ORIGINAL RESEARCH

Synthesis and anticonvulsant activity of substituted thiourea derivatives

Ahmet Özgür Çelen[1], Bedia Kaymakçıoğlu[1], Salih Gümrü[2], Hale Zerrin Toklu[2], Feyza Arıcıoğlu[2]

ABSTRACT: Twelve new thiourea derivatives were prepared by the reacting of 4-aminophenylacetic acide with substituted isothiocyanates. Their chemical structures were proved by means of IR, 1H-NMR, mass spectroscopic and elemental analyses. These compounds were tested at dose of 50 mg/kg for their anticonvulsant activity using by pentylenetetrazole induced seizure (PTZ) and maximal electroshock seizure (MES) tests in mice. Compound 1b, (4-{[(4-chlorophenyl)thiocarbamoyl]amino}phenyl)acetic acid, was found to be more active than the other tested compounds. The compound 1b reduced convulsions in all types of grades (from grade I to V), therefore it increased convulsive threshold. It also increased onset time from 1.20 to 2.58 sec. and survival % from 50 to 95.

KEY WORDS: Synthesis, thiourea, anticonvulsant activity.

AFFILIATIONS
[1]Marmara Üniversitesi Eczacılık Fakültesi, Farmasötik Kimya Anabilim dalı, İstanbul, Türkiye
[2]Marmara Üniversitesi Eczacılık Fakültesi, Farmakoloji Anabilim Dalı, İstanbul, Türkiye

CORRESPONDENCE
Bedia Kaymakçıoğlu
E-mail: bkaymakcioglu@marmara.edu.tr

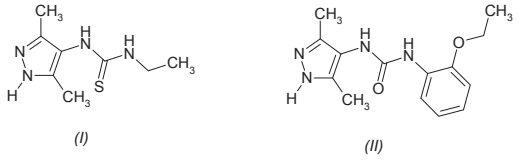
Received:
17.01.2011
Accepted:
05.03.2011

1. INTRODUCTION

Thioureas are important sulphur and nitrogen-containing compounds and they are useful substances in drug research. Some thiourea derivatives possess valuable biological pharmacological activities such as, anti-HIV / antiviral (1-4), antitubercular (5-8), analgesic (9-10) and anticancer properties (11-13). In addition, urea and thioureas (14-16) have emerged as structurally novel anticonvulsant.

In the past 15 years, 13 new antiepileptic drugs (AEDs) have been introduced, some of which are advantageous in terms of pharmacokinetics, tolerability, and potential for drug interactions. These AEDs are regarded as second generation compared with older AEDs, such as phenobarbital, phenytoin, carbamazepine, ethosuximide, and valproic acid. However, the second-generation AEDs marketed so far have not been a breakthrough because, altogether, their use leads to freedom from seizures in no more than 15–20% of patients with epilepsy who are refractory to older AEDs. Therefore, despite the current availability of more than 15 drugs, about 30% of people with epilepsy have uncontrolled disease, and novel and more eff ective third-generation AEDs are needed (17).

As a part of our ongoing research program pertaining to the synthesis of series of thiourea and urea derivatives as potent anticonvulsant activities (18, 19). Among this series, the compounds *N-Ethyl-N′-(3,5-dimethylpyrazole-4-yl)thiourea* ***(I)*** and *N-(2-Ethoxyphenyl)-N′-(3,5-dimethylpyrazole-4-yl) urea* ***(II)*** were found to show a better anticonvulsant activity (Figure 1). In the MES test, these compounds exhibited median effective doses (ED_{50}) of 17.14 and 17.46 mg/kg respectively.



(I) *(II)*

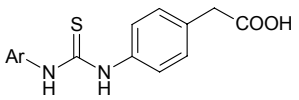
FIGURE 1. Chemical formulas of compound (I) and compound (II)

The anticonvulsant drug design was based on the presumption that for the evaluation of the anticonvulsant activity with maximal electroshock treatment (MES) at least one phenyl or similar aromatic group in close proximity to two electron donor atoms were required and that for the evaluation with pentylenetetrazole (PTZ) an alkyl group substituted close to two electron donor atoms was required (20). As a part of our continuous research, we designed compounds **1a-1l** according to pharmacophoric features with the one phenyl ring as a hydrophobic aryl ring, serving as thiourea and carboxylic acide group to provide an electron donor/acceptor system (Figure

