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SYNTHESIS, CHARACTERIZATION AND ANTICONVULSANT ACTIVITY OF NEW 4-THIAZOLIDINONE AND 1,2,4-TRIAZOLE-3-THIONE DERIVATIVES

YENİ 4-TİYAZOLİDİNON VE 1,2,4-TRİAZOL-3-TİYON TÜREVLERİNİN SENTEZİ VE ANTIKONVULSAN ETKİLERİNİN ARAŞTIRILMASI

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*A series of new 2-[[[[4-phenyl-5-(2-furyl)-1,2,4-triazol - 3 -yl] thio] acetyl] hydrazono] -3 - alkyl/aryl - 4 - thiazolidinones (**3a-h**) and 4-alkyl/aryl-2,4-dihydro-5-[[[4-phenyl-5-(2-furyl)-1,2,4-triazol-3-yl]-thio] methyl] -3H-1,2,4-triazole -3-thiones (**4a-h**) were synthesized, characterized and evaluated for anticonvulsant activity against pentylenetetrazole induced seizures. Among the tested compounds, the highest protection (40%) was demonstrated by the 4-allyl substituted derivative **4d**.*

*Bir seri yeni 2-[[[[4-fenil-5-(2-furil)-1,2,4-triazol-3-il]tiyo]asetil]hidrazono]-3-alkil/aril-4-tiyazolidinon (**3a-h**) ve 4-alkil/aril-2,4-dihidro-5-[[[4-fenil-5-(2-furil)-1,2,4-triazol-3-il]tiyo]metil]-3H-1,2,4-triazol-3-tiyon(**4a-h**) sentezlenmiş ve yapıları aydınlatılmıştır. Yeni bileşiklerin pentilentetrazol ile oluşturulan konvulsiyonlarda antikonvulsan etkileri araştırılmış ve prototip olarak seçilen bileşikler için de en yüksek korunayı sağlayan bileşiğin 4-allil sübstitüe türev **4d** olduğu saptanmıştır (%40)*

Keywords: *Thiazolidinones; Triazoles; Anticonvulsant activity*

Anahtar kelimeler: *Tiyazolidinonlar; Triazoller; Antikonvulsan aktivite*

Introduction

4-Thiazolidinones are reported to possess anticonvulsant activity (1-3). Furthermore recent investigations on new 1,2,4-triazole derivatives revealed anticonvulsant properties associated with this ring system (4,5). In continuation of our studies on the synthesis of compounds which may demonstrate anticonvulsant properties (2,4,6), we report here synthesis, characterization and anticonvulsant activity of new substituted 4-thiazolidinone and 1,2,4-triazole-3-thione derivatives.

Materials and Methods

Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Melting points were determined in a Büchi 530 apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 577 (Grating) spectrophotometer. ^{1}H-NMR spectra were measured on a Bruker AC 200 (200 MHz) instrument. EIMS were recorded at the Pennsylvania State University, USA.

*2[[[[4-phenyl-5-(2-furyl)-1,2,4-triazol-3-yl]thio]acetyl] hydrazono] -3-alkyl/aryl-4-thiazolidinones (**3a-h**)*

