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

Imre Győjtő, Gyula Simig©, Márta Porcs-Makkay© and Balázs Volk *©

Directorate of Drug Substance Development, Egis Pharmaceuticals Plc., P.O. Box 100, H-1475 Budapest, Hungary; gyujto.imre@egis.hu (I.G.); simig.gyula@egis.hu (G.S.); porcs-makkay.marta@egis.hu (M.P.-M.)
* Correspondence: volk.balazs@egis.hu; Tel.: +36-1-8035874

Received: 22 May 2020; Accepted: 1 July 2020; Published: 21 July 2020

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.](image_url)

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 2H-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.
Nearly 20 years ago, our focus at Egis Pharmaceuticals (Hungary) turned to the chemistry of 2-(50%, two steps). 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].
A widely applicable procedure, based on ortho-lithiation methodology, has been developed at our laboratory for the synthesis of a significant variety of 4-unsaturated, 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 sulfonyl 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-aryl- 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 1,1,1,3,3,3′-tetramethylthietlenediamine (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.
Chemistry 2020, 2

Scheme 4. Lithiation-based synthetic approaches for the synthesis of 4-unsubstituted (1), 4-aryl- (5) and 4-alkyl-BTDs (9). (i) HOCH\textsubscript{2}CH\textsubscript{2}OH, 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\textsubscript{2}, THF or DEE; 2. SO\textsubscript{2}Cl\textsubscript{2}, hexane at (−30) (−5) °C, 0.5–2 h; (iv) H\textsubscript{2}SO\textsubscript{4}, CHCl\textsubscript{3}, Kieselgel, rt, 4 h; (v) NH\textsubscript{2}NH\textsubscript{2} × H\textsubscript{2}O, THF, reflux, 4 h; (vi) NH\textsubscript{2}NH\textsubscript{2} × H\textsubscript{2}O, THF, reflux, 4 h; (vii) 10% HCl reflux, 2 h.

Scheme 5. Synthesis of BTDs (5, 9, 18) by directed ortho-lithiation-cyclization reactions. (i) RC(OEt)\textsubscript{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](image)

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 2H-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](image)

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 (R1, R2 = H, Scheme 7). Here, a large variety of alkylation 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 aminooalkyl 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 1H 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].
Alkylation of 4-aryl derivatives 5 with various alkylation 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-aryl-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 R1 substituent of compound 35 was further transformed before removal of the protecting groups (Scheme 11) [34].
2.2.2. Acylations and Carbamoylations

Three Japanese patent applications were filed for the synthesis of \( N(2) \)-carbamoyl-2H-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.

\[
\text{Scheme 12. } N(2)\text{-Carbamoylation of BTD 1a.}
\]

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].

\[
\text{Scheme 13. } N(2)\text{-Acylation of 6-chloro-4-phenyl-BTD (5c).}
\]

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 \( \text{NaBH}_4 \) 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].
was carried out with 4-alkyl compounds resulting in 2,3,4-trialkyl derivatives furnishing 3,4-dihydro derivatives in high yield \[39\]. When treating the latter with t-BuOK and methyl iodide in DMF (Scheme 17), 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 \[24,30,38\].

\[
\text{Scheme 14. Preparation of N(3)-alkyl-3,4-dihydro-BTDs (39). (i) Method A: H}_2\text{, PtO}_2\text{ or Pd/C, AcOH or THF–AcOH, 3.5 or 10–15 bar, rt (43–71%); Method B: NaBH}_4\text{/TFA, CH}_2\text{Cl}_2\text{, 0–5 °C (80–97%); (ii) aldehydes or acetone, H}_2\text{, PtO}_2\text{ or Pd/C, AcOH, 10 bar, rt (29–60%).}
\]

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 \[30,38\].

\[
\text{Scheme 15. Reduction and subsequent alkylation reactions of N}(2)\text{-alkyl-BTDs (25, 27, 29). (i) Method A: H}_2\text{PtO}_2\text{ or Pd/C, AcOH or THF–AcOH, 10–15 bar, rt (44–94%); Method B: NaBH}_4\text{/TFA, CH}_2\text{Cl}_2\text{, 0–5 °C (29–100%); (ii) CH}_2\text{O or CH}_3\text{CHO, THF; or THF–AcOH, H}_2\text{, Pd/C, 10–15 bar, rt (21–89%).}
\]

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-diacylated derivatives.

\[
\text{Scheme 16. Reduction of mesoions 26 and subsequent N}(2)\text{-alkylation. (i) Method A: NaBH}_4\text{, MeOH, rt (80–96%); Method B: H}_2\text{/PtO}_2\text{, THF–AcOH, 10 bar, rt (73–75%); (ii) (a) Me}_3\text{, t-BuOK, DMF, rt (51–72%); or (b) Me}_3\text{, NaH, THF, rt (33–38%).}
\]
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.](image)

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-2H-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).](image)
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.

