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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME 2-PYRAZOLINES DERIVED FROM CHALCONES

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ABSTRACT

In the present study, a series of chalcones were prepared by Claisen Schmidt condensation as starting compounds and 2-pyrazoline derivatives have been synthesized by the reaction of chalcones with thiosemicarbazide. Their structures have been confirmed by IR, ^{1}H-NMR, mass spectral data and elemental analysis. These synthesized 2-pyrazoline compounds have been tested *in vivo* anticonvulsant activity by using pentylenetetrazole (PTZ) induced seizure and maximal electroshock (MES) seizure tests at a dose of 50 mg/kg. None of the compounds have *in vivo* anticonvulsant properties in PTZ test whereas some compounds showed *in vivo* anticonvulsant activity in MES test. Therefore, 2-pyrazoline compounds have a promising *in vivo* anticonvulsant activity especially on generalized absence seizures.

Keywords: Chalcones, 2-Pyrazolines, Thiocarbamide, Anticonvulsant activity.

ŞALKONLARDAN TÜRETİLEN BAZI 2 –PİRAZOLİNLERİN SENTEZİ VE ANTİKONVULSAN AKTİVİTELERİ

ÖZ

Bu çalışmada, başlangıç maddesi olarak bir seri şalkon, Claisen Schmidt kondensasyonu kullanılarak hazırlanmış ve bu şalkonların tiyosemikarbazid ile reaksiyonu sonucu 2-pirazolin türevleri sentezlenmiştir. Bileşiklerin kimyasal yapıları IR, ^{1}H-NMR ve kütle gibi spektral yöntemler ve elementel analiz yöntemi kullanılarak kanıtlanmıştır. Sentezlenen bu 2-pirazolin türevlerinin *in vivo* antikonvulsan aktiviteleri, pentilentetrazol (PTZ) ve maksimal elektroşok (MES) ile uyarılmış nöbetlere karşı 50 mg/kg dozda test edilmiştir. Hiçbir bileşik PTZ testinde herhangi bir *in vivo* antikonvulsan özellik göstermemesine karşın, bazı bileşikler MES testinde *in vivo* antikonvulsan aktivite göstermişlerdir. Dolayısıyla 2-pirazolin türevleri özellikle generalize absens nöbetlerine karşı ümit verici *in vivo* antikonvulsan aktiviteye sahiptirler.

Anahtar Kelimeler: Şalkon, 2-Pirazolin, Tiyoamid, Antikonvulsan aktivite.

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1. INTRODUCTION

Epilepsy is a common and serious chronic neurological disorder characterized by recurring seizures (Munjal, et al., 2008). Although several drugs are in use for the treatment of epilepsy, they are not effective enough. Therefore researchers in medicinal chemistry are still proceeding to study on potential compounds (Stefan and Feuerstein, 2007; Siddiqui and Ahsan, 2010; Guan, et al., 2010).

Among these compounds, 2-pyrazolines are promising structure as a anticonvulsant agents (Küçükgüzel, et al., 2000; Özdemir et al., 2007; Nikhil and Kishore, 2010). Pyrazoles and their reduced forms, pyrazolines, are well known nitrogen containing heterocylic compounds and various methods have been reported for their syntheses (Abid, et al., 2009).

In the present study, a series of chalcones were prepared by Claisen Schmidt condensation as starting compounds and 2-pyrazoline derivatives have been synthesized by the reaction of chalcones with thiosemicarbazide. Among the synthesized compounds, two of nine chalcones and six of seven 2-pyrazolines are new compounds and their structures have been confirmed by IR, ^{1}H-NMR, mass spectral data and elemental analysis. 2-Pyrazolines have been tested anticonvulsant activity by using pentylenetetrazole induced seizure (PTZ) and maximal electroshock seizure (MES) tests.

2. EXPERIMENTAL

2.1 Chemistry

Chemicals were procured from Aldrich Chemical Co. The reactions were monitored on Merck pre-coated aluminium TLC plates 60F-254 and the products were visualized by UV-light using chloroform and methanol as solvent system. Melting points were determined on a Schmelzpunktbestimmer SMP II apparatus and are uncorrected. The IR spectra were recorded on a Schimadzu FTIR 8400S spectrometry. ^{1}H NMR spectra were recorded on Bruker (400 MHz) spectrometer instruments, in DMSO. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. The splitting patterns of ^{1}H-NMR were designed as follows: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. The mass spectrometry was recorded on LC–MS-Agilent 1100 series in the electrospray mode. Elemental analysis was performed on Leco CHNS-932 analyzer.

