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ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · MARCH 1987

Impact Factor: 3.45 · DOI: 10.1016/0223-5234(87)90012-2

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Synthesis and biological evaluation of 10-substituted imidazo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxides and their 2,10-dihydro analogs

A. V. N. REDDY, Ahmed KAMAL, A. Bhaskar RAO and P. B. SATTUR

Medicinal Chemistry & Natural Products Division, Regional Research Laboratory, Hyderabad 500 007, India

(Received December 9 1985, accepted October 3 1986)

Abstract — ...zo-benzothiadiazines / analgesic, anti-inflammatory and anti-hypertensive activities

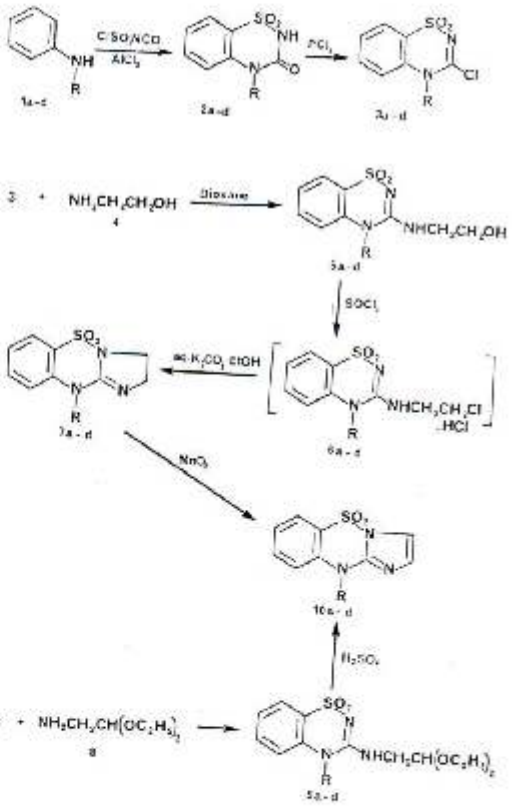
Introduction

A number of 3-substituted 1,2,4-benzothiadiazine 1,1-dioxides have been extensively studied as diuretic and anti-hypertensive agents [1, 2]. Many of these heterocyclic compounds are presently employed as therapeutic agents such as, chlorothiazide, diazoxide and pazoxide. However, fused 1,2,4-benzothiadiazine 1,1-dioxides have not been investigated in detail. Earlier, Friary and Gold reported that 2,10-dihydro-1-substituted imidazo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxides were found to be devoid of hypotensive activity [3]. In accordance with the program of the laboratory directed towards the synthesis of new heterocycles with potential biological applications, a number of fused 1,2,4-benzothiadiazine 1,1-dioxides were prepared and the products screened for a broad spectrum of biological properties [4, 5]. Furthermore, the biological importance of the imidazole system [6] encouraged us to synthesize 10-substituted imidazo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxides and their 2,10-dihydro analogs in view of exploring their analgesic, anti-inflammatory, anti-hypertensive and anti-cancer activities.

Chemistry

For the synthesis of title compounds, 1,2,4-benzothiadiazine 3(4H)-one 1,1-dioxides **2** required as starting materials were prepared by the reaction of *N*-substituted anilines **1** with chlorosulfonyl isocyanate followed by cyclization with aluminium chloride [7]. These were converted to 3-chloro-4-substituted 2H-1,2,4-benzothiadiazine 1,1-dioxides **3** by the reaction of **1** with PCl_5 [5].

Compound **3** upon refluxing with an excess of aminoethanol **4** in dry dioxane, gave 3-(2-hydroxyethyl amino)-4-substituted-2H-1,2,4-benzothiadiazine 1,1-dioxides **5**. When **5** was stirred with thionylchloride and the reaction mixture was evaporated to dryness under pressure, the intermediate



hydrochloride **6** was obtained. Intermediate **6** upon cyclization in aqueous potassium carbonate yielded the product 2,10-dihydro-10-substituted 3H-imidazo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxides **7**.