2.2.6. Chlorination and Thermolysis of 2H-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 19. Ring contraction of 3,4-dihydro-1,2,3-benzothiadiazine 1,1-dioxides (45) leading to 1,2-benzisothiazole 1,1-dioxides (46).

Scheme 20. Products of chlorinations and thermolysis of BTD 1a. (i) CH₂Cl₂, CHCl₃, 0–2 °C, 1.5 h (47%); (ii) CH₂Cl₂, 1 h, then aqueous workup (crude 75%); (iii) CH₂Cl₂/H₂O (52%); (iv) DMF, 0 °C, 2 min (21%); (v) ClCH₂CH₂Cl, −20 °C, 1 h (26%); (vi) 500 °C, 12 sec (25%).
3. Synthesis and Transformations of 4-Hydrazino-2H-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 54c, 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 (R1 = Ph, R2 = 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].

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].

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-sulphobenzoic 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].
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 POC13. 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 D2 receptor and exhibited an anti-asthmatic effect [53].

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].
with hydrazine, resulting in the formation of hydrazone 81 (Scheme 29) instead of ring expansion to

5. Synthesis and Transformations of 4-Amino-2H-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-C₆H₄) may prevent the overproliferation of cancer cells [57,58].

```
\[
\text{\textbf{Scheme 27.} Synthesis and further transformation of 6,7-dibromo-2,3-diphenyl-1,2,3,4-tetrahydro-1,2,3-benzothiadiazine-1,1,4-trione (77). (i) SO₂Cl₂, 0-Cl₂C₆H₄, DMF, 80-85 °C, 4 h (100%); (ii) PhNH-NHPh, TEA, 0-Cl₂C₆H₄, 0 °C to rt, 4 h (68%); (iii) carboxyl, K₂CO₃, 18-crown-6, CuI, o-phenanthroline, reflux, 28 h (60%).}
\]
```

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].

```
\[
\text{\textbf{Scheme 28.} Synthesis of 4-amino-BTDs (78) with ring expansion.}
\]
```

```
\[
\text{\textbf{Scheme 29.} Synthesis of N(2)-substituted 4-amino-BTDs (82).}
\]
```

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.

