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Short Communication

Synthesis and anticonvulsant activity of some (2/4-substituted)benzaldehyde (2-oxobenzothiazolin-3-yl)acetohydrazones

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Abstract

Fifteen new (2/4-substituted)benzaldehyde (2-oxobenzothiazolin-3-yl)acetohydrazones were synthesized and their structures were elucidated by NMR and elemental analysis. Their anticonvulsant activity was tested by a pentylenetetrazole induced seizure test. Compounds **4e** and **4h** were found to be the most promising among the others.

Keywords: Anticonvulsant activity; Acetohydrazones; Pentylenetetrazole

1. Introduction

Epilepsy is the most frequent neurologic disorder characterized by excessive temporary neuronal discharge in the brain. The occurrence of the disorder is about 0.8% of the population. Currently employed drugs are effective towards only 60–80% of the patients and exhibit some undesirable side effects such as headache, nausea, anorexia, ataxia, hepatotoxicity, drowsiness, gastrointestinal disturbances, gingival hyperplasia and hirsutism [1].

The need in anticonvulsant therapy is to develop new anticonvulsant drugs with new modes of action, and with minimal side effects to cure seizures, which are so far resistant to the present anticonvulsant drugs [1].

As it is well known, the general feature of various anticonvulsants is the presence of polar groups such as amido, imido functions together with lipophilic moieties. Hydrazones of benzenesulfonyl hydrazide are well known anticonvulsants whose activity was found comparable to that of valproic acid in the MES test [2].

Darias and co-workers also showed the anticonvulsant activity of aryl and heteroarylsulphonylhydrazones [3].

It was also pointed out that some thiosemicarbazones of arylidene ketones had significant anticonvulsant activity [4]. Popp showed the anticonvulsant activity of hydrazones of some heterocyclic aldehydes [5].

In 1998, Ucar et al. [6] synthesized some benzoxazolone and benzothiazolone derivatives with substitutions at positions 3 and 6. They also investigated the anticonvulsant activity of 'naked' 2(3*H*)-benzothiazolone and 2(3*H*)-benzoxazolone and reported that those compounds had low anticonvulsant activity in the MES test. They reported active compounds at 30 mg/kg dose in both MES and sc-MET tests and also pointed out that 3-methyl-2(3*H*)-benzothiazolone was the most active one in the group and they reported that this compound was included in the phase II tests. In the same study it has also been reported that 3-ethyl-2(3*H*)-benzothiazolone was another active compound in the anticonvulsant tests. Dalkara and co-workers [7] reported the anticonvulsant activity of 3-(2-hydroxyethyl)benzoxazolone and 3-(2-oxoethyl)benzoxazolone derivatives at fairly high doses (300 mg/kg). These data have prompted us to synthesize new 3-substituted ben-

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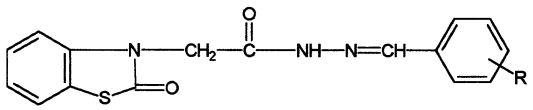

R : H, 2-Cl, 4-Cl, 2-CH_3, 4-CH_3, 2-OCH_3, 4-OCH_3, 2-OH, 4-OH, 2-F, 4-F, 4-OC_2H_5, 4-Br, 4-NO_2, 4-$N(CH_3)_2$

Fig. 1. Structure of synthesized compounds.

zothiazolone derivatives, shown in Fig. 1, and test their anticonvulsant activity.

2. Chemistry

The synthesis of 2(3*H*)-benzothiazolone (**1**) was carried out by the reaction of *o*-aminothiophenol with urea [8]. The physical and spectral properties of benzothiazolone were in accordance with the data in the literature [8,9]; therefore, we carried out the next steps of the reaction without any further analysis of **1**. Compound **1** was reacted with methyl chloroacetate to obtain methyl 2(3*H*)-benzothiazolinon-3-ylacetate (**2**). [2(3*H*)-Benzothiazolinon-3-yl]acetohydrazide (**3**) was obtained by the reaction of **2** with hydrazine hydrate. The hydrazide thus obtained was reacted with benzaldehyde derivatives to obtain the title compound (**4**). The synthetic route of the title compound is illustrated in Fig. 2.