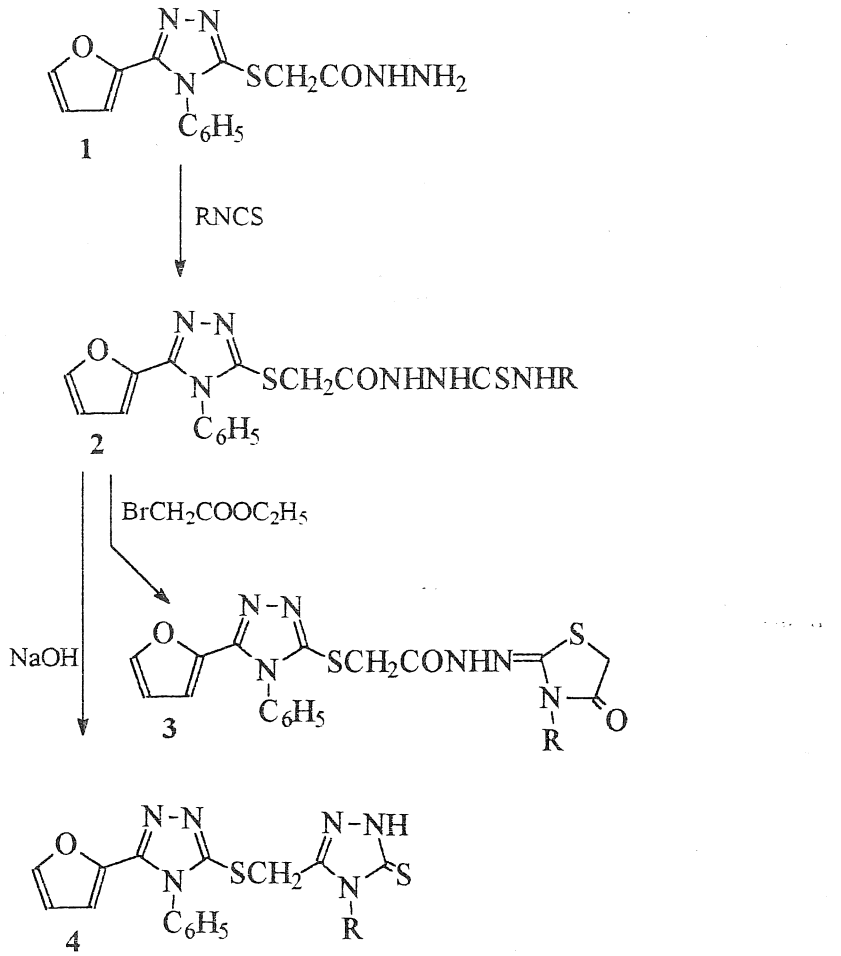
An appropriate thiosemicarbazide (0.005 mol) (**2**) and ethyl bromoacetate (0.0055 mol) were refluxed in 30 ml absolute C_2H_5OH in the presence of anhydrous CH3COONa (0.020 mol) for 2h. After cooling, H_2O was added dropwise until the precipitate (NaBr) dissolved and the reaction mixture was allowed to stand overnight. The crystals thus obtained were filtered and recrystallized from C_2H_5OH (96%) to afford **3a-h**.

3b : IR(KBr) ν (cm^{-1}): 3585 (O-H), 3126 (N-H), 1716 (C=O, ring), 1675 (C=O), 1596, 1514, 1497, 1455 (C=N, C=C). ^{1}H-NMR (DMSO-d_6) δ ppm: 10.48 (s, 1H, CONH), 7.73 (s, 1H, C5-H), 7.63-7.60 (m, 4H, Ar-H), 7.49-7.45 (m, 1H, Ar-H), 6.49 (dd, J= 3.12 Hz, 1.76 Hz, 1H, C4-H), 6.16 (d, J=3.33 Hz, 1H, C3-H), 4.14, 4.02 (2s, 4H, $2SCH_2$), 3.66 (q, J=6.92 Hz, 2H, N-CH_2), 1.12 (t, J=7.03 Hz, 3H, N-CH_2-CH_3). EIMS m/z (rel.abun.%): 442 (M^+, 15), 284 (100), 257 (16), 243 (23), 224 (9), 189(8), 170(15), 148 (18), 121 (23), 91 (55), 87 (10), 77 (44), 59 (8), 51 (11), 39 (8), 28 (22).

3f: IR(KBr) ν (cm^{-1}) : 3407 (O-H), 3150 (N-H), 1716 (C=O, ring), 1699 (C=O), 1625, 1513, 1495, 1447 (C=N, C=C). ^{1}H-NMR (DMSO-d_6) δ ppm: 10.44 (s, 1H, CONH), 7.73 (s, 1H, C5-H), 7.61-7.53 (m, 4H, Ar-H), 7.46-7.44 (m, 1H, Ar-H), 7.27 (d, J=8.27 Hz, 2H, Ar-H), 7.16 (d, J=8.20 Hz, 2H, Ar-H), 6.49 (dd, J=3.41 Hz, 1.60 Hz, 1H, C4-H), 6.15 (d, J=3.33 Hz, 1H, C3-H), 4.15, 3.98 (2s, 4H, $2SCH_2$), 2.33 (s, 3H, Ar-CH_3). EIMS m/z (rel.abun.%): 504 (M^+, 14), 284 (100), 257 (16), 243 (27), 224 (8), 186 (7), 170 (12), 149 (16), 121 (16), 91 (53), 77 (28), 65 (8), 51 (7), 39 (5), 28 (7).

*4-Alkyl/aryl-2,4-dihydro-5-[[[4-phenyl-5-(2-furyl)-1,2,4-triazol-3yl]thio]methyl]-3H-1,2,4-triazole-3-thiones (**4a-h**)*

A solution of an appropriate thiosemicarbazide (0.005 mol) (**2**) in 2N aqueous NaOH (20 ml) was heated under



Scheme 1

reflux for 2h. After cooling the reaction mixture was acidified by the addition of 12.5% aqueous HCl. The precipitate thus obtained was collected by filtration, washed with water several times and purified by recrystallization from C_2H_5OH (96%) to afford **4a-h**.