**Funding:** This research received no external funding.

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

**References**

1. Ernst, M.E.; Grimm, R.H., Jr. Thiazide Diuretics: 50 Years and Beyond. *Curr. Hypertens. Rev.* 2008, 4, 256–265. [CrossRef]
2. Duarte, J.D.; Cooper-DeHoff, R.M. Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. *Expert Rev. Cardiovasc. Ther.* 2010, 8, 793–802. [CrossRef] [PubMed]
3. Whitehead, C.W.; Traverso, J.J.; Sullivan, H.R.; Marshall, F.J.; Diuretics, V. 3,4-Dihydro-1,2,4-benzothiadiazine 1,1-Dioxides. *J. Org. Chem.* 1961, 26, 2814–2818. [CrossRef]
4. Doyle, M.E.; Egan, J.M. Pharmacological Agents That Directly Modulate Insulin Secretion. *Pharmacol. Rev.* 2003, 55, 105–131. [CrossRef]
5. Schroeder, H.A. The Effect of 1-Hydrasinophthalasine in Hypertension. *Circulation* 1952, 5, 28–37. [CrossRef]
6. Cohn, J.N.; McInnes, G.T.; Shepherd, A.M. Direct-Acting Vasodilators. *J. Clin. Hypertens.* 2011, 13, 690–692. [CrossRef]
7. McNeely, W.; Wiseman, L.R. Intranasal azelastine. A review of its efficacy in the management of allergic rhinitis. *Drugs* 1998, 56, 91–114. [CrossRef] [PubMed]
8. Horak, F.; Zieglmayer, U.P. Azelastine nasal spray for the treatment of allergic and nonallergic rhinitis. *Expert Rev. Clin. Immunol.* 2009, 5, 659–669. [CrossRef] [PubMed]
9. King, J.F.; Hawson, A.; Deaken, D.M.; Komery, J. Synthesis and chlorinolysis of 2H-1,2,3-benzothiadiazine 1,1-dioxide. *Chem. Commun.* 1969, 1, 33–34. [CrossRef]
10. King, J.F.; Huston, B.L.; Hawson, A.; Komery, J.; Deaken, D.M.; Harding, D.R.K. Synthesis and Thermolysis of 2H-1,2,3-Benzothiadiazine 1,1-Dioxide and 2,1-Benzoxathiin-3-one 1,1-Dioxide. *J. Heterocycl. Chem.* 1968, 5, 936–942. [CrossRef]
11. McNeely, W.; Wiseman, L.R. Intranasal azelastine. A review of its efficacy in the management of allergic rhinitis. *Drugs* 1998, 56, 91–114. [CrossRef] [PubMed]
12. Horak, F.; Ziegelmayer, U.P. Azelastine nasal spray for the treatment of allergic and nonallergic rhinitis. *Expert Rev. Clin. Immunol.* 2009, 5, 659–669. [CrossRef] [PubMed]
13. King, J.F.; Hawson, A.; Deaken, D.M.; Komery, J. Synthesis and chlorinolysis of 2H-1,2,3-benzothiadiazine 1,1-dioxide. *Chem. Commun.* 1969, 1, 33–34. [CrossRef]
14. King, J.F.; Huston, B.L.; Hawson, A.; Komery, J.; Deaken, D.M.; Harding, D.R.K. Synthesis and Thermolysis of 2H-1,2,3-Benzothiadiazine 1,1-Dioxide and 2,1-Benzoxathiin-3-one 1,1-Dioxide. *Can. J. Chem.* 1971, 49, 936–942. [CrossRef]
15. J. R. Geigy & Co. Representation the Benzaldehyde-o-sulfonic Acid. German Patent Application DE88952, 25 February 1896.
16. Chemische Fabrik vorm. Sandoz. Method for the Preparation of Sulfonic Acid of Benzaldehyde from Toluenesulfonic Acid. German Patent Application DE154528, 27 April 1902.
17. Wright, J.B.; Kalamazoo, M. Upjohn Co. 2H-1,2,3-Benzothiadiazine 1,1-dioxides. *Chem. Abstr.* 1969, 70, 57914.
18. Wright, J.B. The preparation of 2H-1,2,3-benzothiadiazine-1,1-dioxides, 11H-11a-dihydrobenzimidazo[1,2-b][1,2]benzisothiazole-5,5-dioxides, 6H-dibenzo[c,g][1,2,5]thiadiazocine-5,5-dioxides and 5H-dibenzo[c,g][1,2,6]thiadiazocine-6,6-dioxides. *J. Heterocycl. Chem.* 1968, 5, 453–459. [CrossRef]
19. Wright, J.B.; Kalamazoo, M. Upjohn Co. 2H-1,2,3-Benzothiadiazine 1,1-dioxides. *Chem. Abstr.* 1969, 70, 28960.
20. Nielsen, O.B.T.; Nielsen, C.K.; Feit, P.W. Aminobenzoic acid diuretics. 5. 3-Amino-4-arylmethyl-5-sulfamylbenzoic acid derivatives and related compounds. *J. Med. Chem.* 1973, 16, 1170–1177. [CrossRef] [PubMed]
21. Porcs-Makkay, M.; Lukács, G.; Pandur, A.; Simig, G.; Volk, B. Synthesis of 4-unsubstituted 2H-1,2,3-benzothiadiazine 1,1-dioxides via ortho lithiation of protected benzaldehyde derivatives. Tetrahedron 2014, 70, 286–293. [CrossRef]

22. Lukács, G.; Porcs-Makkay, M.; Simig, G. Lithiation of 2-Aryl-2-(chloroaryl)-1,3-dioxolanes and Its Application in the Synthesis of New ortho-Functionalized Benzophenone Derivatives. Eur. J. Org. Chem. 2004, 20, 4130–4140. [CrossRef]

23. Lukács, G.; Porcs-Makkay, M.; Simig, G. Lithiation of 2-(choloroaryl)-2-methyl-1,3-dioxolanes and application in synthesis of new ortho-functionalized acetonaphenone derivatives. Tetrahedron Lett. 2003, 44, 3211–3214. [CrossRef]

24. Győjtő, I.; Porcs-Makkay, M.; Lukács, G.; Pusztaí, G.; Garádi, Z.; Tóth, G.; Nyulası̇, B.; Simig, G.; Volk, B. Synthesis of 4-methyl-2H-1,2,3-benzothiadiazine 1,1-dioxides and their further transformation via alkylation and reduction steps. Synth. Commun. 2019, 49, 3475–3485. [CrossRef]

25. Lukács, G.; Porcs-Makkay, M.; Komáromi, A.; Simig, G. Microwave assisted synthesis of benzophenone and acetonaphenone ethylene ketals. Arkivoc 2008, iii, 17–24. [CrossRef]

26. Porcs-Makkay, M.; Lukács, G.; Kapus, G.; Gacsályi, I.; Simig, G.; Lévay, G.; Mezei, T.; Végh, M.; Kertész, S.; Barkóczy, J.; et al. Egis Gyógyszergyár Nyr.: Preparation of benzo[1,2,3]thiadiazine Derivatives for Treatment of CNS Disorders. Chem. Abstr. 2008, 148, 262627.

