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# BENZOTHIADIAZINE DIOXIDES: A NEW CLASS OF POTENT ANGIOTENSIN-II ($AT_1$) RECEPTOR ANTAGONISTS

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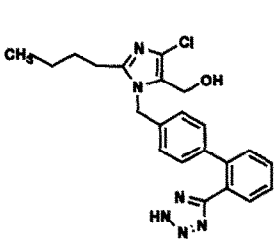
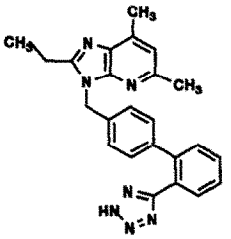
**ABSTRACT:** N-Biphenylmethyl benzothiadiazine dioxides were prepared as potential angiotensin-II receptor antagonists. Stability of the compounds is dependent upon the nature of the substituent at position 3 of the benzothiadiazine ring, while potency is dependent upon the nature of substitution in the benzo fused ring. 3-(Propylthio)-4-[2'-(2H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-4H-1,2,4-benzothiadiazine-6-carboxylic acid, 1,1-dioxide (**17**) is one of the most potent examples, with functional activity ($K_B$) below 0.1 nM.

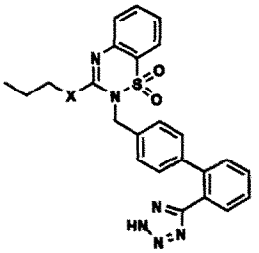
In the course of our research into preparation of novel angiotensin-II receptor antagonists, we sought to identify bioisosteric heterocycles to replace the imidazole ring in prototype compounds such as **DuP-753**[1] and **L-158,809**.[2] Benzothiadiazine dioxides, exemplified by **1** and **2**, appeared to be attractive targets. Literature precedent suggests that compounds such as **1a** and **2a** may be extremely susceptible to hydrolytic decomposition,[3] thus the corresponding alkylthio analogs (**1b** and **2b**) were also considered as potential targets. We now report the results of our investigation, which resulted in synthesis of novel and extremely potent non-peptidic angiotensin-II receptor antagonists.