Reaction of compound **3** with aminoacetaldehyde diethylacetal **8** at room temperature gave 3-(2',2'-diethoxyethylamino)-4-substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxide **9**. It was observed in this reaction that when **3** and **8** were refluxed, even in a low boiling solvent such as dichloromethane, the reaction mixture polymerized. Compound **9** was cyclized with dilute sulfuric acid below 30°C to obtain the product, 10-substituted-10H-imidazo-[1,2-b][1,2,4]benzothiadiazine 5,5-dioxide **10**. It was also observed during the cyclization of **9** that it was essential to maintain the temperature below 30°C, whereas increase of the temperature of the reaction mixture led to a dark colored residue. Compounds **10** were also obtained by the oxidation of **7** with manganese dioxide in refluxing benzene, whereas attempt to oxidize **7** with manganese dioxide in chloroform did not succeed after stirring the reaction mixture for several hours [20] and even refluxing. The structure of these compounds was confirmed by elemental analysis, IR ^{1}H NMR and mass spectra. The compounds synthesized are described in the Tables I and II.

Table I. 3-(2-Hydroxyethylamino)-4-alkylaryl-2H-1,2,4-benzothiadiazine 1,1-dioxides **5a—d** and 3-(2',2'-diethoxyethylamino)-4-alkylaryl-2H-1,2,4-benzothiadiazine 1,1-dioxides **9a—d**.

Compounds	R	mp (°C)	Yield (%)	Formula[a]	Analgesic and anti-inflammatory actions[b]	
					% protection from pain	% inhibition of inflammation
5a	CH_3	200	54	$C_{15}H_{15}N_3O_3S$	41	—
5b	C_2H_5	192—194	60	$C_{11}H_{13}N_3O_3S$	55[c]	30
5c	i-C_3H_7	210—211	52	$C_{12}H_{15}N_3O_3S$	72	
5d	C_6H_5	189—190	46	$C_{17}H_{17}N_3O_3S$	43	15
9a	CH_3	120—122	64	$C_{14}H_{23}N_3O_4S$	31	64[c]
9b	C_2H_5	140	68	$C_{15}H_{25}N_3O_4S$	51[c]	63[c]
9c	i-C_3H_7	85	59	$C_{16}H_{27}N_3O_4S$	26	26
9d	C_6H_5	130—131	52	$C_{20}H_{25}N_3O_4S$	41	52[c]
Aspirin	—	—	—	—	57[c]	—
Phenylbutazone	—	—	—	—	—	46[c]

[a]All compounds were analyzed for C, H and N; the result had a maximum deviation of ± 0.4% from the theoretical value except for **5d** ($\Delta N\% = -0.74$).
[b]Dose: 100 mg/kg, p.o.
[c]$P < 0.01$; Student's *t* test versus controls.

Table II. 2,10-Dihydro-10-alkylaryl-3H-imidazo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxides **7a—d** and 10-alkylaryl-10H-imidazo[1,2-b][1,2,4]-benzothiadiazine 5,5-dioxides **10a—d**.

Compounds	R	mp (°C)	Yield (%)	Formula[a]	Analgesic and anti-inflammatory actions[b]		Anti-hypertensive action % fall in B.P.[c]
					% protection from pain	% inhibition of inflammation	
7a	CH_3	135—136	40	$C_{10}H_{11}N_3O_2S$ (237.28)	56[d]	44[d]	7
7b	C_2H_5	106	45	$C_{11}H_{13}N_3O_2S$ (251.30)	37	34	9
7c	i-C_3H_7	180	42	$C_{12}H_{15}N_3O_2S$ (265.33)	—	22	—
7d	C_6H_5	263—264	51	$C_{16}H_{13}N_3O_2S$ (299.35)	—	15	10
10a	CH_3	159	45	$C_{10}H_9N_3O_2S$ (235.26)	48[d]	33	7
10b	C_2H_5	215—220	36	$C_{11}H_{11}N_3O_2S$ (249.29)	44[d]	—	12
10c	i-C_3H_7	180	34	$C_{12}H_{13}N_3O_2S$ (263.31)	33	—	—
10d	C_6H_5	185	40	$C_{16}H_{11}N_3O_2S$ (297.34)	31	—	30
Diuretide	—	—	—	—	—	—	56[d]

[a]All compounds were analyzed for C, H, and N; the result had a maximum deviation of ± 0.4% from the theoretical value.
[b]Dose: 100 mg/kg p.o.
[c]Dose: 2 mg/kg I.V. mean of 3 experiments.
[d]$P < 0.01$; Student's *t* test versus controls.