4b: IR(KBr) ν (cm^{-1}) : 3420 (N-H), 1570, 1490, 1460, 1420 (C=N, C=C). ^{1}H-NMR (DMSO-d_6) δ ppm: 13.54 (s, 1H, NH), 7.74 (s, 1H, C5-H), 7.62-7.47 (m, 4H, Ar-H), 7.40-7.33 (m, 1H, Ar-H), 6.50 (dd, J=3.30 Hz, 1.57 Hz, 1H, C4-H), 6.16 (d, J=3.41 Hz, 1H, C3-H), 4.38 (s, 2H, SCH_2), 3.94 (q, J=7.04 Hz, 2H, N-CH_2), 116 (t, J=7.05 Hz, 3H, N-CH_2-CH_3). EIMS m/z (rel.abun.%): 384 (M^+, 25), 352 (5), 270 (10), 243 (56), 189 (21), 170 (17), 87 (6), 77 (100), 69 (21), 60 (26), 51 (47), 39 (36).

4g: IR(KBr) ν (cm^{-1}) : 3400 (N-H), 1570, 1500, 1440, 1400 (C=N, C=C). ^{1}H-NMR (DMSO-d_6) δ ppm: 13.71 (s, 1H, NH), 7.74 (s, 1H, C5-H), 7.67-7.53 (m, 4H, Ar-H), 7.31-7.23 (m, 3H, Ar-H), 7.13 (d, J= 8.21 Hz, 2H, Ar-H), 6.50 (dd, J=3.38 Hz, 1.93 Hz, 1H, C4-H), 6.15 (d, J=3.51 Hz, 1H, C3-H), 4.10 (s, 2H, SCH_2), 2.35 (s, 3H, Ar-CH_3). EIMS m/z (rel.abun.%): 446 (M^+, 3), 243 (100), 189 (34), 170 (9), 149 (16), 108 (28), 91 (22), 77 (75), 63 (23), 51 (49), 39 (34), 28 (64).

Anticonvulsant Activity

The anticonvulsant activity of the compounds synthesized was determined against pentylenetetrazole induced seizures in male Albino Swiss mice weighing 20-24 g. The animals were housed in groups of 10 and acclimated to their environment for at least 2 days before the experiments were done. The animals were allowed free access to food and water before being tested. The test compounds were suspended in 5% aqueous suspension of gum acacia and were administered to a group of 10 animals at a dose of 100 mg/kg intraperitoneally. 2 hrs after the administration mice

Table 1. Physicochemical data of compounds 3 and 4

Compound	R	Formula (MW)	Mp (°C)	Yield (%)	Analysis(calcd./found) C	H	N
3a	CH_3	$C_{18}H_{16}N_6O_3S_2 \cdot H_2O$ (446.51)	169-70	76	48.41 48.89	4.06 3.78	18.82 19.02
3b	C_2H_5	$C_{19}H_{18}N_6O_3S_2 \cdot ½H_2O$ (451.51)	227-8	71	50.54 50.58	4.24 4.13	18.61 18.53
3c	CH_2=CH-CH_2	$C_{20}H_{18}N_6O_3S_2$ (454.52)	182-3	88	52.85 52.48	3.99 3.98	18.48 18.11
3d	C_4H_9	$C_{21}H_{22}N_6O_3S_2 \cdot H_2O$ (488.59)	123-4	86	51.62 51.79	4.95 4.90	17.20 17.07
3e	C_6H_5	$C_{23}H_{18}N_6O_3S_2$ (490.55)	273-4	84	56.31 56.28	3.69 3.65	17.13 17.18
3f	$C_6H_4CH_3$(4)	$C_{24}H_{20}N_6O_3S_2 \cdot H_2O$ (522.60)	154-5	74	55.15 54.97	4.24 4.27	16.08 15.83
3g	C_6H_4Cl(4)	$C_{23}H_{17}ClN_6O_3S_2 \cdot H_2O$ (543.02)	154-5	67	50.87 50.77	3.52 3.45	15.47 15.42
3h	C_6H_4Br(4)	$C_{23}H_{17}BrN_6O_3S_2$ (569.46)	224-5	63	48.51 47.99	3.00 2.98	14.75 14.37
4a	CH_3	$C_{16}H_{14}N_6OS_2 \cdot ½H_2O$ (379.45)	192	93	50.64 50.60	3.98 3.93	22.14 22.14
4b	C_2H_5	$C_{17}H_{16}N_6OS_2$ (384.48)	226-7	97	53.10 52.91	4.19 4.26	21.85 22.08
4c	$CH_2CH_2C_6H_5$	$C_{23}H_{20}N_6OS_2$ (460.57)	225-6	98	59.98 59.42	4.37 4.27	18.24 18.20
4d	CH_2=CH-CH_2	$C_{18}H_{16}N_6OS_2$ (396.49)	193-5	96	54.52 54.47	4.06 4.12	21.19 21.78
4e	C_4H_9	$C_{19}H_{20}N_6OS_2$ (412.53)	200-1	97	55.31 55.16	4.88 5.04	20.37 21.05
4f	C_6H_5	$C_{21}H_{16}N_6OS_2 \cdot ½H_2O$ (441.52)	243	93	57.12 56.83	3.88 3.52	19.03 19.56
4g	$C_6H_4CH_3$(4)	$C_{22}H_{18}N_6OS_2$ (446.54)	228-30	99	59.17 58.57	4.06 3.76	18.82 18.42
4h	C_6H_4Cl(4)	$C_{21}H_{15}ClN_6OS_2$ (466.96)	204-5	98	54.01 53.44	3.23 3.14	17.99 17.86