2.1.1 General Procedure of Preparation of Chalcones (1a-g).

A mixture of 4-Pyridyl carboxaldehyde (50 mmol), aromatic ketone (50 mmol) and 50% aqueous sodium hydroxide (30 mL) in methanol (150 mL) was stirred at room temperature for about 8 h. The resulting solid was crushed on ice-water, filtered and crystallized from MeOH (Satyanarayana et al., 2004).

Chalcone derivatives **1a** (Aeppli, et al., 1980) **1b** (Vatsadze, et al., 2004), **1c** (Buu-Hoi et al., 1962), **1e** (Basnet, et al., 2007) and **1f** (Mamolo, et al., 1999) were known compounds. Compounds **1d** and **1g** were new compounds and their structure determination was given below.

1-(5-Bromo-2-thienyl)-3-(4-pyridyl)-2-propen-1-one (1d): Yield 82 %, mp 197-200 ^{o}C, IR (cm^{-1}): 3101-3024 (Ar-CH), 2914 (CH), 1637 (C=O), 1593 (C=C), 1410 (C=N), ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 7.42 (2H, dd, J=4.13 Hz, J= 8.57 Hz, CH=CH), 7.73 (1H, d, J: 4.22 Hz, H_3 proton of thiophen), 8.15 (1H, d, J: 4.33 Hz, H_4 proton of thiophen), 8.42 (2H, d, J=7.66 Hz, H_2 and H_6 protons of pyridine) 8.60 (2H, d, J= 7.75 Hz, H_3 and H_5 protons of pyridine). Anal. Calcd. for $C_{12}H_8BrNOS$: C, 49.00; H, 2.74; N, 4.76; S, 10.90. Found: C, 45.87; H, 2.75; N, 3.46, S,11.97.

1-(2-Pyrrolyl)-3-(4-pyridyl)- 2-propen-1-one (1g): Yield 60 %, mp 232-233^{o}C, IR (cm^{-1}): 3100-3030 (Ar-CH), 2930 (CH), 1640 (C=O), 1595 (C=C), 1410 (C=N), ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 6.06 (1H, s, H_4 proton of pyrrole), 6.40 (1H, s, H_3 proton of pyrrole), 6.83 (1H, s, H_5 proton of pyrrole), 7.46 (2H, dd, J=4.21 Hz, J= 8.39 Hz, CH=CH); 8.18 (2H, d, J=8.66 Hz, H_2 and H_6 protons of pyridine) 8.37 (2H, d, J= 8.75 Hz, H_3 and H_5 protons of pyridine). 11.45 (1H, s, NH of pyrrole). Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.80; H, 4.75; N, 13.46.

2.1.2 General Procedure of Preparation of 5-(4-Pyridyl)-3-aryl-1-thiocarbamoyl-2-pyrazolines (2a-g).

A mixture of chalcone **(1a-g)** (0.01 mol), thiosemicarbazide (0.012 mol) and NaOH (1 g, 0.025 mol) was refluxed in ethanol (50 mL) for 8 h. The products were poured into crushed ice and the solid mass which separated out was filtered, dried and crystallized from an appropriate solvents (Özdemir, et al., 2007).

Compound **2a** has been synthesized by Özdemir et al., (2007) as an intermediate product but the structure determination was made firstly in this research.

5-(4-Pyridyl)-3-(2-thienyl)-1-thiocarbamoyl-2-pyrazoline (2a): Yield 60%, mp 210-212 ^{o}C, IR (cm^{-1}); 3430, 3206 (NH), 1590 (C=N), 1180 (C=S), ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 3.20 (1H, dd, H_A, J_{AB}= 17.60 Hz, J_{AX}= 3.61 Hz), 3.60 (1H, dd, H_B, J_{AB}= 17.67 Hz, J_{BX}= 11.47 Hz), 6.15 (1H, H_X, J_{AX}= 3.55 Hz, J_{BX}= 11.41 Hz), 6.70 (1H, t, H_4 proton of thiophen), 6.90 (1H, d, J= 3.26 Hz, H_3 proton of thiophen), 7.10 (1H, bs, NH), 7.69 (1H, d, 4.81 Hz, H_5 proton of thiophen), 7.80 (1H, bs, NH), 8.40 (2H, d, J= 8.50 Hz, H_3 and H_5 protons of pyridine), 8.60 (2H, d, J= 8.50 Hz, H_2 and H_6 protons of pyridine). Anal. Calcd. for $C_{13}H_{12}N_4S_2$: C, 54.14; H, 4.19; N, 19.43; S, 22.24. Found: C, 54.54; H, 4.83; N, 19.81; S, 21.90. MS-ES: 289.39 (MH^+).