Results and Discussion

All the compounds exhibited an interesting profile of analgesic activity. In the case of the intermediates **5** and **9**, the analgesic activity is maximum (51—55%) when there is an ethyl substituent at the 4 position (**5b** and **9b**). Replacement of the ethyl group by methyl, isopropyl and phenyl substituents (**5a**, **5c—d**, **9a** and **9c—d**) show mild to moderate analgesic activities (22—42%).

In cyclized compounds **7** and **10**, **7a** and **10a** which have a methyl substituent at the 10 position, exhibit maximum analgesic activity (55 and 48%), whereas other substituted compounds **7b—d** and **10b—d** (Table II) show mild to moderate activity (31—44%).

In anti-inflammatory testing, the intermediates **9a**, **9b** and **9d**, which have methyl, ethyl and phenyl substituents, show promising anti-inflammatory activity being superior to phenylbutazone, while others are less active (Table I).

The 2,10-dihydro compounds **7a—d** show moderate anti-inflammatory activity which is maximum in **7a** (44%) which has a methyl substituent, while the compounds **10a—d** do not possess significant anti-inflammatory activity, except for **10a** which has a methyl substituent (23%).

Thus, from the results it is observed that in the case of cyclized compounds **7** and **10**, the presence of a methyl group confers promising analgesic and anti-inflammatory activities.

The anti-hypertensive activity of these compounds **7** and **10** is not significant as is evident from the Table II. Furthermore, the decrease in blood pressure was transient (lasting less than 15 min).

The anti-cancer screening (3PS31) of some representative compounds was performed under the auspices of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. The results revealed that the test compounds were inactive as the percent *T/C* was less than 125.

Experimental protocols

Chemistry

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin—Elmer 283B spectrophotometer in a potassium bromide pellet. The NMR spectra were determined on a Jeol FX90Q FT NMR spectrometer using TMS as an internal reference. Mass spectra were recorded on a VG 7070H mass spectrometer. All evaporations were carried out on a rotary evaporator at reduced pressure. The purity of all the compounds was verified on TLC.

3-(2-Hydroxyethylamino)-4-methyl-2H-1, 2, 4-benzothiadiazine 1,1-dioxide **5a**

General procedure. A solution of **3a** (4.6 g, 0.02 mol) and 2-aminoethanol **4** (6.1 g, 0.1 mol) in dry dioxane (60 ml) was heated under reflux for 4 h. The reaction mixture was concentrated to give an oily substance, which upon treatment with the ice cold water gave a solid. The crude product was washed with ice cold water, filtered and recrystallized from a mixture of water:ethanol (1:1) to give the product **5a**. IR (KBr): 3400 (OH), 3200 (NH), 1600 (C = N), 1370, 1160 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 7.19—7.84 (m, 4H, aromatic); 4.20—4.83 (broad signal, 1H, N*H*, D_2O exchangeable); 3.92—4.2 (broad, 1H, —O*H*, D_2O exchangeable); 3.53—3.68 (m, 4H, $—CH_2—CH_2$); 3.1 (s, N—CH_3).

2,10-Dihydro-10-methyl-3H-imidazo[1,2-b] [1,2,4]benzothiadiazine 5,5-dioxide 7a

General procedure. Finely powdered **5a** (2.55 g, 0.01 mol) was added in small portions to 25 ml of thionylchloride with stirring and cooling (ice bath). The reaction mixture was stirred for an additional 2 h at 15°C and then allowed to stand overnight at room temperature. Chloroform (40 ml) was added to the clear solution obtained and evaporated to dryness under reduced pressure at 40°C. The intermediate hydrochloride **6** was not purified but reacted as described below.

The viscous liquid was dissolved in absolute ethanol (100 ml). This was poured into a solution containing potassium carbonate (7 g) in water (80 ml). The entire reaction mixture was stirred at room temperature for 15 min. The white solid separated was filtered, washed with water and recrystallized from chloroform—*n*-pentane to give **7a**. IR (KBr): 1600 (C = N), 1380, 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): 7.17—7.89 (m, 4H, aromatic); 3.85—3.93 (t, ^2H, $—CH_2—CH_2$); 3.81 (s, 3H, N—CH_3); MS: *m/e* 237 (M^+, 60), 236 (M^+—H, 100), 173 (M^+—SO_2, 43).