were injected pentylenetetrazole (90 mg/kg) subscutaneously. This dose of pentylenetetrazole has been shown not only to produce convulsions in almost all untreated mice, but also to exhibit 100% mortality during the 24 h period in the control group (7,8). The mortality within 24 h was recorded.

Results and Discussion

5 - (2 - Furyl) - 4 - phenyl - 1,2,4 -triazole -3-mercaptoacetic acid hydrazide (9) **1** functioned as a versatile synthetic intermediate from which **2-4** were prepared by the routes depicted in Scheme 1. Reaction of **1** with alky/arylisothocyanates provided 4-alkyl/aryl-1-[[[4-phenyl-5-(2-furyl)-1,2,4-triazol-3-yl] thio]acetyl]-3-thiosemicarbazides **2** (10) which were cyclized to the corresponding 2-[[[[4-phenyl-5-(2-furyl)-1,2,4-triazol-3-yl] thio] acetyl] hydrazono]-3-alkyl/aryl-4-thiazoli - dinones on treatment with ethyl bromoacetate. Access to the 4-alkyl/aryl-2,4-dihydro-5-[[[4-phenyl-5-(2-furyl)-1, 2, 4-triazol-3-yl]methyl]thio] -*3H*-1,2,4-triazole-3-thiones was readily accomplished by cyclodehyhdration of **2** in aqueous NaOH.

The structures of **3** and **4** were confirmed by spectral (IR, ^{1}H-NMR, EIMS) and analytical data (Table 1). The IR spectra of **3** and **4** exhibited N-H bands in the 3200-3122 and 3440-3300 cm^{-1}, respectively. The ring and the exocyclic C=O bands of **3** were observed in the 1757-1716 and 1700-1675 cm^{-1} regions. Presence of an additional C=O band in **3** and absence of the C=O absorption in **4** provided definitive proof for the formation of new products. The ^{1}H-NMR of **3** and **4** showed single NH resonances in the 10.48-10.44 (6) and 13.71-13.54 ppm (4) regions, respectively. The S-CH_2 resonances of **3** were observed in the 4.15-4.14 and 4.02-3.98 ppm regions where the former was attributed to the methylene group of the 4-thiazolidinone ring system. The exocyclic S-CH_2 protons of **4** resonated at a lower field (4.38-4.10 ppm) when compared to those of **3** presumably due to the inductive effect of the newly formed 1,2,4-triazole ring.

The EIMS of selected compounds **3b**,**3f**,**4b** and **4g** readily displayed molecular ions at m/z 442, 504,384 and 446 which confirmed their molecular weights. The major fragmentation route in **3b** and **3f** was the cleavage of the exocyclic CO-NH linkage which afforded the base peak at m/z 284. Fission of the exocyclic S-CH_2 bond with succesive protonation was a prominent fragmentation route in **3b**,**3f**,**4b** and **4g** and led to high intensity fragments (m/z 243; **3b**, 23%; **3f**, 27%; **4b**, 56%) or to the base peak (**4g**, 100%). Further spectral details are presented in the Materials and Methods.

Selected members from both series were evaluated for anticonvulsant activity against pentylenetetrazole induced seizures. As can be seen in Table 2, among the tested compounds the 1,2,4-triazole derivatives **4b**, **4d**, and **4g** showed a better anticonvulsant profile compared to the 4-thiazolidinones **3b-e**. The highest protection (40%) was demonstrated by **4d**, the 4-allyl substituted derivative.

Table 2. Anticonvulsant activity of compounds **3b-e**, **4b-d** and **4g**

Compound	Pentylenetetrazole mortality (%)	Protection (%)
3b	100	nil
3c	90	10
3d	80	20
3e	80	20
4b	70	30
4c	80	20
4d	60	40
4g	70	30

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