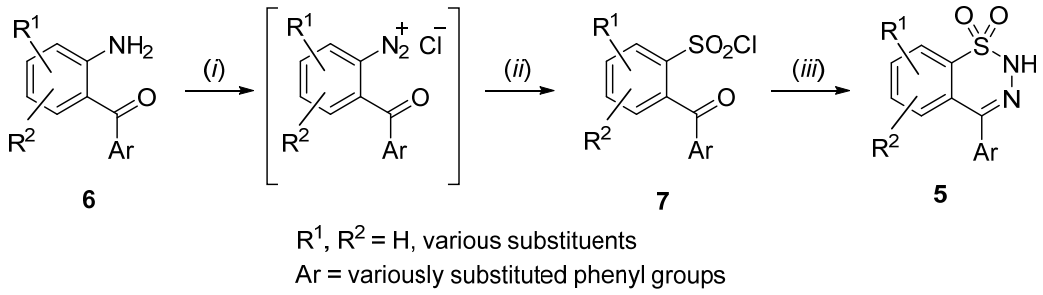
2.1. Synthesis of 4-Unsubstituted, 4-Aryl and 4-Alkyl Derivatives

The synthesis of the parent compound (**1a**) was first described by King et al. in 1969, starting from sodium 2-formylbenzenesulfonate (**2**) via hydrazone **3** with erratic reproducibility and low yields (Scheme 1). Better results were obtained by changing the order of the two steps, i.e., by transformation of the sulfonate salt **2** to 2-formylbenzenesulfonyl chloride **4a** and cyclization of the latter with hydrazine [13,14].

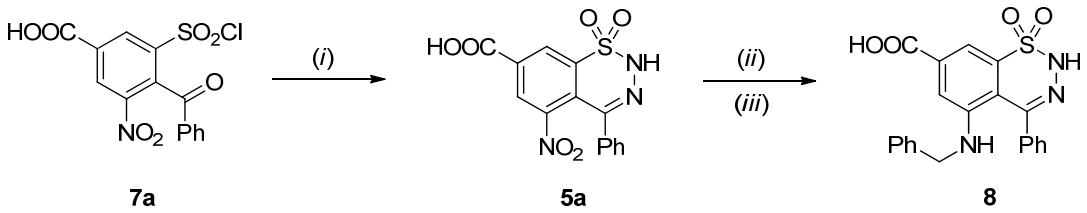
It is obvious that the key issue regarding the construction of the heterocyclic ring is the availability of an *ortho*-disubstituted benzene derivative suitable for cyclization with hydrazine. The syntheses of the "commercially available" [14] key intermediate **2** were already described at the turn of the 20th century in German patents [15,16].

Simultaneously with the aforementioned work, Wright et al. published the synthesis of 4-arylbenzothiadiazine dioxides **5** (Scheme 2) [17–19]. Diazotation of 2-aminobenzophenones **6** followed by reaction with sulfur dioxide in the presence of copper (II) chloride gave *ortho*-benzoylbenzenesulfonyl chlorides **7**, which were cyclized with hydrazine to give 4-aryl-substituted target compounds **5**.

Some representatives of the 4-aryl-BTD family (**5**) are useful as intermediates for the preparation of disinfectants, mothproofing agents, pickling inhibitors and herbicides [17]. Cyclization of the suitably substituted *ortho*-benzoylbenzenesulfonyl chloride **7a** with hydrazine to give **5a**, followed by reduction of the nitro group and subsequent *N*-benzylation, afforded aminobenzoic acid **8** (Scheme 3). However, it was devoid of the expected diuretic activity [20].



Scheme 2. The first synthesis of 4-aryl-BTDs (**5**). (*i*) $NaNO_2$, AcOH, HCl; (*ii*) SO_2, $CuCl_2$; (*iii*) NH_2NH_2, NaOAc, EtOH.

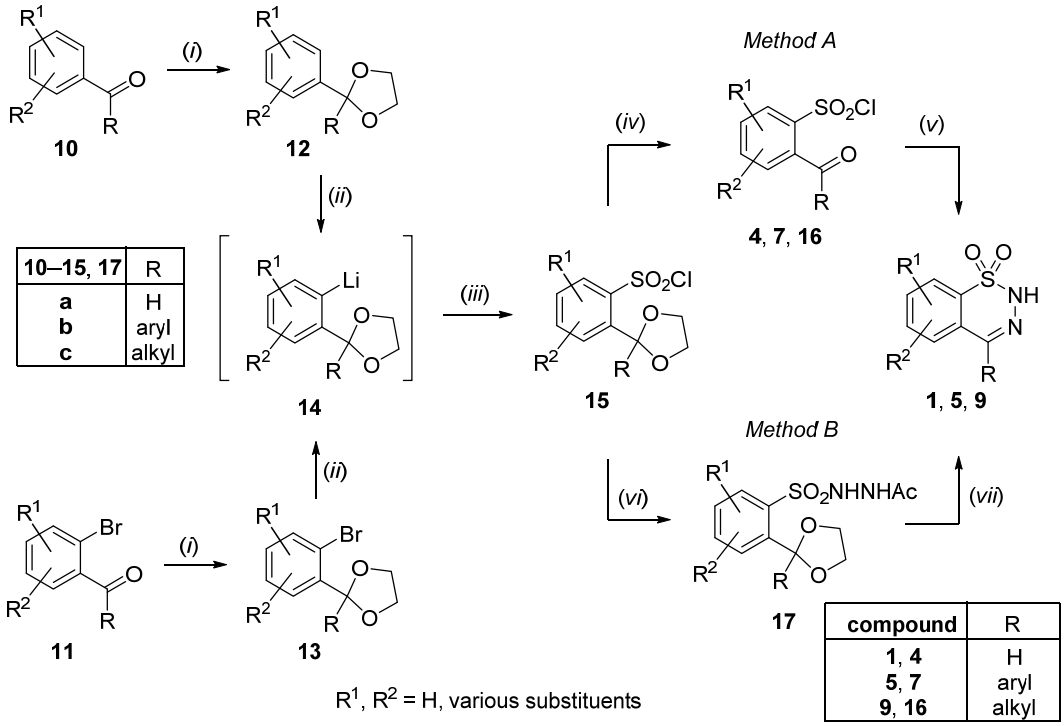


Scheme 3. Synthesis of diuretic candidate **8**. (*i*) $NH_2NH_2{\cdot}H_2O$, H_2O, 5 °C, 1.5 h (42%); (*ii*) $FeSO_4$, NH_3, H_2O, rt, 0.5 h (35%); (*iii*) $PhCH_2Br$, $MeOCH_2CH_2OH$, 100 °C, 24 h (32%).