TABLE 1. Structure and physical data of thiourea derivatives 1a-ll

Compound	Ar	Formula	M. p. (oC)	Yield (%)
1a	4-F-C6H4-	C15H13FN2O2S	200-201	67
1b	4-Cl-C6H4-	C15H13ClN2O2S	206-207	48
1c	2,4,6-triCl-C6H2-	C15H11Cl3N2O2S	214-215	50
1d	4-CH3-C6H4-	C16H16N2O2S	215-216	56
1e	4-CH3O-C6H4-	C16H16N2O3S	193-194	61
1f	4-CH3S-C6H4-	C16H16N2O2S2	206-207	70
1g	4-CF3-C6H4-	C16H13F3N2O2S	197-198	45
1h	4-CF3O-C6H4-	C16H13F3N2O3S	210-211	42
1i	4-NO2-C6H4-	C15H13N3O4S	139-140	63
1j	C6H5-CH2-	C16H16N2O2S	178-179	67
1k	C6H5-CH2-CH2-	C17H18N2O2S	170-171	64
1l	C6H5-CO-	C16H14N2O3S	168-169	55

2). The other phenyl ring served as a second hydrophobic region.



1a-1l

FIGURE 2. General chemical formula of compounds 1a-1l

The current work encompasses synthesis of a new series of thioureas by reaction of (4-aminophenyl)acetic acid with different isothiocyanates and evaluation for anticonvulsant activity using by PTZ and MES tests in mice.

2. EXPERIMENTAL

2.1. Chemistry

All chemicals and solvents were purchased from Merck, Aldrich, or Fluka. Melting points were determined with a "Schmelzpunktbestimmer" SMP II and were uncorrected. ^{1}H-NMR spectra were recorded in DMSO on a Bruker Avance-DPX-400 spectrometer in DMSO-d_6 and chemical shifts were given in δ ppm with tetramethylsilane. The splitting patterns of ^{1}H-NMR were designed as follows: s: singlet, d: doublet, t: triplet, q: quarlet, m: multiplet. The Mass spectrometry was performed using an Agilent 1100 MSD spectrometer in the electrospray mode. All new compounds were analyzed for C, H, N and the results were in an acceptable range (^{1}H-NMR, mass and elemental analysis were provided by the Scientific and Technical Research Council of Turkey, TUBITAK).

General procedure for the preparation of 1a-1l

0.500 g (3.3 mmol) 4-(Aminophenyl)acetic acid is solved in acetone at 100^{o}C. Then, a solution of corresponding isothiocyanate (3.3 mmol) in 5 mL acetone is added as three parts per 30 minutes. After 6-8 hours, reaction is finalized by TLC control. Solid material is filtered and recrystallized from acetonitrile.

(4-{[(4-Fluorophenyl)thiocarbamoyl]amino}phenyl)acetic acid (**1a**): UV $\lambda_{max.}$ (EtOH) (nm) (log e): 275 (3,98). IR Spectroscopy ($u_{max,}$ cm^{-1}): 3196 (N-H, O-H), 3005 (C-H), 1693 (C=O), 1236 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.55 (2H, s, -CH_2), 6.87-7.71 (8H, m, aromatic protons), 9.72 (1H, s, -NH-), 9.72 (1H, s, -NH-), 12.26 (1H, s, OH). Anal. Calcd. for $C_{15}H_{13}FN_2O_2S$; C: % 59.20; H: % 4.31; N: % 9.20; S: % 10.54. Found: C: % 57.55; H: % 4.30; N: % 8.74; S: % 9.63.

(4-{[(4-chlorophenyl)thiocarbamoyl]amino}phenyl)acetic acid (**1b**) UV $\lambda_{max.}$ (EtOH) (nm) (log e): 278 (3,51). IR (u_{max}, cm^{-1}): 3194 (N-H, O-H), 3012 (C-H), 1689 (C=O), 1240 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.47 (2H, s, -CH_2), 7.15-7.59 (8H, m, aromatic protons), 9.68 (1H, s, -NH-), 9.79 (1H, s, -NH-), 11.98 (1H, s, OH). Anal. Calcd. for $C_{15}H_{13}ClN_2O_2S$; C: % 56.16; H: % 4.08; N: % 8.73; S: % 10.00. Found: C: % 57.80; H: % 4.49; N: % 8.38; S: % 9.34.