3. Experimental

3.1. Chemistry

All the chemicals used for the synthesis of the compounds were purchased from either Aldrich Chemicals or E. Merck AG.

Melting points were determined with an Electrothermal-9200 digital melting point apparatus and are uncorrected.

The IR spectra of the compounds were recorded on a Perkin–Elmer 1330 IR spectrophotometer. The ^1H NMR spectra were recorded on a Bruker 200 FT NMR spectrometer using tetramethysilane as the internal standard and $CHCl_3$-d_1 or DMSO-d_6 as solvents. All chemical shifts were recorded as δ (ppm).

Microanalyses for C, H, N were performed by TÜBITAK Analytical Laboratory, Ankara, Turkey and were within the range of $\pm 0.4\%$ of theoretical values.

3.1.1. Synthesis of methyl (2-oxobenzothiazolin-3-yl)-acetate

2-Oxobenzothiazoline (0.02 mol) was dissolved in 30 ml of acetone, and 0.021 mol of potassium carbonate was added. Methyl chloroacetate (0.022 mol) was added to the final mixture and refluxed for 4 h, cooled to 0°C, poured into 100 ml of ice–water mixture and stirred for 1 h at 0–10°C. The precipitate formed in the meantime was filtered and washed with water until at

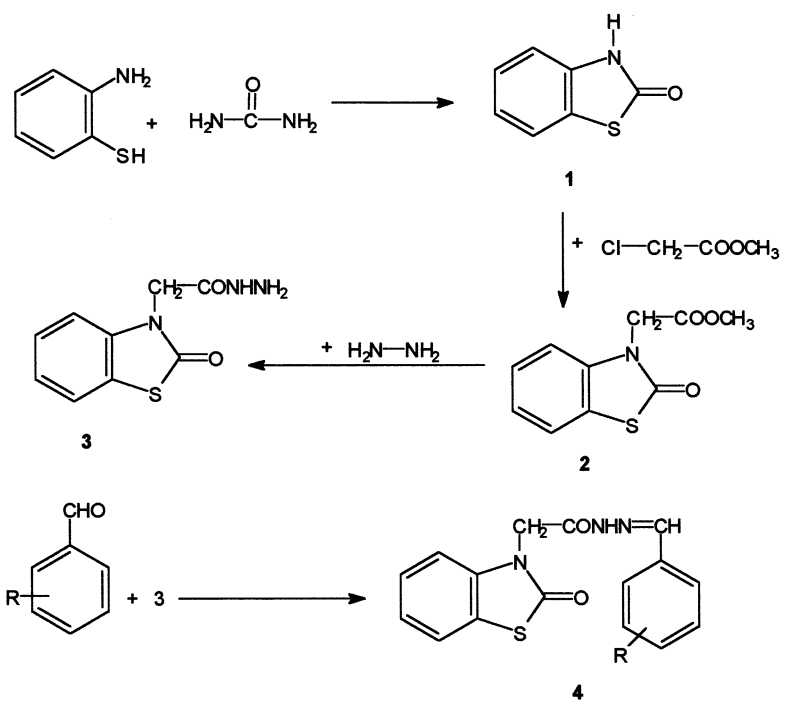

Fig. 2. Route to (2/4-substituted)benzaldehyde 2(3*H*)-benzothiazolinon-3-ylacetohydrazones.