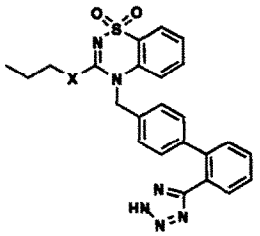
**DuP-753**



**L-158,809**

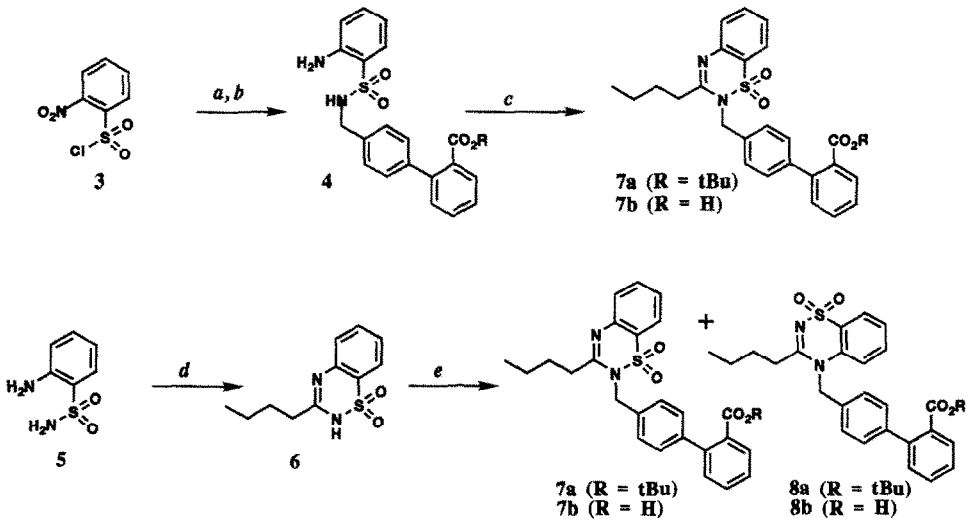


**1a** (X = $CH_2$)
**1b** (X = S)



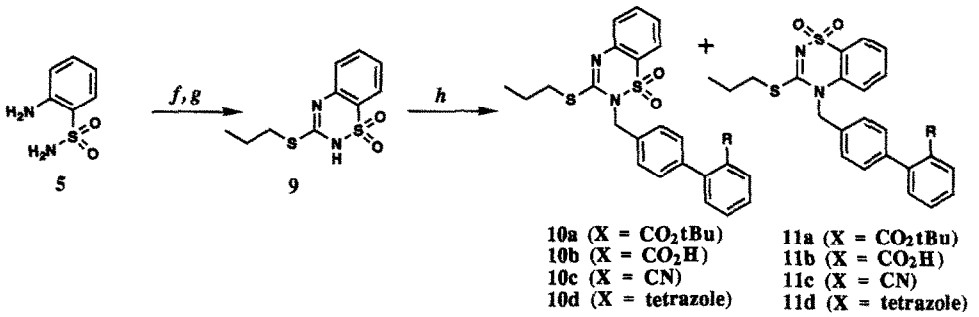
**2a** (X = $CH_2$)
**2b** (X = S)

Reaction of aminosulfonamide **4** with trimethylorthovalerate led to benzothiadiazine dioxide **7a** in low yield but with unambiguous regiochemistry, whereas alkylation of benzothiadiazine **6** led to a mixture of regioisomers **7a** and **8a**.[4] The isomers were separated and converted to their corresponding carboxylic acids **7b** and **8b**. Both compounds showed promising biological activity (Table 2) but were unstable to hydrolytic conditions at pH extremes (Table 1).[5] For example, compounds **7b** and **8b** have half lives of only a few minutes at pH 1.5 and pH 12, respectively.[6]




*a.* $ArCH_2NH_2$; *b.* $H_2/Pd(OH)_2$; *c.* trimethylorthovalerate/$P_2O_5$; *d.* trimethylorthovalerate/reflux
*e.* $ArCH_2Br/NaH/DMF$

Several 2-alkyl-3-alkylthio- and 4-alkyl-3-alkylthio- benzothiadiazine dioxides have been reported in the literature without specific mention of hydrolytic instability.[7] We prepared 3-propylthiobenzothiadiazine dioxide **9** by reaction of aminosulfonamide **5** with thiocarbonyldiimidazole, followed by S-propylation.[8] Reaction of **9** with the appropriate biphenylmethyl bromide gave mixtures of regioisomers **10** (**a** and **c**) and **11** (**a** and **c**), which were converted to the corresponding acid and tetrazole derivatives **10b**, **11b**, **10d**, and **11d** by standard means.[9] The alkylthio compounds **10b** and **11b** were considerably more stable than the carbon analogs **7b** and **8b** as shown in Table 1.[5,6] The 4-biphenylmethyl-3-alkylthio compounds (**11b** and **11d**) were more active angiotensin-II antagonists than the carbon counterpart (**8b**), while the 2-biphenylmethyl analogs (**10b** and **10d**) were less active than their carbon counterpart (**7b**, Table 2).

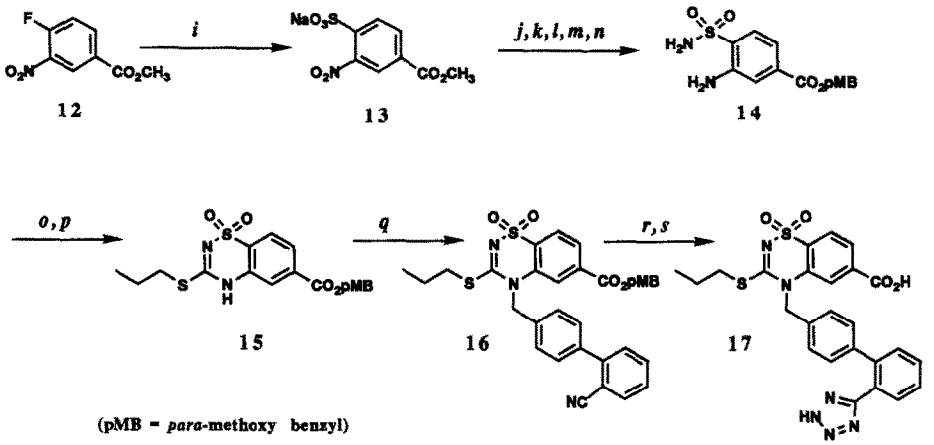



*f.* thiocarbonyldiimidazole/$Cs_2CO_3$/DMF; *g.* n-Propyl iodide/$Cs_2CO_3$/DMF;
*h.* $ArCH_2Br/KOtBu/THF$.