27. Porcs-Makkay, M.; Győjtő, I.; Lukács, G.; Komáromi, A.; Tóth, G.; Garádi, Z.; Simig, G.; Volk, B. Synthesis, Alkylation and Reduction of 4-Aryl-2H-1,2,3-benzothiadiazine 1,1-dioxides. ChemistrySelect 2019, 4, 8295–8300. [CrossRef]

28. Kacem, Y.; Hassine, B.B. A new procedure for the synthesis of 4-substituted-2H-1,2,3-benzothiadiazine 1,1-dioxides via directed ortho-lithiation of N1-arylsulfonylhydrazonates. Tetrahedron Lett. 2013, 54, 4023–4025. [CrossRef]

29. Chandra, K.; Naoum, J.N.; Roy, T.K.; Gilon, C.; Gerber, R.B.; Friedler, A. Mechanistic studies of malonic acid-mediated in situ acylation. Biopolymers 2015, 104, 495–505. [CrossRef]

30. Porcs-Makkay, M.; Lukács, G.; Kapus, G.; Gacsályi, I.; Simig, G.; Lévay, G.; Mezei, T.; Végh, M.; Kertész, S.; Barkóczy, J.; et al. Egis Gyógyszergyár Nyr.: 3,4-Dihydrobenzo[1,2,3]thiadiazine-1,1-dioxide Derivatives, Process for Preparation Thereof, Medicaments Containing Said Derivatives and Their Use in Treating CNS disorders. Chem. Abstr. 2008, 148, 262626.

31. Porcs-Makkay, M.; Kapiller-Dezsöfi, R.; Párkányi, L.; Pandur, A.; Simig, G.; Volk, B. Alkylation of 2H-1,2,3-benzothiadiazine 1,1-dioxides. Formation of a new family of mesoionic compounds. Tetrahedron 2014, 70, 2169–2174. [CrossRef]

32. Aoki, K.; Sasatake, K.; Kimura, T.; Hatakeyama, N. Kureha Chemical Industry Co., Ltd.: Benzothiadiazine Dioxides as Bactericides and Fungicides. Chem. Abstr. 1975, 82, 165882.

33. Aoki, K.; Sasatake, K.; Kimura, T.; Hatakeyama, N. Kureha Chemical Industry Co., Ltd.: 2-Substituted-1,2,3-benzothiadiazine 1,1-dioxides as Fungicides. Chem. Abstr. 1975, 82, 120070.

34. Ratcliffe, R.W.; Waddell, S.T.; Morgan, J.D., II; Blizzard, T.A. Merck and Co. Inc.: Preparation of Heterocyclic Substituted Carbapenem Antibacterials. Chem. Abstr. 1999, 132, 64104.

35. Aoki, K.; Kimura, T.; Satake, K.; Yamazaki, S. Kureha Chemical Industry Co., Ltd.: 2-(N-Alkylcarbamoyl)-1,2,3-benzothiadiazine 1,1-dioxide for Rice Blast Control. Chem. Abstr. 1974, 80, 141813.

36. Aoki, K.; Sasatake, K.; Kimura, T.; Yamazaki, S. Kureha Chemical Industry Co., Ltd.: Benzothiadiazine Dioxides as Bactericides and Fungicides. Chem. Abstr. 1975, 82, 150500.

37. Aoki, K.; Sasatake, K.; Kimura, T.; Yamazaki, S. Kureha Chemical Industry Co., Ltd.: Benzothiadiazine Dioxides as Bactericides and Fungicides. Chem. Abstr. 1975, 82, 150499.