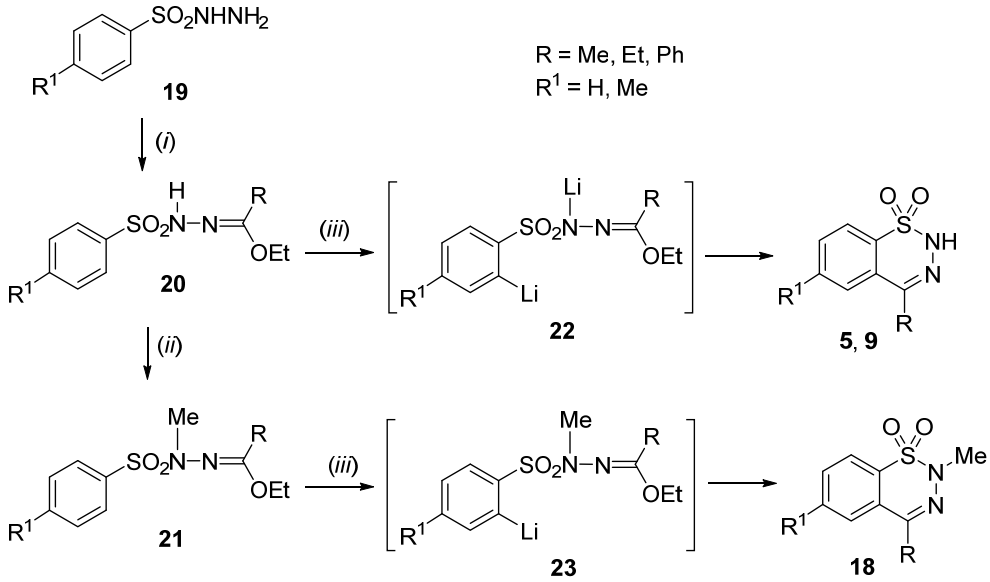
A widely applicable procedure, based on *ortho*-lithiation methodology, has been developed at our laboratory for the synthesis of a significant variety of 4-unsubstituted, 4-aryl- and 4-alkyl-BTDs (**1**, **5** and **9**, Scheme 4), starting from variously substituted benzaldehydes (R = H) [21] benzophenones (R = aryl) [22] or acetophenones (R = Me) [23,24] of type **10** or **11**, which were masked in the first step as 1,3-dioxolanes (**12**, **13**, Scheme 4) using microwave technology [25]. *Ortho*-lithiation was carried out by exploiting the combined *ortho*-directing ability of the 1,3-dioxolan-2-yl group and another substituent of the aromatic ring, or by Br→Li exchange. Trapping aryllithiums (**14**) with sulfur dioxide and subsequent treatment with sulfuryl chloride gave the corresponding sulfonyl chlorides (**15**).

From this point, two reaction sequences were applied for the synthesis of BTDs **1**, **5** and **9**. Hydrolysis of 1,3-dioxolanes **15** under acidic conditions followed by cyclization of the resulting 2-formyl-, 2-aroyl- and 2-acylbenzenesulfonyl chlorides (**4**, **7**, **16**) with hydrazine monohydrate gave target compounds **1**, **5** and **9** in good yields (Method A). An alternative route was also elaborated (Method B): treatment of acetal **15a** and ketals **15b** and **15c** with acetohydrazide afforded sulfonyl-acetohydrazides **17**. Removal of the 1,3-dioxolane protecting group, *N*-deacetylation and ring closure took place under strongly acidic conditions in one pot, giving rise to the formation of target compounds **1** [21,26] **5** [27] and **9** [25,26].

A new approach was disclosed by Kacem et al. for the synthesis of BTDs **5**, **9** and **18** [28]. Treatment of *N*-arylsulfonylhydrazides **19** (Scheme 5) with orthoesters afforded *N*-arylsulfonylhydrazonates **20**, which underwent *ortho*-lithiation with lithium diisopropylamide (LDA) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Subsequent cyclization of lithium derivative **22** provided BTDs **5** and **9** in reasonable yields. Better yields were achieved by a similar cyclization of *N*-methylated derivative **21** to 2-methyl-BTDs **18** via lithium derivative **23**.



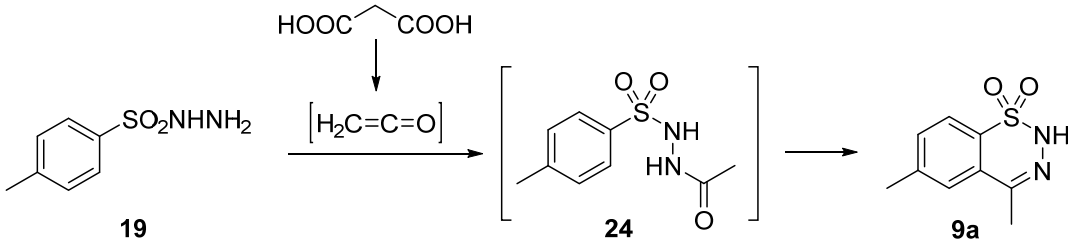
Scheme 4. Lithiation-based synthetic approaches for the synthesis of 4-unsubstituted (**1**), 4-aryl- (**5**) and 4-alkyl-BTDs (**9**). (*i*) $HOCH_2CH_2OH$, *p*-TsOH, toluene, reflux, MW, 450–650 W, 2–3 h or traditional heating; (*ii*) BuLi, THF or DEE, −78–(−5) °C, 2–4 h; (*iii*) 1. SO_2, THF or DEE; 2. SO_2Cl_2, hexane at (−30)–(+5) °C, 0.5–2 h; (*iv*) H_2SO_4, $CHCl_3$, Kieselgel, rt, 4 h; (*v*) $NH_2NH_2 \times H_2O$, THF, reflux, 4 h; (*vi*) NH_2NHAc, iPrOH, rt, 2 h; (*vii*) 10% HCl reflux, 2 h.



Scheme 5. Synthesis of BTDs (**5**, **9**, **18**) by directed *ortho*-lithiation-cyclization reactions. (*i*) $RC(OEt)_3$, AcOH, 80–90 °C (87–95%); (*ii*) NaH, THF, 0 °C, MeI (76–90%); (*iii*) LDA/TMEDA, 0 °C, 1.5 h (43–85%).

Chandra et al. elaborated a method for the *N*-acylation reactions of peptides by ketenes, generated from malonic acids in the presence of a coupling agent (HBTU, HATU, TATU, etc.) and bases (DIPEA, TEA) in DMF or DMSO at 0 °C [29]. When extending this procedure to the *N*-acetylation of sulfonylhydrazide **19** (Scheme 6), they concluded that under the reaction conditions applied for

the acetylation (not specified in detail), intermediate **24** underwent immediate cyclization to BTD **9a**. However, the attached spectroscopic data are not in accordance with structure **9a**, which was previously convincingly characterized by Kacem et al. [28].

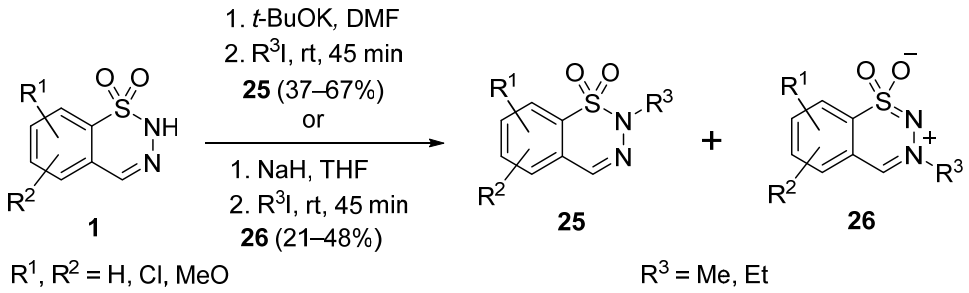


Scheme 6. Synthesis of 4,6-dimethyl-BTD (**9a**) by cyclization of *para*-toluenesulfonyl-acetohydrazide (**24**).

2.2. Reactions of 4-Unsubstituted, 4-Aryl and 4-Alkyl Derivatives

2.2.1. Alkylations

We found that alkylation of 2*H*-1,2,3-benzothiadiazine 1,1-dioxide and its derivatives substituted on the aromatic ring (**1**) with methyl and ethyl iodide occurred both at *N*(2) and *N*(3) atoms (**25** and **26**, Scheme 7) [30,31]. The *N*(3)-alkylated derivative (**26**) exhibited a unique mesoionic structure. When using *t*-BuOK as the base in DMF, compound **25** was the main product, while deprotonation with NaH in THF followed by alkylation preferred the formation of the *N*(3)-alkyl compound **26**. The two products could be selectively isolated without chromatography.