**Table 1: Approximate half lives of benzothiadiazine dioxides in aqueous solution at various pH**

| pH | 7b | 10b | 8b | 11b |
|---|---|---|---|---|
| 1.5 | 7 min | > 24 hr | >> 24 hr | >> 24 hr |
| 4.0 | 420 min | >> 24 hr | >> 24 hr | >> 24 hr |
| 7.0 | >> 24 hr | >> 24 hr | >> 24 hr | >> 24 hr |
| 9.0 | >> 24 hr | >> 24 hr | >> 24 hr | >> 24 hr |
| 11.0 | >> 24 hr | >> 24 hr | 40 min | 300 min |
| 12.0 | >> 24 hr | >> 24 hr | 15 min | 180 min |

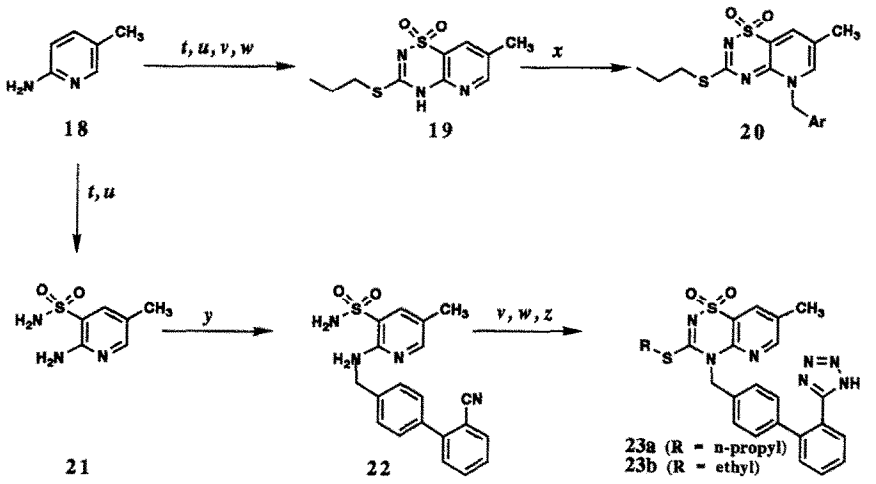
The good binding activity of biphenylmethyl tetrazole **11d** prompted us to target the corresponding carboxy substituted analog (**17**) and the related pyridylthiadiazine dioxides (**23a** and **23b**) in the hope of gaining improved functional activity. The carboxyl analog (**17**) was prepared by N-alkylation of the corresponding heterocycle (**15**) with the appropriate biphenylmethyl bromide, followed by tetrazole formation and deprotection. The heterocycle (**15**) was prepared from **12** by direct displacement of fluoride by sodium sulfite,[10] followed by standard functional group manipulations and thiocarbonyldiimidazole cyclization.




*i.* $Na_2SO_3$; *j.* $SOCl_2$; *k.* $NH_3$/tBuOH; *l.* KOH; *m.* pMB-OH/DCC/DMAP; *n.* $H_2$/Ra Ni; *o.* thiocarbonyldiimidazole/$Cs_2CO_3$/DMF; *p.* n-propyl iodide; *q.* $ArCH_2Br$/KOtBu/18-C-6/THF; *r.* TFA; *s.* tributyltin azide

Alkylation of pyridyl-thiadiazine **19** with the appropriate benzylic bromide led to ring alkylation product **20**, while alkylation of aminosulfonamide **21** under standard conditions gave mixtures of pyridyl ring alkylation and alkylation of the sulfonamide nitrogen atom (the latter product was identical with the product from reaction of the corresponding sulfonyl chloride and biphenylmethylamine). Conversion of **21** to **22** was ultimately

achieved by silylation of **21**, followed by alkylation of a presumed bis-trimethylsilyl intermediate. Ring closure was difficult for the N-alkyl example (**22**), but was ultimately achieved by reaction of **22** with thiocarbonyldiimidazole in the presence of DBU and dimethylaminopyridine. S-alkylation and tetrazole formation then led to the target pyridylthiadiazine dioxides **23a** and **23b**.