3-(2', 2'-Diethoxyethylamino)-4-methyl-2H-1, 2, 4-benzothiadiazine 1,1-dioxide 9

General procedure. A solution of **3** (4.6 g, 0.02 mol) in dry dichloromethane (50 ml) was stirred at room temperature (25—30°C). Aminoacetaldehyde diethylacetal **8** (5.32 g, 0.04 mol) in dichloromethane (10 ml) was added over a period of 10 min maintaining the temperature at 25°C. The stirring was continued for 8 h at room temperature. After the completion of the stirring, dichloromethane was removed under vacuum at 15°C. The oily residue obtained was repeatedly washed with ice cold water (3 × 100 ml) to remove excess reactants **8**.

The separated solid was dried and recrystallized from dichloromethane—*n*-pentane to give **9a**, mp 120°C; IR (KBr): 3340 (NH), 1600 (C = N), 1365, 1130 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): 7.09—7.84 (m, 4H, aromatic); 5.63 (broad, 1H, N*H*, D_2O exchangeable), 4.63—4.68 (t, 1H, —C*H*); 3.16—3.99 (m, 9H, N—CH_2, N—CH_2 (O—CH_2)$_2$); 1.3—1.56 (t, 6H, (C—CH_3)$_2$); MS: *m/e* 327 (M^+, 25), 281 (M^+—C_2H_5OH, 23).

10-Methyl-10H-imidazo[1,2-b] [1,2,4]benzothiazine 5,5-dioxide 10a

General procedures

Method A. Finely powdered **9a** (3.27 g, 0.01 mol) was stirred with cold dilute sulfuric acid (40 ml) for 2 h, maintaining the temperature at 5—10°C with an ice water bath. The clear solution obtained was neutralized with potassium carbonate (20%). The solid obtained was filtered, dried and recrystallized from dichloromethane—*n*-pentane to give the product **10a**; IR (KBr): 1600 (C = N), 1335, 1180 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): 7.13—8.13 (m, 4H, aromatic); 6.52—6.74 (dd, 2H, *HC*—C*H*); 3.28 (s, 3H, N—CH_3); MS: *m/e* 235 (M^+, 82), 171 (M^+—SO_2, 100).

Method B. To a solution of **5a** (2.37 g, 0.01 mol) in sodium dried benzene (30 ml) was added activated manganese dioxide [9] (9.48 g) and the mixture was refluxed at steam bath temperature for 5 h. The reaction was followed by TLC. After the completion of the reaction, the reaction mixture was filtered. The filtrate, upon evaporation under vacuum, gave a solid which was purified by column chromatography (silica gel, 300 mesh) using chloroform as the eluant to give 1.69 g (72%) of 10-methyl-10*H*-imidazo[1,2-*b*] [1,2,4]benzothiadiazine 1,1-dioxide **10a**. The IR spectrum exhibited a spectrum superimposable upon that of the product obtained by Method A.

Biological activity

These compounds, **7a—d** and **10a—d**, and their intermediates, **5a—d** and **9a—d**, were screened for analgesic and anti-inflammatory activities while only **7** and **10** were also screened for anti-hypertensive and anti-cancer activities. All test compounds were administered orally by gavage in a 3% gum acacia suspension at a dose of 100 mg/kg in the analgesic and anti-inflammatory assays, whereas doses of 2 mg/kg (i.p.) were used to assess the anti-hypertensive action. Aspirin and phenylbutazone were included in all analgesic and anti-inflammatory tests respectively, whereas diazoxide was used in the anti-hypertensive screening for comparison purposes. Stastitical analyses were made using the Student's *t* test *versus* controls.

Analgesic activity
A modified version of the acetic acid writhing test described by Koster *et al.* [5, 10] was used. Results are given in Tables I and II.

Anti-inflammatory (anti-edematous) activity
Carrageenin induced rat paw edema [5, 11] was used. Results are given in Tables I and II.

Acknowledgements

One of the authors (A. V. N. Reddy) is thankful to the Council of Scientific and Industrial Research, New Delhi, for financial assistance. We are also thankful to Cadila Laboratories, Ahmedabad, India, for performing the anti-hypertensive screening of some of the compounds and to Dr. K. L. Loening, Chemical Abstracts Service, for his assistance in the nomenclature of these compounds.

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