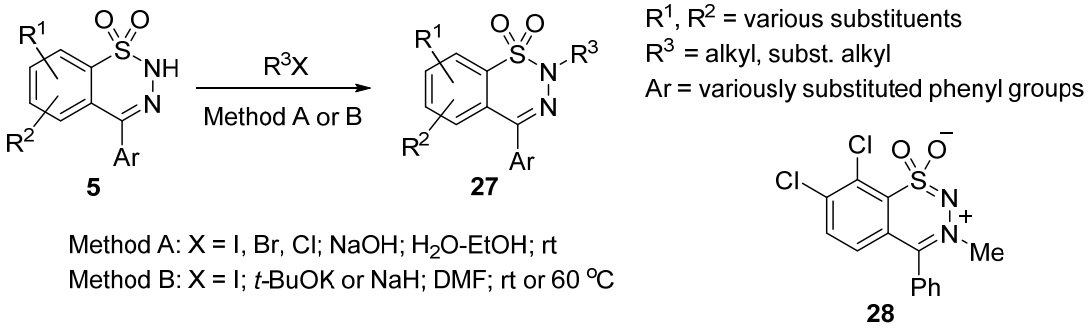


Scheme 7. Alkylation of 4-unsubstituted BTDs (**1**) leading to two different products (**25**, **26**).

It is interesting to mention that two earlier Japanese patents dealt with the alkylation reactions of compound **1a** (R^1, R^2 = H, Scheme 7). Here, a large variety of alkylating agents were used (e.g., ω-halogen carboxylic acid esters); however, only *N*(2)-substituted derivatives were isolated, and no *N*(3)-alkylation was mentioned [32,33]. Some derivatives proved to be efficient fungicides preventing rice blast, one of the most destructive diseases of rice.

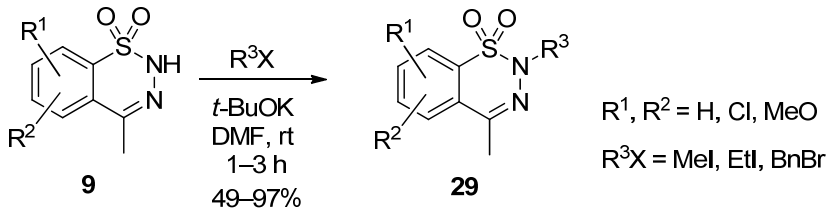
Wright described the alkylations of variously substituted 4-aryl-BTDs **5** with alkyl iodides [17,18] and aminoalkyl bromides and chlorides [19] in the presence of sodium hydroxide (NaOH) in aqueous ethanol solution resulting in *N*(2)-alkyl derivatives **27** (Scheme 8, Method A). We carried out *N*(2)-methylation of compounds **5** at room temperature in DMF using either *t*-BuOK or NaH as the base (Method B). Similar alkylation with butyl iodide was conducted at an elevated temperature (60 °C) [27].

N(2)-Alkylations of 4-aryl derivatives **5** occurred more selectively than in the case of 4-unsubstituted congeners **1**. For the sake of completeness, a detailed examination was carried out in one case: a small amount of mesoionic derivative **28** (Scheme 8) could be isolated. According to ^{1}H NMR measurements, the ratio of the *N*(2)- and *N*(3)-alkylated compounds in the crude product mixture was 10:1 in this case [27].



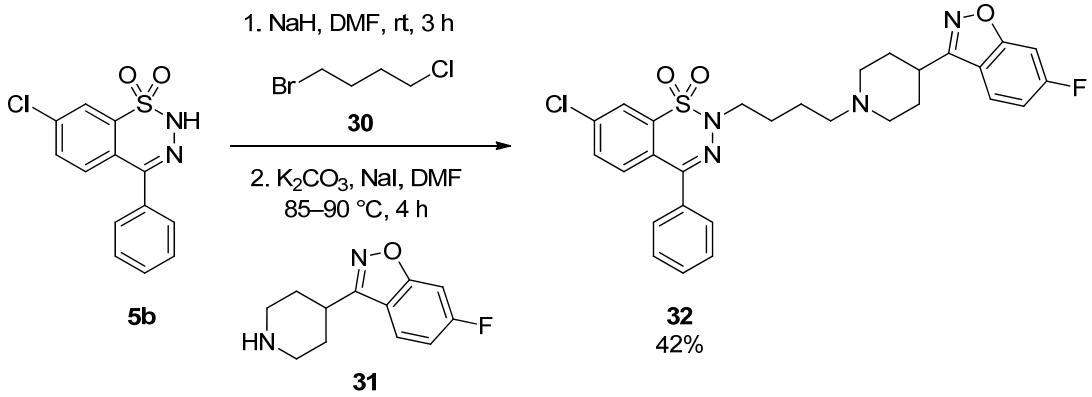
Scheme 8. Alkylation of 4-aryl-BTDs (**5**).

Alkylation of 4-methyl derivatives **9** with various alkylating agents (Scheme 9) in the presence of *t*-BuOK in DMF afforded the corresponding *N*(2)-alkylated derivatives **29** [24,30].



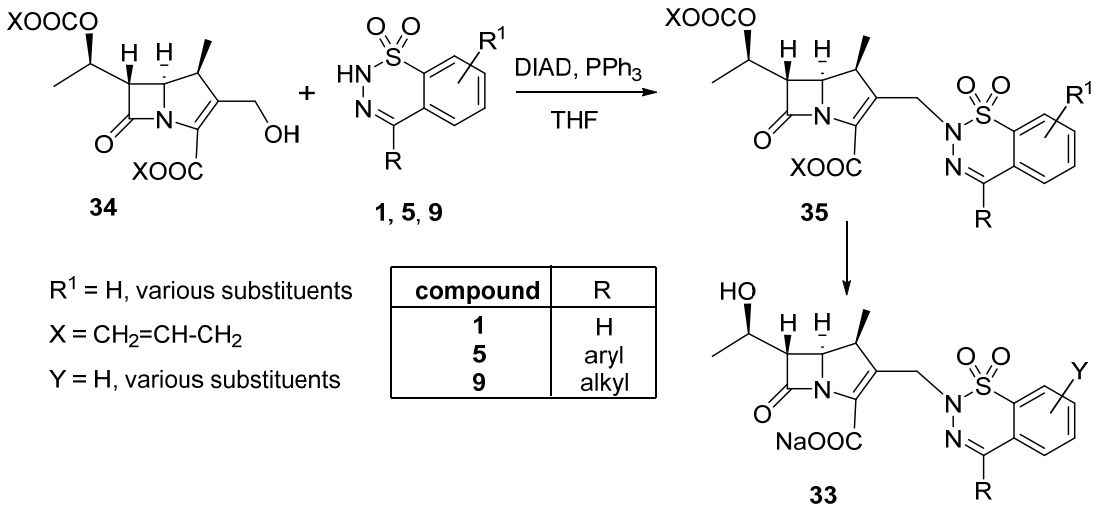
Scheme 9. Alkylation of 4-methyl-BTDs (**9**).

N(2)-Haloalkylations enable the attachment of pharmacologically interesting ligands to the BTD core, as demonstrated by the alkylation of compound **5b** with 1-bromo-4-chlorobutane (**30**) and the subsequent reaction with pharmacophore **31,** resulting in compound **32,** which was expected to exhibit serotonergic activity (Scheme 10) [27].



Scheme 10. Synthesis of a potential serotonergic compound (**32**).