(4-{[(2,4,6-trichlorophenyl)thiocarbamoyl]amino}phenyl)acetic acid (**1c**): UV $\lambda_{max.}$ (EtOH) (nm) (log e): 259 (3,63). IR (u_{max}, cm^{-1}): 3155 (N-H, O-H), 2989 (C-H), 1693 (C=O), 1224 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.56 (2H, s, -CH_2), 7.18-7.79 (6H, m, aromatic protons), 9.39 (1H, s, -NH-), 9.93 (1H, s, -NH-), 12.32 (1H, s, OH). Anal. Calcd. for $C_{15}H_{11}Cl_3N_2O_2S$; C: % 46.23; H: % 2.85; N: % 7.19; S: % 8.23. Found: C: % 46.69; H: % 3.07; N: % 7.15; S: % 7.93.

(4-{[(4-methylphenyl)thiocarbamoyl]amino}phenyl)acetic acid (**1d**): UV $\lambda_{max.}$ (EtOH) (nm) (log e) **:** 278 (3,55). IR (u_{max}, cm^{-1}): 3201 (N-H, O-H), 3001 (C-H), 1695 (C=O), 1238 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 2.22 (2H, s, -CH_2), 3.26 (3H, s, -CH_3), 7.10-7.50 (8H, m, aromatic protons), 9.55 (1H, s, -NH-), 9.74 (1H, s, -NH-), 12.31 (1H, s, OH). Anal. Calcd. for $C_{16}H_{16}N_2O_2S$; C: % 62.95; H: % 5.58; N: % 8.16; S: % 9.34. Found: C: % 61.21; H: % 4.96; N: % 8.55; S: % 9.71.

(4-{[(4-methoxyphenyl)thiocarbamoyl]amino}phenyl)acetic acid (**1e**): UV $\lambda_{max.}$ (EtOH) (nm) (log e): 276 (3,34). IR (u_{max}, cm^{-1}): 3215 (N-H, O-H), 3026 (C-H), 1689 (C=O), 1234 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.49 (2H, s, -CH_2), 3.69 (3H, s, -CH_3), 6.90 (2H, d, J= 8.94 Hz, H3', H5'), 7.20 (2H, d, J= 8.41 Hz, H2, H6), 7.30 (2H, d, J= 8.93 Hz, H2', H6'), 7.40 (2H, d, J= 8.41 Hz, H3, H5), 9.46 (1H, s, -NH-), 9.46 (1H, s, -NH-), 12.08 (1H, s, OH). Anal. Calcd. for $C_{16}H_{16}N_2O_3S$; C: % 60.74; H: % 5.10; N: % 8.85; S: % 10.14. Found: C: % 59.95; H: % 4.90; N: % 8.75; S: % 9.81.

(4-{[(4-Methylsulfanylphenyl)carbamothioyl]amino}phenyl) acetic acid (**1f**): UV $\lambda_{max.}$ (EtOH) (nm) (log e): 279 (3,12). IR (u_{max}, cm^{-1}): 3209 (N-H, O-H), 3007 (C-H), 1695 (C=O), 1242 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.35

(3H, s, -CH_3), 3.54 (2H, s, -CH_2), 7.17-7.47 (8H, m, aromatic protons), 9.75 (1H, s, -NH-), 9.75 (1H, s, -NH-), 12.31 (1H, s, OH). Anal. Calcd. for $C_{16}H_{16}N_2O_2S_2$; C: % 57.81; H: % 4.85; N: % 8.43; S: % 19.29. Found: C: % 57.87; H: % 4.75; N: % 8.38; S: % 19.21.

(4-{[(4-Trifluoromethylphenyl)carbamothioyl]amino}phenyl) acetic acid (**1g**): UV $\lambda_{max.}$ (EtOH) (nm) (log e): 281 (3,86). IR (u_{max}, cm^{-1}): 3196 (N-H, O-H), 3014 (C-H), 1683 (C=O), 1242 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.54 (2H, s, CH_2), 7.20-7.80 (8H, m, aromatic protons), 9.74 (1H, s, -NH-), 10.11 (1H, s, -NH-), 12.27 (1H, s, OH). Anal. Calcd. for $C_{16}H_{13}F_3N_2O_2S$; C: % 54.23; H: % 3.70; N: % 7.91; S: % 9.05. Found: C: % 55.02; H: % 4.21; N: % 7.94; S: % 9.00.