*t.* **chlorosulfonic acid;** *u.* **ammonium hydroxide;** *v.* **thiocarbonyldiimidazole/base;** *w.* **iodopropane or iodoethane/$Cs_2CO_3$/DMF;** *x.* **$ArCH_2Br/Cs_2CO_3$/DMF;** *y.* **TMS-Cl/$Et_3N$, then NaH/$ArCH_2Br$;** *z.* **tributyltin azide.**

Target compounds were tested in a radioligand binding assay using rat adrenal cortical membranes prepared as described by Chiu et al.[11] Binding experiments were performed as described, using [$^{125}$I]Sar1Ile8 angiotensin-II as the radioligand. The BSA concentration was reduced in some cases to 0.01% to attenuate drug binding to BSA.[12] Results ($K_i$) are shown in Table 2. Compounds were also tested for functional antagonism of angiotensin-II induced contraction of isolated rabbit aorta as described elsewhere;[13] results ($K_B$) are also shown in Table 2. Introduction of a sulfur atom at the 3 position of the benzothiadiazine dioxide ring led to a modest improvement in both binding and functional activity in the 4-alkyl series (**11b** vs. **8b**), whereas the same modification was detrimental to activity in the 2-alkyl series (**10b** vs. **7b**). Replacement of carboxyl with tetrazole in the 4-alkyl-3-alkylthio series led to improvement in binding, but not functional, activity (**11d** vs. **11b**). Introduction of a pyridyl nitrogen atom into the fused benzo ring (analogous with **L-158,809**[2]) led to significant improvement in both activities (**23a** vs. **11d**), while introduction of a carboxyl group into the fused ring improved only functional activity (**17** vs. **11d**). Replacement of the 3-propylthio group with 3-ethylthio improved functional activity (**23a** vs. **23b**). These new compounds, especially **17** and **23b**, are among the most potent non-peptidic angiotensin-II receptor antagonists yet reported. Studies concerning their efficacy in animal models of hypertension are underway and will be reported in due course.

**Table 2: Biological Data for Target Compounds**

| Compound | $K_i$ (nM) | $K_B$ (nM) |
|---|---|---|
| **7b** | **230 ± 80** | **160 ± 11** |
| **8b** | **550 ± 24** | **130 ± 11** |
| **10b** | **4,900 ± 67** | **1,200 ± 400** |
| **11b** | **180 ± 38** | **20 ± 5** |
| **10d** | **57 ± 12** | **640 ± 340** |
| **11d** | **4.8 ± 1.5** | **93 ± 33** |
| **17** | **8.5 ± 2.5** | **0.08 ± 0.02** |
| **23a** | **0.6 ± 0.18** | **11 ± 4** |
| **23b** | **0.8 ± 0.04** | **0.6 ± 0.2** |
| **DuP-753** | **5.7 ± 0.6** | **2.6 ± 0.13** |

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4. The chemical shift of the benzylic methylene carbon in the $^{13}C$ NMR spectrum appears to be a good marker to assign regiochemistry. For the 2-alkyl isomers (e.g., **7** and **10**) the chemical shift is in the range 46.3 - 47.7 ppm and for the 4-alkyl isomers (**8**, **11**, **16**, and **17**) it is in the range 51.4 - 54.5 ppm. We believe that the downfield shift is due to a steric influence of the adjacent aromatic proton. For the pyridyl analogs (**22**, **23**, and their respective regioisomers) which lack the adjacent aromatic proton the chemical shift difference disappears (48.8 ± 0.1 ppm). The 2-alkyl isomers were consistently more

mobile on silica gel chromatography, and less mobile on reverse phase chromatography, than the corresponding 4-alkyl isomers.

5. Stability studies were performed as follows: Test compounds were dissolved in methanol (1 mg/ml) then diluted (4:1) with aqueous buffer solutions of the stated pH. For pH 1.5 and pH 4.0 additional methanol was added (to a final ratio of 1:1 methanol:buffer) due to poor aqueous solubility of the test compounds. Aliquots of the solutions (20 μl) were then repeatedly injected by autosampler onto a reverse phase HPLC column. The integrated area of the peak corresponding to test compound was plotted versus time and the half life was estimated graphically. When no decomposition was observed after 24 hours, the half life is indicated in Table 1 as >> 24 hours; when less than 50% decomposition was observed after 24 hours, the half life is indicated as > 24 hours.
6. LCMS analysis of the hydrolysis products of **7b** (at pH 1.5) and **8b** (at pH 12) was consistent with addition of water to form acyclic amides of molecular weight 466 as suggested in reference 3. LCMS of the hydrolysis product of **11b** (at pH 12) suggested a molecular weight of 408, consistent with a cyclic sulfonylurea structure.
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