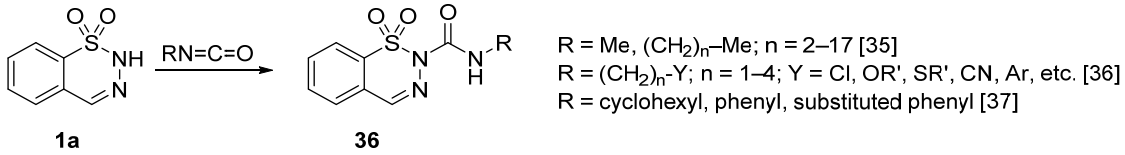
Carbapenem antibacterials, useful against Gram-positive microorganisms containing a BTD building block (**33**), were synthesized using Mitsunobu chemistry for *N*(2)-alkylation of BTDs (**1**, **5**, **9**) with hydroxymethyl-carbapenem derivative **34**. Optionally, a R^1 substituent of compound **35** was further transformed before removal of the protecting groups (Scheme 11) [34].



Scheme 11. Synthesis of antibacterials possessing a carbapenem core (**33**).

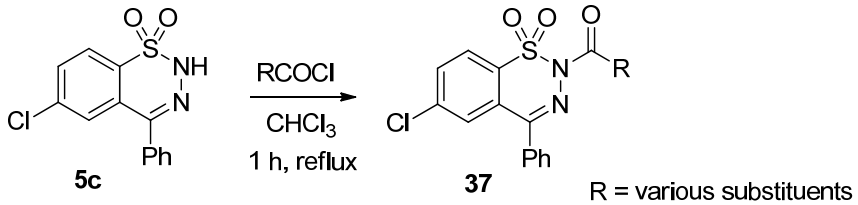
2.2.2. Acylations and Carbamoylations

Three Japanese patent applications were filed for the synthesis of *N*(2)-carbamoyl-2*H*-1,2,3-benzothiadiazine 1,1-dioxides (**36**) by the treatment of compound **1a** with various isocyanates (Scheme 12) [35–37]. In all cases, the aim was to develop effective bactericides and fungicides.



Scheme 12. *N*(2)-Carbamoylation of BTD **1a**.

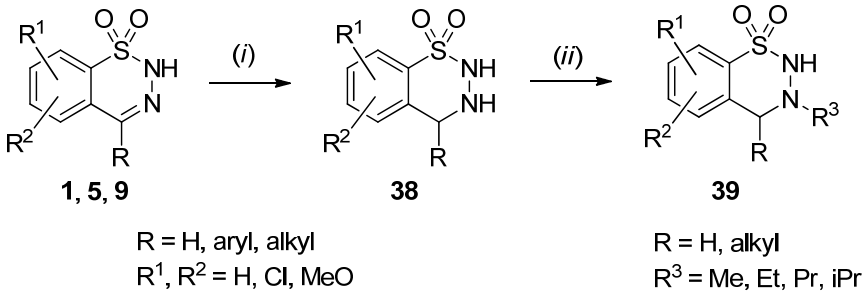
Wright published the acylation of 4-phenyl derivative **5c** with some acyl chlorides in refluxing chloroform to afford *N*(2)-acyl derivative **37** (Scheme 13) [17,18]. In a Japanese patent, similar acetylation and propionylation of compound **1a** are mentioned [33].



Scheme 13. *N*(2)-Acylation of 6-chloro-4-phenyl-BTD (**5c**).

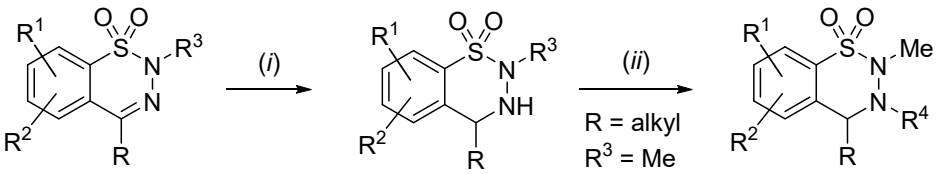
2.2.3. Reductions of the C=N Double Bond and Subsequent Alkylations and Acylations

There are two ways to perform the reduction of the C=N double bond of BTDs **1**, **5** and **9**. 3,4-Dihydro derivatives **38** were obtained either: (a) through catalytic reduction in the presence of platinum(IV) oxide or palladium on activated charcoal at 3.5 or 10–15 bar hydrogen pressure in acetic acid (Scheme 14, Method A), or (b) with $NaBH_4$ in a mixture of trifluoroacetic acid (TFA) and dichloromethane (Method B) [19,24,26,27,30,38]. Compounds **38** were regioselectively alkylated at position *N*(3) by catalytic reductive alkylation using aldehydes or acetone to give derivatives **39** [24,30,38].



Scheme 14. Preparation of *N*(3)-alkyl-3,4-dihydro-BTDs (**39**). (*i*) Method A: H_2, PtO_2 or Pd/C, AcOH or THF–AcOH, 3.5 or 10–15 bar, rt (43–71%); Method B: $NaBH_4$/TFA, CH_2Cl_2, 0–5 °C (80–97%); (*ii*) aldehydes or acetone, H_2, PtO_2; or Pd/C, AcOH, 10 bar, rt (29–60%).

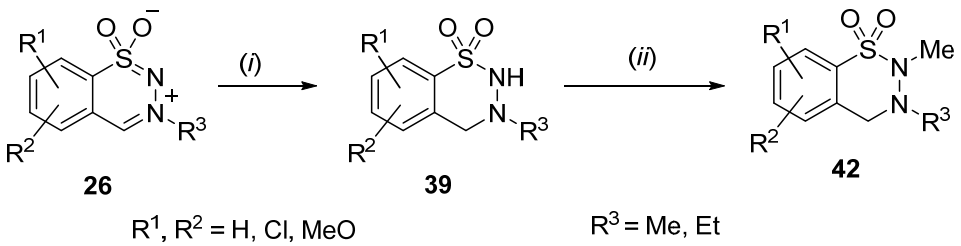
Reduction of the C=N double bond of *N*(2)-alkyl derivatives **25**, **27** and **29** was executed in the same ways as in the case of the corresponding *N*(2)-unsubstituted compounds (Method A or B) to furnish 3,4-dihydro derivatives **40** (Scheme 15) [24,27,30,38]. Catalytic reductive alkylation of the latter was carried out with 4-alkyl compounds resulting in 2,3,4-trialkyl derivatives **41** [24,30,38].



compound	R
25	H
27	aryl
29	alkyl

Scheme 15. Reduction and subsequent alkylation reactions of *N*(2)-alkyl-BTDs (**25**, **27**, **29**). (*i*) Method A: H_2/PtO_2 or Pd/C, AcOH or THF–AcOH, 10–15 bar, rt (44–94%); Method B: $NaBH_4$/TFA, CH_2Cl_2, 0–5 °C (29–100%); (*ii*) CH_2O or CH_3CHO, THF; or THF–AcOH, H_2, Pd/C, 10–15 bar, rt (21–89%).