(4-{[(4-Trifluoromethoxyphenyl)carbamothioyl]amino}phenyl)acetic acid (**1h**): UV $\lambda_{max.}$ (EtOH) (nm) (log e): 278 (3,80). IR (u_{max}, cm^{-1}): 3201 (N-H, O-H), 3016 (C-H), 1693 (C=O), 1244 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.54 (2H, s, -CH_2), 7.09-7.68 (8H, m, aromatic protons), 9.73 (1H, s, -NH-), 9.88 (1H, s, -NH-), 12.28 (1H, s, OH). Anal. Calcd. for $C_{16}H_{13}F_3N_2O_3S$; C: % 51.89; H: % 3.54; N: % 7.56; S: % 8.66. Found: C: % 53.54; H: % 3.87; N: % 7.61; S: % 8.50.

(4-{[(4-Nitrophenyl)thiocarbamoyl]amino}phenyl)acetic acid **(1i):** UV $\lambda_{max.}$ (EtOH) (nm) (log e): 242 (4,11). IR (u_{max}, cm^{-1}): 3564 (N-H, O-H), 3323 (C-H), 1683 (C=O), 1298 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.55 (2H, s, -CH_2), 7.11-8.36 (8H, m, aromatic protons), 10.26 (1H, s, -NH-), 10.39 (1H, s, -NH-), 12.30 (1H, s, OH). Anal. Calcd. for $C_{15}H_{13}N_3O_4S$; C: % 54.37; H: % 3.95; N: % 12.68; S: % 9.68. Found: C: % 53.76; H: % 4.25; N: %12.11; S: % 8.32.

(4-[(Benzylthiocarbamoyl)amino]phenyl)acetic acid (**1j):** UV $\lambda_{max.}$ (EtOH) (nm) (log e): 258 (3,70). IR (u_{max}, cm^{-1}): 3252 (N-H, O-H), 3057–3030 (C-H), 1687 (C=O), 1290 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.52 (2H, s, -CH_2), 4.73 (2H, s, -CH_2), 7.10-7.47 (9H, m, aromatic protons), 8.12 (1H, s, -NH-), 9.56 (1H, s, -NH-), 12.30 (1H, s, OH). Anal. Calcd. for $C_{16}H_{16}N_2O_2S$; C: % 63.98; H: % 5.37; N: % 9.33; S: % 10.67. Found: C: % 63.73; H: % 5.31; N: % 9.20; S. % 10.54.

TABLE 2. Anticonvulsant activity results of the compounds

Compound	dose, mg/kg	PTZ test (%)		MES test (%)	
		Grade 5	Survival	Grade 5	Survival
Control	0	52	50	55	60
1a	50	85	40	68	75
1b	50	10***	95***	85	40
1c	50	76	60	90	70
1d	50	85	40	68	75
1e	50	100	39	98	58
1f	50	89	20	68	65
1g	50	61	38	80	60
1h	50	55	92	83	75
1i	50	90	12	98	60
1j	50	100	23	90	72
1k	50	65	90	87	52
1l	50	85	45	80	70

Each group consists of 6-10 mice. Compounds were compaired to contol group and statistical significance is expressed as ***p<0,001.

(4-{[(2-Phenylethyl)thiocarbamoyl]amino}phenyl)acetic acid (**1k**): UV $\lambda_{max.}$ (EtOH) (nm) (log e): 250 (4,19). IR (u_{max}, cm^{-1}): 3184 (N-H, O-H), 3024 (C-H), 1695 (C=O), 1298 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 2.85 (2H, t, phenethyl CH_2), 3.52 (2H, s, CH_2), 3.70 (2H, t, phenethyl CH_2), 7.00-7.50 (9H, m, aromatic protons), 7.67 (1H, s, -NH-), 9.50 (1H, s, -NH-), 12.29 (1H, s, OH). Anal. Calcd. for $C_{17}H_{18}N_2O_2S$; C: % 64.56; H: % 5.66; N: % 8.85; S: % 9.83. Found: C: % 64.94; H: % 5.77; N: % 8.91; S: % 10.20.