5-(4-Pyridyl)-3-(4-pyridyl)-1-thiocarbamoyl-2-pyrazoline (2b): Yield 40%, mp 198-202 ^{o}C, IR (cm^{-1}); 3400, 3210 (NH), 1585 (C=N), 1160 (C=S), ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 3.20 (1H, dd, H_A, J_{AB}= 17.60 Hz, J_{AX}= 3.61 Hz), 3.60 (1H, dd, H_B, J_{AB}= 17.67 Hz, J_{BX}= 11.47 Hz), 6.15 (1H, H_X, J_{AX}= 3.55 Hz, J_{BX}= 11.41 Hz), 7.10 (1H, bs, NH), 7.80 (1H, bs, NH), 8.02 (2H, d, J=7.60 Hz, H_3 and H_5 protons of pyridine), 8.40 (2H, d, J= 8.50 Hz, H_2 and H_6 protons of pyridine), 8.60 (2H, d, J= 8.50 Hz, H_3 and H_5 protons of pyridine), 8.83 (2H, d, J= 7.60 Hz, H_2 and H_6 protons of pyridine). Anal. Calcd. for $C_{14}H_{13}N_5S$: C, 59.34; H, 4.62; N, 24.72; S, 11.32. Found: C, 587.54; H, 4.83; N, 25.10; S, 11.82. MS-ES: 284.35 (MH^+).

5-(4-Pyridyl)-3-(5-chloro-2-thienyl)-1-thiocarbamoyl-2-pyrazoline (2c): Yield 45%, mp 204-206 ^{o}C, IR (cm^{-1}); 3380, 3230 (NH), 1595 (C=N), 1140 (C=S), ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 3.15 (1H, dd, H_A, J_{AB}= 17.60 Hz, J_{AX}= 3.61 Hz), 3.30 (1H, dd, H_B, J_{AB}= 17.67 Hz, J_{BX}= 11.47 Hz), 6.05 (1H, H_X, J_{AX}= 3.55 Hz, J_{BX}= 11.41 Hz), 6.70 (1H, d, J= 4.20 Hz, H_3 proton of thiophen), 6.90 (1H, bs, NH), 7.10 (1H, bs, NH), 7.41 (2H, d, J=7.50 Hz, H_3 and H_5 protons of pyridine), 7.90 (1H, d, J= 4.26 Hz, H_4 proton of thiophen), 8.60 (2H, d, J= 8.50 Hz, H_2 and H_6 protons of pyridine). Anal. Calcd. for $C_{13}H_{11}ClN_4S_2$: C, 48.36; H, 3.43; N, 17.35; S, 19.86. Found: C, 47.54; H, 3.83; N, 17.81; S, 19.82. MS-ES: 323.83 (MH^+).

5-(4-Pyridyl)-3-(5-bromo-2-thienyl)-1-thiocarbamoyl-2-pyrazoline (2d): Yield 65%, mp 214-216 ^{o}C, IR (cm^{-1}); 3420, 3230 (NH), 1560 (C=N), 1145 (C=S), ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 3.10 (1H, dd, H_A, J_{AB}= 17.60 Hz, J_{AX}= 3.61 Hz), 3.40 (1H, dd, H_B, J_{AB}= 17.67 Hz, J_{BX}= 11.47 Hz), 6.10 (1H, H_X, J_{AX}= 3.55 Hz, J_{BX}= 11.41 Hz), 6.20 (1H, d, J= 3.40 Hz, H_3 proton of thiophen), 6.90 (1H, d, J= 3.42 Hz, H_4 proton of thiophen), 6.90 (1H, bs, NH), 7.20 (1H, bs, NH), 7.35 (2H, d, J=7.50 Hz, H_3 and H_5 protons of pyridine), 8.20 (2H, d, J= 8.50 Hz, H_2 and H_6 protons of pyridine). Anal. Calcd. for $C_{13}H_{11}BrN_4S_2$: C, 42.51; H, 3.02; N, 15.25; S, 17.46. Found: C, 42.54; H, 3.83; N, 15.81; S, 17.84. MS-ES: 368.28 (MH^+).