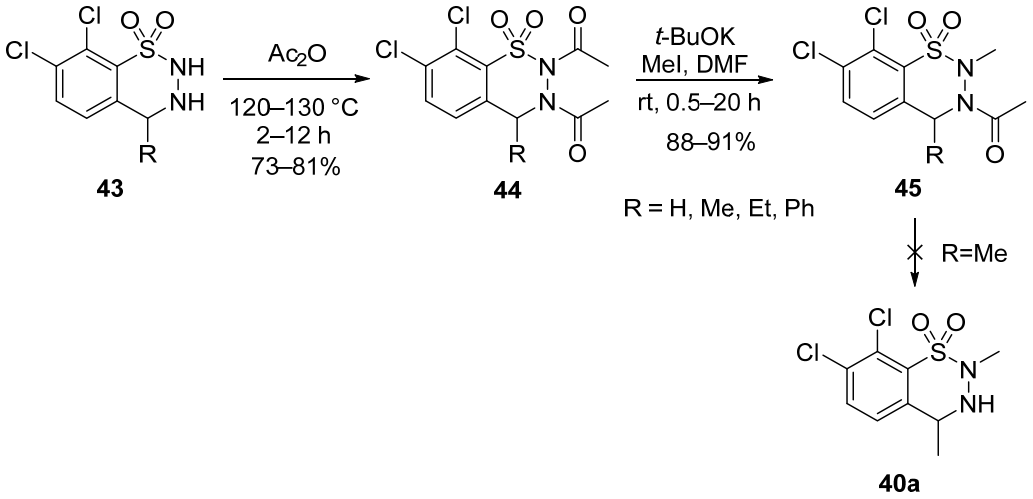
The case of mesoionic compounds **26** deserves a special mention. Their reduction to 3,4-dihydro derivatives **39** with sodium borohydride in methanol (Scheme 16, Method A) gave excellent yields and catalytic hydrogenation in the presence of PtO_2 catalyst (Method B) was also feasible. Compounds **39** may serve as precursors of 2,3-dialkylated products, e.g., **42** [30,38].



Scheme 16. Reduction of mesoions **26** and subsequent *N*(2)-alkylation. (*i*) Method A: $NaBH_4$, MeOH, rt (80–96%); Method B: H_2/PtO_2, THF–AcOH, 10 bar, rt (73–75%); (*ii*) (a) MeI, *t*-BuOK, DMF, rt (51–72%); or (b) MeI, NaH, THF, rt (33–38%).

An unexpected result was obtained in the course of acetylation and alkylation reactions of compounds **43**. Treatment of the latter with acetic anhydride resulted in 2,3-diacetylated derivatives

44 in high yield [39]. When treating the latter with *t*-BuOK and methyl iodide in DMF (Scheme 17), 3-acetyl-2-methyl product **45** was obtained. It was planned to replace the 3-acetyl function by an alkyl group as well. However, attempts to remove the 3-acetyl function of **45** (R = Me) to give compound **40a** even under drastic conditions were unsuccessful.

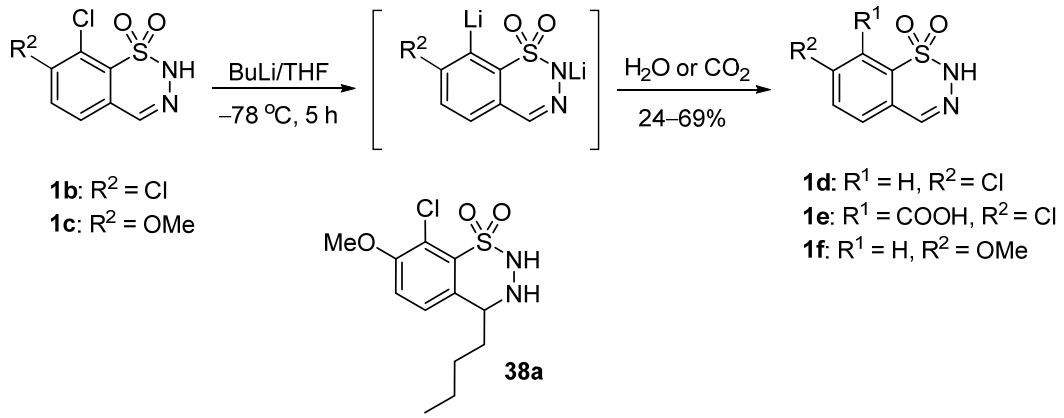


Scheme 17. Synthesis of 3-acetyl-2-methyl derivatives **45**.

BTDs **1**, **5**, **25**, **29** as well as their 3,4-dihydro congeners **38**, **40** acted as positive allosteric modulators of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor, with promising cognition enhancing and antidepressant activity [24,26,27,30].

2.2.4. Lithiation of 7,8-Dichloro- and 8-Chloro-7-methoxy-2*H*-1,2,3-benzothiadiazine 1,1-dioxides

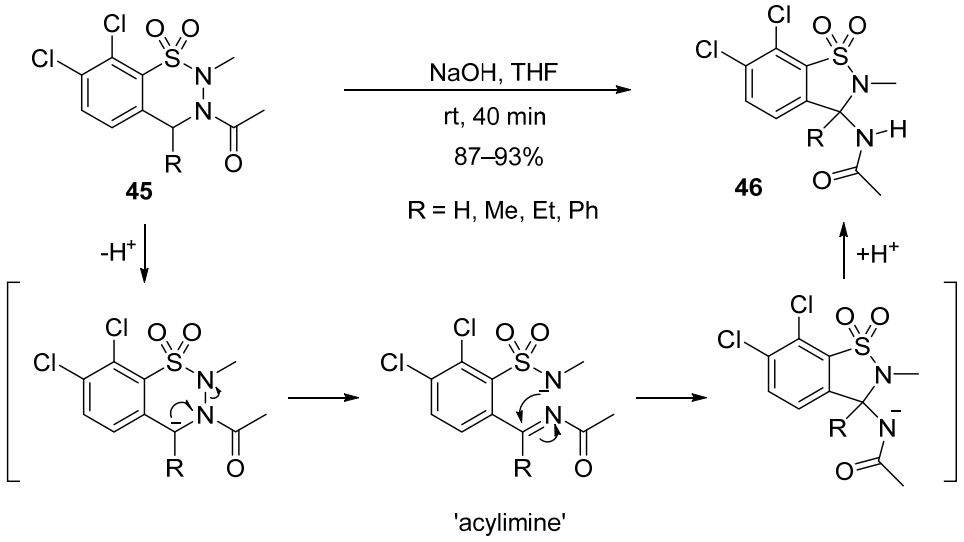
Attempts were made to replace the 8-chloro substituent of BTDs with other functional groups via lithiation, exploiting the *ortho*-directing ability of the neighboring substituents. Lithiation of **1b** with BuLi (−78 °C, 5 h) and subsequent quenching with water led to **1d** in 69% yield (Scheme 18). Quenching of the lithium salt with dry ice gave 8-carboxy-7-chloro congener **1e** in 60% yield. However, the lithiation of 8-chloro-7-methoxy derivative **1c** under similar conditions followed by quenching with water afforded 7-methoxy target compound **1f** only with poor yield (24%) and a substantial amount of the starting material was recovered. With the reaction temperature elevated to 0 °C, 4-butyl derivative **38a** was formed as the main product, due to the addition of BuLi to the C=N double bond [21].



Scheme 18. Lithiation of BTDs containing a 8-chloro substituent (**1b**, **1c**).