38. Porcs-Makkay, M.; Pandur, A.; Simig, G.; Volk, B. Consecutive alkylation–reduction reactions of 2H-1,2,3-benzothiadiazine 1,1-dioxide derivatives. Synthesis of 2-alkyl-, 3-alkyl-, and 2,3-dialkyl-3,4-dihydro-2H-1,2,3-benzothiadiazine 1,1-dioxides. Tetrahedron 2015, 71, 44–50. [CrossRef]

39. Porcs-Makkay, M.; Győjtő, I.; Simig, G.; Volk, B. Synthesis and base-mediated rearrangement of 3-acetyl-2-methyl-3,4-dihydro-2H-1,2,3-benzothiadiazine 1,1-dioxides. Tetrahedron 2016, 72, 8463–8469. [CrossRef]

40. King, J.F.; Hawson, A.; Huston, B.L.; Danks, L.J.; Komery, J. Chlorination of Heterocyclic and Acyclic Sulfonhydrazones. Can. J. Chem. 1971, 49, 943–955. [CrossRef]
41. Schrader, E. Über Hydrazide und Azide von Sulfocarbonsäuren III. Die Einwirkung von Hydrazin auf o-Cyanbenzolsulfochlorid. J. Prakt. Chem. 1917, 96, 180–185. [CrossRef]

42. Robertson, J.E.; Biel, J.H. Colgate-Palmolive Co.: 4-Hydrazino-1,2,3-benzothiadiazine 1,1-dioxides. Chem. Abstr. 1965, 62, 9171.

43. Goudal, M.; Goudal, A.; Vernadeau, P.; Vernadeau, J. 1-Hydrazino-4-thiaphthalazine 4,4-dioxide. Chem. Abstr. 1964, 60, 45789.

44. CIBA Ltd. 1,1-Dioxides of 4-hydrazino-7-substituted-2H-1,2,3-benzothiadiazines. Chem. Abstr. 1962, 57, 62827.

45. Severs, W.B.; Kinnard, W.J.; Buckley, J.P. Evaluation of certain hypertensive agents VII. Tetramethylpiperidine and benzothiadiazide derivatives. J. Pharm. Sci. 1965, 54, 1025–1029. [CrossRef]

46. Schmidt, P.; Eichenberger, K.; Wilhelm, M. Heilmittelchemische Studien in der heterocyclischen Reihe. 31. Mitteilung. Benzo-1,2,3-thiadiazine mit hypertensiver und diuretischer Wirkung. Helv. Chim. Acta 1962, 45, 996–999. [CrossRef]

47. Edlin, A.I.; Kinnard, W.J.; Vogin, E.E.; Buckley, J.P. Hypotensive activity of two benzothiadiazine derivatives. J. Pharm. Sci. 1965, 54, 20–24. [CrossRef]

48. CIBA Ltd. 1-Heterobicyclo-4-piperazinoalkanopyrazoles. Chem. Abstr. 1969, 70, 57898.

49. Arya, V.P.; Grewal, R.S.; Kaul, C.L.; Ghate, S.P.; Mehta, D.V.; George, T. Antihypertensive Agents II: Synthesis and Hypotensive Activity of Certain 1,4,5-Trisubstituted Pyrazoles. J. Pharm. Sci. 1969, 58, 432–440. [CrossRef]

50. Robertson, J.E.; Dusterhoft, D.A.; Mitchell, T.F., Jr. Diuretics. 6-Substituted 3-Ketoalkyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-Dioxides and Related Anils, Oximes, and Hydrazones. J. Med. Chem. 1965, 8, 90–95. [CrossRef]

51. Loev, B.; Kormendy, M. 2-Sulfobenzoic Acid Esters. I. 2-Sulfamyl Derivatives. J. Org. Chem. 1962, 27, 1703–1709. [CrossRef]

52. Ramana, P.V.; Reddy, A.R. Synthesis of a few cyclothiadiazanones and aminosulfonyl benzamides from saccharin. J. Sulfur Chem. 2010, 31, 71–81. [CrossRef]

53. Bennani, Y.; Tumey, L.N.; Gleason, E.A.; Robarge, M.J. Athersys, Inc.: Indole acetic Acids Exhibiting CRTH2 Receptor Antagonism and Uses Thereof. Chem. Abstr. 2006, 144, 350540.

54. Kelley, M.J.; Nakagawa, K.; Dent, B.R. United States Dept. of Health and Human Services: Cyclin-Dependent Kinase (cdk)4 Inhibitors and Their Use for Treating Cancer. Chem. Abstr. 1998, 130, 483.

55. Kubo, A.; Nakagawa, K.; Varma, R.K.; Conrad, N.K.; Cheng, J.Q.; Lee, W.C.; Testa, J.R.; Johnson, B.E.; Kaye, F.J.; Kelley, M.J. The p16 Status of Tumor Cell Lines Identifies Small Molecule Inhibitors Specific for Cyclin-dependent Kinase 4. Clin. Cancer Res. 1999, 5, 4279–4286. [PubMed]

56. Sadana, G.S.; Pradhan, N.S.; Deodhar, K.D. Potential antimicrobial agents—synthesis of 2,4-disubstituted-1,2,3-benzothiadiazine-1,1-dioxides. Indian Drugs 1991, 28, 259–261.