Table 1
Melting points and yields of compounds **4a–4o**

Compound	R	Empirical formula	M.p. (°C)	Yield (%)
4a	H	$C_{16}H_{13}N_3O_2S$	248	91.30
4b	2-Cl	$C_{16}H_{12}ClN_3O_2S$	225	91.73
4c	4-Cl	$C_{16}H_{12}ClN_3O_2S$	259	92.25
4d	2-CH_3	$C_{17}H_{15}N_3O_2S$	220	92.78
4e	4-CH_3	$C_{17}H_{15}N_3O_2S$	286	87.50
4f	2-OCH_3	$C_{17}H_{15}N_3O_3S$	243	81.73
4g	4-OCH_3	$C_{17}H_{15}N_3O_3S$	265	85.00
4h	2-OH	$C_{16}H_{13}N_3O_3S$	295	75.02
4i	4-OH	$C_{16}H_{13}N_3O_3S$	280	54.60
4j	2-F	$C_{16}H_{12}FN_3O_2S$	255	86.44
4k	4-F	$C_{16}H_{12}FN_3O_2S$	245	84.74
4l	4-OC_2H_5	$C_{18}H_{17}N_3O_3S$	267	87.95
4m	4-Br	$C_{16}H_{12}BrN_3O_2S$	276	77.60
4n	4-NO_2	$C_{16}H_{12}N_4O_4S$	301	78.32
4o	4-$N(CH_3)_2$	$C_{18}H_{18}N_4O_2S$	256	72.44

neutral pH. The filtrate was dried at 25–30°C. Yield: 72%; m.p.: 92–94°C.

3.1.2. Synthesis of (2-oxobenzothiazolin-3-yl)-acetohydrazide

Methyl (2-oxobenzothiazolin-3-yl)acetate (0.005 mol) and 0.1 mol of 98% hydrazine hydrate were dissolved in 10 ml of alcohol. The final mixture was stirred for 6 days. At the end of this period, the reaction mixture was poured into 50 ml of water with stirring. The precipitate formed was filtered, washed with water. The solid material was dried at room temperature. Yield: 76%; m.p. 211°C.

3.1.3. Synthesis of hydrazones of (2-oxobenzothiazolin-3-yl)acetohydrazide

2-Oxobenzothiazolin-3-ylacetohydrazide (0.018 mol) was dissolved in 30 ml of ethanol and 0.018 mol of an appropriate benzaldehyde derivative added, then the final mixture was refluxed for 1 h. The precipitate formed was filtered and washed with hot alcohol and dried at room temperature. These compounds, were already pure and were not recrystallized.

3.2. Anticonvulsant activity testing

Male albino mice weighing 25–30 g were used in this study. Seven animals were used in each group.

3.2.1. Methods

The compounds were dissolved in DMSO and administered intraperitoneally at 4 mg/kg doses. A dose