2.2.5. Ring Contraction

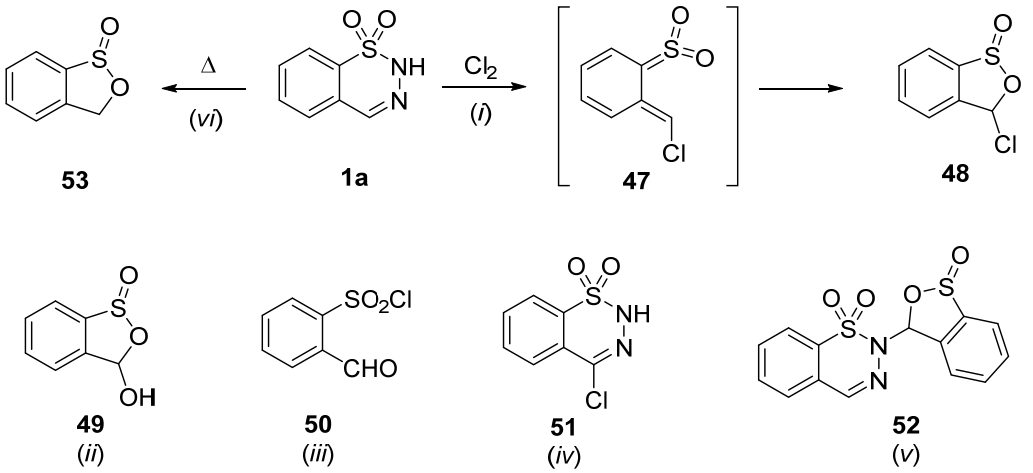
On treatment of 3,4-dihydro-1,2,3-benzothiadiazine 1,1-dioxides **45** with NaOH powder in THF, a ring contraction leading to 1,2-benzisothiazoles **46** was discovered (Scheme 19) [39]. We supposed that the deprotonation at C(4) followed by ring opening leads to an acylimine intermediate, which undergoes an intramolecular Michael addition and subsequent protonation, resulting in 1,2-benzisothiazole 1,1-dioxides **46**.



Scheme 19. Ring contraction of 3,4-dihydro-1,2,3-benzothiadiazine 1,1-dioxides (**45**) leading to 1,2-benzisothiazole 1,1-dioxides (**46**).

2.2.6. Chlorination and Thermolysis of 2*H*-1,2,3-Benzothiadiazine 1,1-dioxide (**1a**)

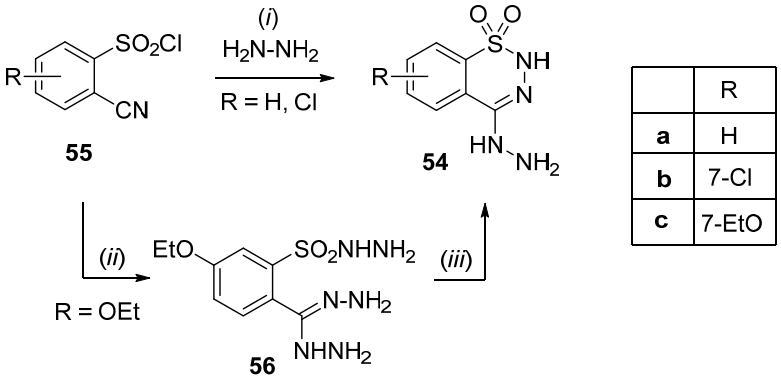
In an early study, attempts were made to generate sulfene **47** by chlorination of BTD **1a** (Scheme 20). The formation of compound **48** in dry dichloromethane/chloroform mixture at 0–2 °C argues for the intermediacy of sulfene **47**. Depending on the reaction conditions, various reaction sequences involving chlorination, nitrogen extrusion, hydrolysis, ring opening, etc. led to compounds **48**–**52** [40]. Thermolysis of **1a** at 500 °C in a quartz tube gave sultine **53** in 25% yield [14].



Scheme 20. Products of chlorinations and thermolysis of BTD **1a**. (*i*) CH_2Cl_2, $CHCl_3$, 0–2 °C, 1.5 h (47%); (*ii*) CH_2Cl_2, 1 h, then aqueous workup (crude 75%); (*iii*) CH_2Cl_2/H_2O (52%); (*iv*) DMF, 0 °C, 2 min (21%); (*v*) $ClCH_2CH_2Cl$, −20 °C, 1 h (26%); (*vi*) 500 °C, 12 sec (25%).

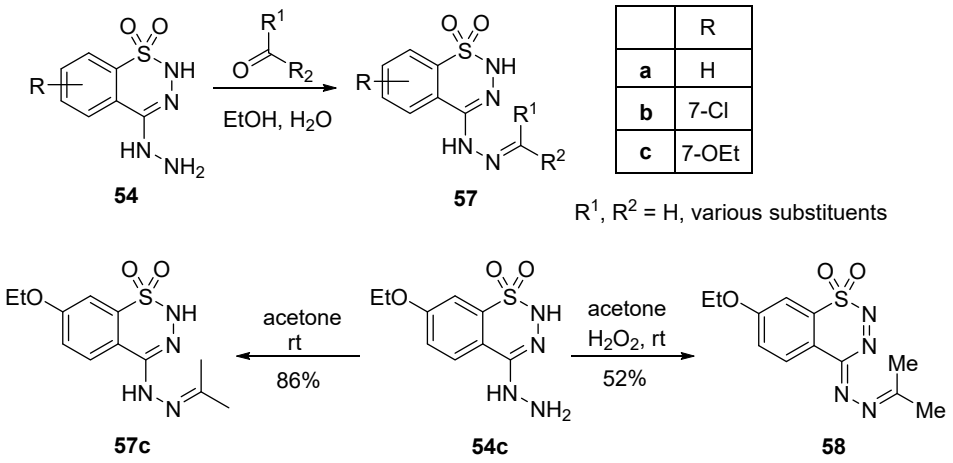
3. Synthesis and Transformations of 4-Hydrazino-2*H*-1,2,3-benzothiadiazine 1,1-dioxides

The first published compound exhibiting a BTD skeleton was 4-hydrazino derivative **54a** (R = H) disclosed by Schrader in 1917 (Scheme 21, Method A) [41]. It was obtained by treatment of 2-cyanobenzenesulfonylchloride (**55a**) with hydrazine. More attention was paid to the compound family when two related compounds, the diuretic agent hydrochlorothiazide (Figure 1) and the antihypertensive compound hydralazine (Figure 2), successfully entered the pharmaceutical market in the 1950s [42–45]. In 1962, Schmidt et al. prepared the corresponding 7-chloro derivative **54b** similarly (Method B), but with a much simpler work-up of the reaction mixture. When starting from 7-ethoxy derivative **55c**, intermediate **56** was also isolated [46]. A detailed study on the hypotensive activity of **54a** was published in 1965 [47].



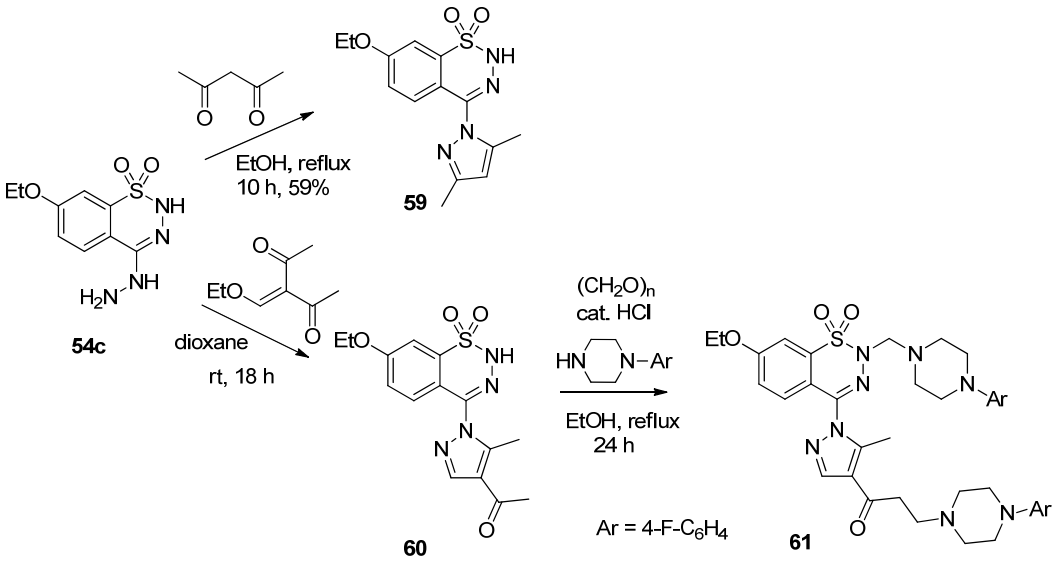
Scheme 21. The syntheses of 4-hydrazino-BTDs (**54**). (*i*) Method A: R = H, benzene, 1 h, rt (**54a**·HCl, 41%) [42]; Method B: R = Cl, EtOH, 5 min, reflux (**54b**, 78%) [44]; (*ii*) R = OEt, hydrazine, EtOH, 5 min, 60 °C (74%); (*iii*) EtOH/HCl, 60 °C (**54c**·HCl, >99%) [46].