(4-{[(Phenylcarbonyl)thiocarbamoyl]amino}phenyl)acetic acid (**1l**) UV $\lambda_{max.}$ (EtOH) (nm) (log e): 266 (4,18). IR (u_{max}, cm^{-1}): 3284 (N-H, O-H), 3000-2950 (C-H), 1666,1597 (C=O), 1263 (C=S). ^{1}H-NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.59 (2H, s, -CH_2), 7.23-8.04 (9H, m, aromatic protons), 11.55 (1H, s, -NH-), 12.23 (1H, s, -NH-), 12.58 (1H, s, OH). Anal. Calcd. for $C_{16}H_{14}N_2O_3S$; C: % 61.13; H: % 4.49; N: % 8.91; S: % 10.20. Found: C: % 61.01; H: % 4.78; N: % 8.34; S: % 9.36.

2.2. Pharmacology

Male and female adult Balb/C mice weighing 20-30 g were used. The animals were housed in colongy cages, under standard laboratory conditions, with free access to food and tap water. Room temperature and relative humidity were maintained at 22 ± 1 °C and 60% respectively. A 12 hr/12 hour (8 a.m./8 p.m.) light-dark cycle was used. All testing was conducted in the light phase of the day. After the adaption period of 2 days, experimental groups were chosen randomly. Each mouse was used only once. The experimental protocols were approved by the Animal Care and Use Committee of Marmara University (16.04.2009-02.2009.mar).

2.2.1 Anticonvulsant Activity

The anticonvulsant activity of the new compounds was determined by using PTZ (Sigma) and MES tests. All synthesized compounds were suspended in 0.5 % methyl cellulose and administered at the dose of 50 mg/kg 30 minutes prior the tests. Effective dose 50 (ED_{50}) value for PTZ (60 mg/kg) and convulsive current 50 (CC_{50}) of animals and it's 95% fiducial limits were calculated by the method of Litchfield and Wilcoxon (21).

Statistical analysis were evaluated using one way analysis of variance (ANOVA) followed by unpaired Student's t-test using Prism 3.0 (GraphPad Software, San Diego; CA; USA).

2.2.1.1. PTZ test

The animals of the control group received same volume of saline and standart drug was carbamazepine in PTZ test. Thirty minutes after the administration of the test compounds, all mice were injected with PTZ 60 mg/kg intraperitoneally and observed for 15 minutes. Motor responses were graded 0-5 according to the scale of Racine where, grade 1: no movements, grade 2: head twitching and myoclonic jerks (MKJ), grade 3: clonic forelimb convulsions, grade 4: three plus change in posture, grade 5: falling back and generalized convulsions with tonic extention (22).

2.2.1.2. MES test

MES test was performed 30 minutes after the administration of the test compounds. The electroshocks were evoked through a current transmitter producing square waves (Arı Techinical ECT unit). In the MES test, seizures were elicited with a 60-Hz alternating current of 25 mA intensity in Balb/c mice. The cur-

TABLE 3. Anticonvulsive properties of compound 1b in PTZ test

Parameter	Onset time	Grade I %	Grade II %	Grade III %	Grade IV %	Grade V %	Survival %
PTZ	1.20 sec	99	80	75	71	52	50
1b	2.58 sec	64***	42***	35***	21***	10***	95***

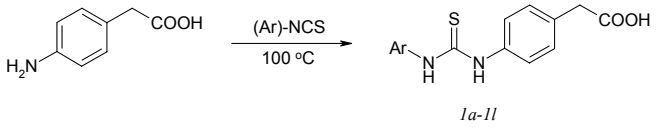
The statistical significance is expressed as ***p<0,001.

rent was applied via ear clip electrodes for 450 ms. In order to apply the shock, electrodes were attached to each animal's ears and the animals lay on their backs, their tails being fixed. Thus observation of the tonic and clonic convulsions that appeared during the seizure was ensured (23).

3. RESULTS AND DISCUSSION

3.1.Chemistry

A series of new thiourea derivatives were prepared according to Figure (3). Target compounds **1a-1l** were prepared by reacting of equimolar 4-(aminophenyl)acetic acid and various isocyanates in acetone. The new compounds were isolated in satisfactory yields (42-70%) and purified by recrystallisation from acetonitril. The purity of the compounds checked by TLC and elemental analyses. Both analytical and spectral data of all the synthesized compounds were in full agreement with the proposed structures. Physical and chemical properties of all compounds are presented in Table (1).