Table 2
NMR spectral data of compounds **4a–4o**

Compound	NMR solvent	NMR spectral data (δ ppm)
4a	DMSO-d_6	4.73, 5.14 (s,s, 2H), 7.15–7.24 (m, 2H), 7.26–7.32 (m, 2H), 7.40–7.43 (m, 2H), 7.63 (d, 1H), 7.66–7.68 (m, 1H), 7.71–7.73 (m, 1H), 8.03, 8.23 (s,s, 1H), 11.74 (s, 1H)
4b	DMSO-d_6	4.80, 5.23 (s,s, 2H), 7.20–7.28 (m, 1H), 7.30–7.42 (m, 2H), 7.43–7.53 (m, 2H), 7.57 (d, 1H), 7.71 (d, 1H), 7.93–8.00, 8.10–8.12 (m,m, 1H), 8.43, 8.67 (s,s, 1H), 12.03 (s, 1H)
4c	DMSO-d_6	4.98, 5.39 (s,s, 2H), 7.70–7.44 (m, 1H), 7.49–7.55 (m, 2H), 7.73 (d, 2H), 7.88 (d, 1H), 8.00 (d, 2H), 8.27, 8.46 (s,s, 1H), 12.05 (s, 1H)
4d	CF_3COOH, $CDCl_3$	2.48, 2.54, 2.70 (s,s,s, 3H), 4.99, 5.40 (s,s, 2H) 7.12 (t, 1H), 7.25–7.43 (m, 5H), 7.57 (d, 1H) 7.82, 7.85 (d,d, 1H), 8.31 (s, 1H), 10.15 (s, 1H)
4e	CF_3COOH, $CDCl_3$	2.42, 2.46, 2.48 (s,s,s, 3H), 4.97, 5.01, 5.39 (s,s,s, 2H), 7.12 (d, 1H), 7.25–7.45 (m, 3H), 7.57 (d, 1H), 7.62, 7.71 (d,d, 2H), 7.86 (d, 1H), 7.98 (s, 1H), 9.81 (s, 1H)
4f	CF_3COOH, $CDCl_3$	4.22 (s, 3H), 5.10 (s, 2H), 7.19 (d, 1H), 7.27 (d, 1H), 7.33–7.39 (m, 2H), 7.45 (t, 1H), 7.59 (d, 1H), 7.77 (d, 1H), 7.95 (t, 1H), 8.86 (s, 1H), 10.20 (s, 1H)
4g	CF_3COOH	4.03, 4.07 (s,s, 3H), 5.14, 5.18 (s,s, 2H), 7.16–7.28 (m, 4H), 7.41–7.51 (m, 2H), 7.61–7.63 (m, 1H), 8.02–8.25 (m, 2H), 8.80, 9.78 (s,s, 1H)
4h	DMSO-d_6	3.31 (s, 1H), 4.78, 5.16 (s,s, 2H), 6.86–6.93 (m, 2H), 7.19–7.37 (m, 4H), 7.68 (t, 1H), 7.56, 7.78 (d,d, 1H), 8.38, 8.47 (s,s, 1H), 11.72 (s, 1H)
4i	DMSO-d_6, $CDCl_3$	3.18 (s, 1H), 4.69, 5.11 (s,s, 2H), 6.82 (d, 2H), 7.04 (d, 1H), 7.16 (t, 1H), 7.29 (t, 1H), 7.48 (d, 1H), 7.51 (d, 2H), 7.84, 7.93 (s,s, 1H) 11.43 (s, 1H)
4j	DMSO-d_6	4.77, 5.19 (s,s, 2H), 7.19, 7.24 (m, 1H), 7.28–7.37 (m, 4H), 7.47–7.53 (m, 1H), 7.68 (d, 1H), 7.87, 8.01 (t,t, 1H), 8.28, 8.48 (s,s, 1H), 11.91 (s, 1H)
4k	DMSO-d_6	4.76, 5.18 (s,s, 2H), 7.19–7.23 (m, 1H), 7.27–7.36 (m, 4H), 7.67 (d, 1H), 7.75–7.84 (m, 2H), 8.06, 8.26 (s,s, 1H), 11.8 (s, 1H)
4l	CF_3COOH, $CDCl_3$	1.43–1.49 (m, 3H), 4.11–4.20 (m, 2H), 4.90, 4.94, 5.32 (s,s,s, 2H), 6.96–7.08 (m, 3H), 7.20–7.32 (m, 1H), 7.37–7.42 (m, 1H), 7.50–7.54 (m, 1H), 7.65 (d, 2H), 7.91 (t, 1H) 9.72 (s, 1H)
4m	DMSO-d_6	4.74, 5.15 (s,s, 2H), 7.15–7.20 (m, 2H), 7.32 (t, 1H), 7.56–7.59 (m, 3H), 7.66 (d, 2H), 8.03, 8.12 (s,s, 1H), 10.9 (s, 1H)
4n	DMSO-d_6	4.80, 5.23 (s,s, 2H), 7.20–7.23 (m, 1H), 7.30–7.37 (m, 2H), 7.68 (d, 1H), 7.94–8.04 (m, 2H), 8.17 (s, 1H), 8.28–8.37 (m, 2H), 12.10 (s, 1H)
4o	CF_3COOH, $CDCl_3$	3.37 (t, 6H), 4.96, 5.37 (s,s, 2H), 7.10 (d, 1H), 7.32–7.34 (m, 1H), 7.40–7.42 (m, 1H), 7.54–7.57 (m, 1H), 7.62 (d, 2H), 7.95 (d, 2H), 8.05 (s, 1H), 10.09 (s, 1H)