The presence of the hydrazino group in the molecule enabled the synthesis of new types of derivatives. Schrader reported the formation of hydrazone **57** (R^1 = Ph, R^2 = H, R = H) in the reaction of **54a** with benzaldehyde as a structure proof for the starting compound (Scheme 22) [41]. A large variety of hydrazones **57** were synthesized starting from compound **54a** using structurally diverse aldehydes and ketones. Some of them showed a significant antihypertensive activity [42]. As regards the stability of hydrazones **57**, when refluxing a solution of **57c** in the presence of air, the formation of dehydrogenated derivative **58** was observed, which was also prepared by reacting **54c** with acetone in the presence of hydrogen peroxide [46].



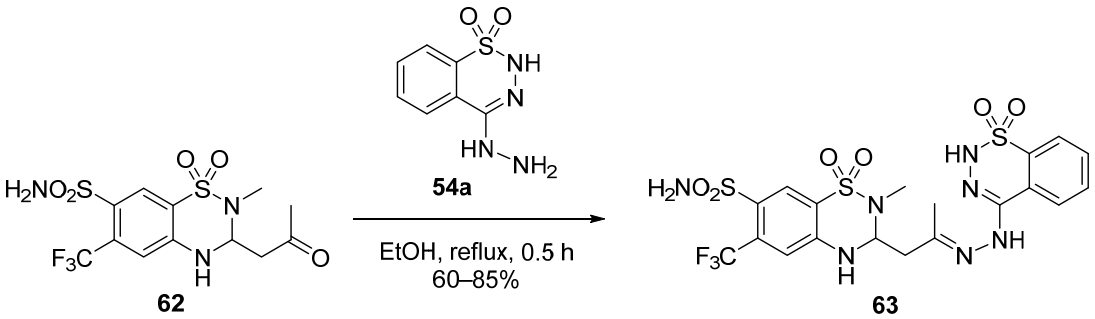
Scheme 22. Reactions of 4-hydrazino-BTDs (**54**) with oxo compounds.

The 4-hydrazino group of compounds **54** retained the doubly nucleophilic character of hydrazine, as demonstrated by the synthesis of pyrazole derivative **59** by the treatment of **54c** with acetylacetone (Scheme 23) [46]. Similar cyclization with ethoxymethylene-acetylacetone afforded 4-acetylpyrazole **60**, which was further functionalized with paraformaldehyde and 4-fluorophenylpiperazine to give arylpiperazinyl derivative **61**. This latter step represents a variant of *N*(2)-alkylation reactions of BTDs. Compound **61** did not show significant activity in antihypertensive and adrenolytic tests [48,49].



Scheme 23. Synthesis of 4-pyrazolo-BTDs (**59**–**61**).

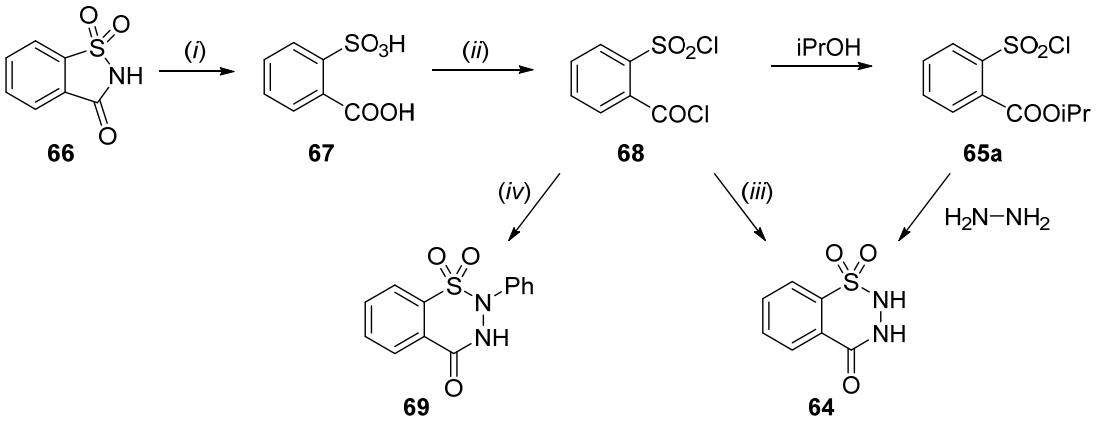
Attempts were made to combine the potentially synergistic pharmacological activities of 1,2,4- and 1,2,3-benzothiadiazine 1,1-dioxides in one molecule. 1,2,4-Benzothiadiazine 1,1-dioxide **62** was coupled with 4-hydrazino-BTD **54a** to give product **63** (Scheme 24), which was evaluated for diuretic activity; however, it did not show efficacy [50].



Scheme 24. Coupling of 1,2,4- and 1,2,3-benzothiadiazine 1,1-dioxide structural units.

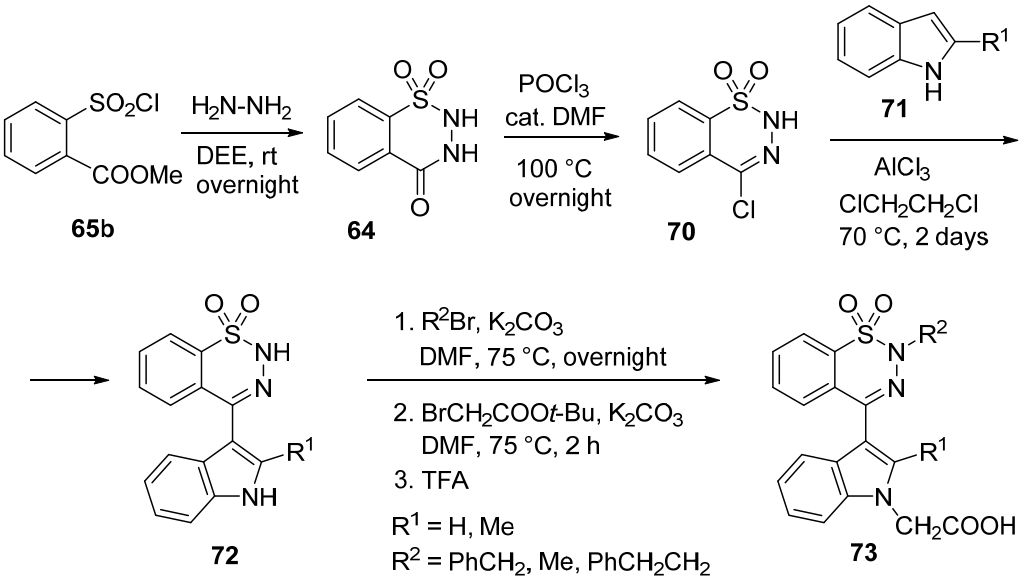
4. Synthesis and Transformations of 1,2,3,4-Tetrahydro-1,2,3-benzothiadiazine-1,1,4-triones

In 1962, Loev and Kormendy observed the formation of the 1,2,3,4-tetrahydro-1,2,3 -benzothiadiazine-1,1,4-trione (**64**) in the reaction of 2-chlorosulfonylbenzoic acid isopropyl ester **65a** with hydrazine (Scheme 25) [51]. Almost fifty years later, Ramana and Reddy described the same synthesis, giving details for the preparation of starting compound **65a** from saccharin (**66**) via 2-sulfobenzoic acid (**67**) and 2-chlorosulfonylbenzoyl chloride (**68**). Cyclization of either **65a** or **68** with hydrazine afforded benzothiadiazine-trione **64**. *N*(2)-Phenyl derivative **69** was obtained by the cyclization of **68** with phenylhydrazine [52].