1a-1l

FIGURE 3. Synthesis scheme of compounds 1a-1l

In general, IR spectra showed the OH and NH stretching vibrations at 3161-3564 cm^{-1}, the C=O stretching vibrations at 1666-1695 cm^{-1} and the C=S stretching vibrations at 1224-1300 cm^{-1}. In the ^{1}H-NMR spectrum, thiourea NH signals were determined at 9.55-12.23 ppm as two different singlets. The OH signals of carboxylic acide were observed at 11.98-12.58 ppm as singlet. The protons belonging to the aromatic ring and the other aliphatic groups are observed with the expected chemical shift and integral values. APCI-MS spectra of the selected compounds showed correct molecular ion peaks (MH^+) which confirmed their molecular weights.

3.2. Anticonvulsant Activity

The anticonvulsant activity of the new compounds was determined by using PTZ (Sigma) and MES tests. The use of current animal models in the discovery of new AEDs development has advantages. The advantages include the use of intact rodents as easy models that detect anticonvulsant effects regardless of the mechanisms of action. MES and PTZ testing can be used in highthroughput screening, as shown by the National Institutes of Health Anticonvulsant Screening Program. Furthermore, these models can provide insight into pharmacokinetic–pharmacodynamic relations, which are of value for human studies (17).

All compounds were suspended in 0.5% methyl cellulose and administered intraperitoneally at the dose of 50 mg/kg 30 minutes prior the tests. The anticonvulsant potential of these compounds was invastigated by both PTZ and MES models and shown in Table 2. Within the context of the MES model none of the compounds tested showed an anticonvulsant effect. The results from PTZ model basically simulate petit mal seizures. The introduction of chloro group at 4- position of phenyl ring in thiourea moiety (compound **1b**) resulted better activity than bearing 4-fluoro, 4-nitro, 4-methoxy, 4-methlsulfanyl, 4-trifluoromethyl and 4-trifluoromethoxy group of phenyl ring in PTZ test. The compound **1b** reduced convulsions in all types of grades (from grade I to V), therefore it increased convulsive threshould. It also increased onset time from 1.20 to 2.58 sec. and survival % from 50 to 95 (Table 3). Therefore, the compound **1b** has a potantial to be an anticonvulsant drug for petit mal seizures.

Interestingly we expected the compound **1c** which had chloro group at 2-, 4-, and 6-position of phenyl ring, displayed good activity because of lipophpilicity. But it was found less potent than compound **1b** having one chloro goup at 4-position on phenyl ring. The thioureas bearing benzyl, phenylethyl or phenylcarbonyl were inactive both PTZ and MES test.

Sübstitüe Tiyoüre Türevlerinin Sentezi ve Antikonvulsan Aktiviteleri

ÖZET: 4-Aminofenilasetik asitin sübstitüe izotiyosiyanatlar ile reaksiyonu sonucu, on iki adet yeni tiyoüre bileşiği sentezlenmiştir. Bileşiklerin kimyasal yapıları IR, 1H-NMR, kütle spektroskopisi ve elementel analiz testleri ile aydınlatılmıştır. Tüm bileşiklerin antikonvulsan aktiviteleri 50mg/kg dozda farelerde pentilentetrazol (PTZ) ve maksimal elektroşok nöbet (MES) testleri kullanılarak tayin edilmiştir. Bileşik 1b'nin (4-{[(4-klorofenil)tiyokarbamoil]amino}fenil)asetik asit, diğer bileşiklere oranla daha aktif olduğu saptanmıştır. Tüm seviyelerde konvulsiyon oranını düşüren 1b bileşiği aynı zamanda nöbet eşiğini de yükseltmiştir. Ayrıca nöbet başlangıç süresini 1.20 saniyeden 2.58 saniyeye, hayatta kalma oranını ise %50'den %95'e yükseltmiştir.

ANAHTAR KELİMELER: Sentez, tiyoüre, antikonvulsan aktivite.

In conclusion, a series of thiourea derivatives have been synthesized and screened for their anticonvulsant activity. The anticonvulsant screening indicated that among the tested compounds, thiourea derivative carrying 4-Cl group on the phenyl ring exhibited noteworthy activity in PTZ test. From these data, ideas for future molecular modification leading to compound with greater favorable pharmacological properties may be derived.

ACKNOWLEDGEMENT

The authors wish to thank Marmara University Scientific Research Projects Commission (BAPKO, Project number, SAG-C-YLP-270109-0013, 2009) to financial support for this study.

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