Table 3
Anticonvulsant activity of compounds **4a–4o**

Compound	Intensity (score)	Latency (s)	Time of death (min)
4a	2.10 ± 0.10 *	35.00 ± 5.54	6.73 ± 1.07
4b	2.31 ± 0.25	41.57 ± 6.52	6.74 ± 1.99
4c	2.36 ± 0.24	31.57 ± 1.95	6.94 ± 1.96
4d	2.47 ± 0.27	24.14 ± 5.42	8.28 ± 2.29
4e	1.99 ± 0.12 *	47.57 ± 6.94 *	6.88 ± 2.81
4f	2.02 ± 0.15 *	39.43 ± 5.56	8.20 ± 1.83
4g	1.91 ± 0.15 *	45.71 ± 6.37	6.19 ± 0.93
4h	2.04 ± 0.13 *	57.71 ± 7.15 *	8.39 ± 2.28
4i	2.45 ± 0.25	33.57 ± 3.66	8.77 ± 2.10
4j	2.47 ± 0.26	46.86 ± 3.27 *	5.74 ± 1.07
4k	2.33 ± 0.123	61.29 ± 8.37 *	8.45 ± 1.41
4l	2.65 ± 0.185	27.71 ± 3.38	5.30 ± 0.97
4m	2.41 ± 0.21	32.00 ± 5.51	5.15 ± 1.07
4n	2.65 ± 0.29	26.57 ± 4.46	6.52 ± 1.77
4o	2.39 ± 0.10	46.43 ± 3.71 *	3.51 ± 0.66
Control	2.85 ± 0.15	26.57 ± 3.51	6.70 ± 1.61

* $P < 0.05$.

of 60 mg/kg pentylenetetrazole (PTZ) was administered intraperitoneally 30 min after the injection of the compounds. DMSO was given intraperitoneally to the control groups instead of the compounds. Convulsion was scored during 20 min. Seizure stages were rated according to the following criteria.

1. No effect.
2. Facial movements.
3. Forelimbs clonic twitches.
4. Clonic convulsions with rearing.
5. Generalized convulsion with rearing and falling episodes.
6. Seizure with falling down and period of tonus.

Three parameters such as seizure stage, seizure latency and the mortality time were used to evaluate antiepileptic activity of the drugs.

Student's *t*-test was used for statistical analysis.

4. Results and discussion

Fifteen new benzothiazolone derivatives were synthesized in this study; their melting points and percentage yields are shown in Table 1. The chemical structures of the compounds were elucidated by their IR and NMR spectral data. Table 2 illustrates NMR spectral data. The IR spectra indicated the presence of two carbonyl bands at 1695–1655 and 1650–1625 cm^{-1} (for the ring carbonyl and hydrazide carbonyl, respectively).

The results obtained from anticonvulsant activity testing are given in Table 3. In this table the scores, latency time (s) and time of death (min) are also indicated. Compounds **4a**, **4e**, **4f**, **4g** and **4h** decreased the intensity of the convulsion induced by pentylenetetrazole and compounds **4e**, **4h**, **4j**, **4k** and **4o** significantly delayed the emergence of the seizure in mice. These findings are in accordance with the suggestion of Dimmock and co-workers [2]. Compounds **4e** and **4h** emerged as promising compounds among the others in exhibiting significant results for both biological parameters considered. Our future research will continue on the synthesis of derivatives of **4e** and **4h.**

Acknowledgements

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