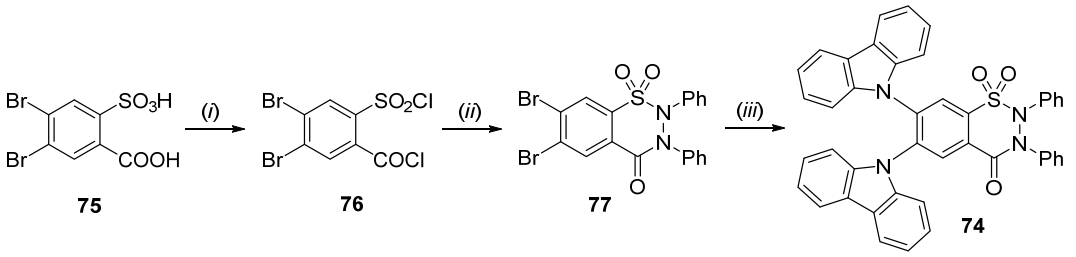
Scheme 25. Synthesis of 1,2,3,4-tetrahydro-1,2,3-benzothiadiazine-1,1,4-trione (**64**). (*i*) aq. H_2SO_4 (33 w/w%), 90 °C, 2 h (85%); (*ii*) PCl_5, 60 °C, 2 h (ca. 70%); (*iii*) hydrazine hydrate, MeOH, rt, 15 min (42%); (*iv*) phenylhydrazine, MeOH, rt, 65 min (20%).

A useful method for coupling the BDT building block with indoles has been disclosed (Scheme 26). 4-Oxo derivative **64** obtained from methyl 2-chlorosulfonyl benzoate (**65b**) was transformed to 4-chloro-BTD **70** with $POCl_3$. The latter was connected to indoles **71** by Friedel–Crafts type reaction to afford compounds **72**, which were further functionalized in three steps to furnish target compounds **73**. BTDs coupled with indole-1-acetic acids (**73**) proved to be antagonists of the prostaglandin D_2 receptor and exhibited an anti-asthmatic effect [53].



Scheme 26. Synthetic route leading to BTDs coupled with indole-1-acetic acids (**73**).

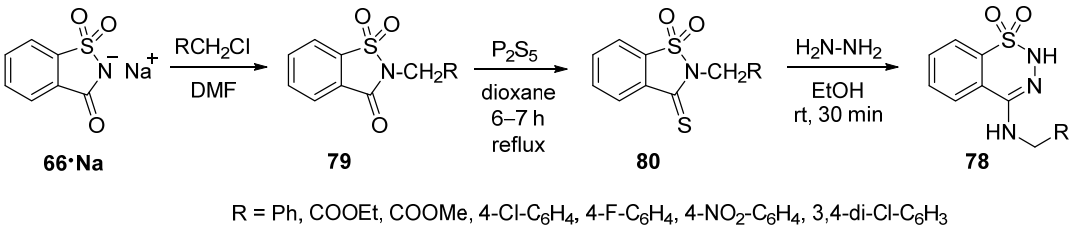
In a recent Chinese patent application, the preparation of variously substituted 2,3-diaryl-1,2,3,4 -tetrahydro-1,2,3-benzothiadiazine-1,1,4-triones was described. The synthesis of a representative example **74** started from the corresponding 2-sulfobenzoic acid **75** via 2-chlorosulfonylbenzoyl chloride **76** (Scheme 27). Trioxo derivative **77** was used as the starting material for the synthesis of molecules emitting light when exposed to electric current, thus they can be utilized in organic light-emitting diodes (OLED). For example, dibromo derivative **77** was treated with carbazole to furnish compound **74** [54].



Scheme 27. Synthesis and further transformation of 6,7-dibromo-2,3-diphenyl-1,2,3,4-tetrahydro-1,2,3 -benzothiadiazine-1,1,4-trione (**77**). (*i*) SO_2Cl_2, *o*-$Cl_2C_6H_4$, DMF, 80–85 °C, 4 h (100%); (*ii*) PhNH-NHPh, TEA, *o*-$Cl_2C_6H_4$, 0 °C to rt, 4 h (68%); (*iii*) carbazole, K_2CO_3, 18-crown-6, CuI, *o*-phenanthroline, reflux, 28 h (60%).

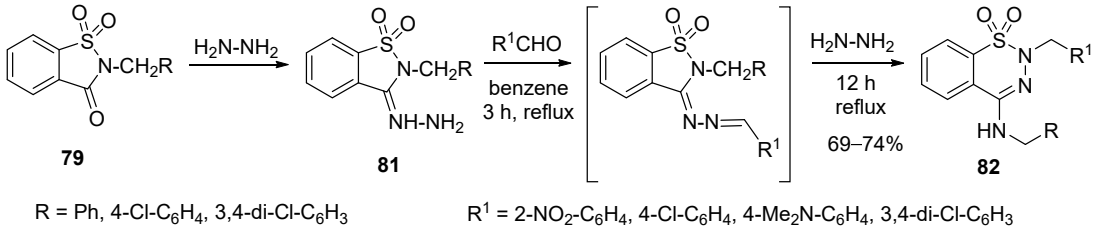
5. Synthesis and Transformations of 4-Amino-2*H*-1,2,3-benzothiadiazine 1,1-dioxides

Deodhar et al. described the synthesis of 4-amino-BTD derivatives **78** (Scheme 28). Sodium saccharinate (**66·Na**) was *N*-alkylated (**79**) and transformed to 3-thio derivative **80** which gave, by treatment with hydrazine, target compounds **78** in a ring expansion reaction (Scheme 28) [55,56]. Cyclin-dependent kinase 4 *(CDK4)* inhibitor activity found in this compound family (e.g., **78**, R = 4-F-C_6H_4) may prevent the overproliferation of cancer cells [57,58].



Scheme 28. Synthesis of 4-amino-BTDs (**78**) with ring expansion.

It was found that compound **79** behaved differently from its thio analogue **80** in the reaction with hydrazine, resulting in the formation of hydrazone 81 (Scheme 29) instead of ring expansion to **78** (Scheme 28). However, the reaction of **81** with substituted benzaldehydes in refluxing benzene and subsequent treatment with hydrazine afforded *N*(2)-alkyl-4-amino-BTDs **82**, a compound family exhibiting a significant antibacterial activity [56,59].



Scheme 29. Synthesis of *N*(2)-substituted 4-amino-BTDs (**82**).

6. Conclusions

1,2,3-Benzothiadiazine 1,1-dioxides combine the structural features of two compound families, 1,2,4-benzothiadiazine 1,1-dioxides and phthalazinones, some of whose members are important medicines on the market. This structural similarity led to an intensive research of 1,2,3-benzothiadiazine 1,1-dioxides, starting from the 1960s. This review summarizes the methods developed for the synthesis of 1,2,3-benzothiadiazine 1,1-dioxides substituted with various functional groups, allowing the

attachment of new building blocks (among other pharmacophores) to the parent molecule. Efforts to use this compound family in drug development are also presented.

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Conflicts of Interest: The authors declare no conflict of interest.

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