5-(4-Pyridyl)-3-(2-furyl)-1-thiocarbamoyl-2-pyrazoline (2e): Yield 72%, mp 165-168 ^{o}C, IR (cm^{-1}); 3380, 3210 (NH), 1560 (C=N), 1165 (C=S), ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 3.40 (1H, dd, H_A, J_{AB}= 17.60 Hz, J_{AX}= 3.61 Hz), 3.60 (1H, dd, H_B, J_{AB}= 17.67 Hz, J_{BX}= 11.47 Hz), 6.10 (1H, H_X, J_{AX}= 3.55 Hz, J_{BX}= 11.41 Hz), 6.35 (1H, m, H_4 proton of furan), 6.60 (1H, d, J: 3.15 Hz, H_3 proton of furan), 7.35 (1H, d, J= 3.20 Hz, H_5 proton of furan), 6.90 (2H, bs, NH_2), 7.41 (2H, d, J=7.50 Hz, H_3 and H_5 protons of pyridine), 8.60 (2H, d, J= 8.50 Hz, H_2 and H_6 protons of pyridine). Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57; S, 11.77. Found: C, 57.54; H, 4.83; N, 20.82; S, 11.78. MS-ES: 273.32 (MH^+).

5-(4-Pyridyl)-3-phenyl-1-thiocarbamoyl-2-pyrazoline (2f): Yield 65%, mp 186-188 ^{o}C, IR (cm^{-1}); 3410, 3250 (NH), 1570 (C=N), 1130 (C=S), ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 3.15 (1H, dd, H_A, J_{AB}= 17.30 Hz, J_{AX}= 3.41 Hz), 3.30 (1H, dd, H_B, J_{AB}= 17.30 Hz, J_{BX}= 11.50 Hz), 6.10 (1H, H_X, J_{AX}= 3.50 Hz, J_{BX}= 11.48 Hz), 6.50 (1H, bs, NH), 7.10 (1H, bs, NH), 7.30-7.60 (7H, m, phenyl protons, H_3 and H_5 protons of pyridine), 8.60 (2H, d, J= 8.50 Hz, H_2 and H_6 protons of pyridine). Anal. Calcd. for $C_{15}H_{14}N_4S$: C, 63.80; H, 5.00; N, 19.84; S, 11.36. Found: C, 63.74; H, 4.83; N, 19.98; S, 11.60. MS-ES: 283.36 (MH^+).

5-(4-Pyridyl)-3-(2-pyrroyl)-1-thiocarbamoyl-2-pyrazoline (2g): Yield 55%, mp 165-167 ^{o}C, IR (cm^{-1}); 3390, 3200 (NH), 1580 (C=N), 1150 (C=S), ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 3.40 (1H, dd, H_A, J_{AB}= 17.60 Hz, J_{AX}= 3.61 Hz), 3.60 (1H, dd, H_B, J_{AB}= 17.67 Hz, J_{BX}= 11.47 Hz), 6.10 (1H, H_X, J_{AX}= 3.55 Hz, J_{BX}= 11.41 Hz), 6.20 (1H, m, H_4 proton of pyrrole), 6.45 (1H, d, J= 3.30 Hz, H_3 proton of pyrrole),

6.80 (1H, d, J= 3.20 Hz, H_5 proton of pyrrole), 6.90 (2H, bs, NH_2), 7.41 (2H, d, J=7.50 Hz, H_3 and H_5 of pyridine), 8.60 (2H, d, J= 8.50 Hz, H_2 and H_6 of pyridine), 11.20 (1H, s, NH of pyrrole). Anal. Calcd. for $C_{13}H_{13}N_5S$: C, 57.54; H, 4.83; N, 25.81; S, 11.82. Found: C, 58.10; H, 4.63; N, 24.88; S, 10.76. MS-ES: 272.34 (MH^+).

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 ^oC 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 activities of the new compounds were determined by using PTZ (Sigma) and MES tests. These rodent models are widely used as standard methods for predicting protection against generalized absense and tonic-clonic seizures in humans (Borowicz, 2010).

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 (1949).

Statistical analysis were evaluated using analysis of variance (ANOVA) followed by unpaired Student's t-test using Prism 3.0 (GraphPad Software, San Diego; CA; USA). ED_{50} values, as well as their statistical evaluation, were estimated by computer probit analysis, according to Litchfield and Wilcoxon (1949).

2.2.1.1 PTZ test:

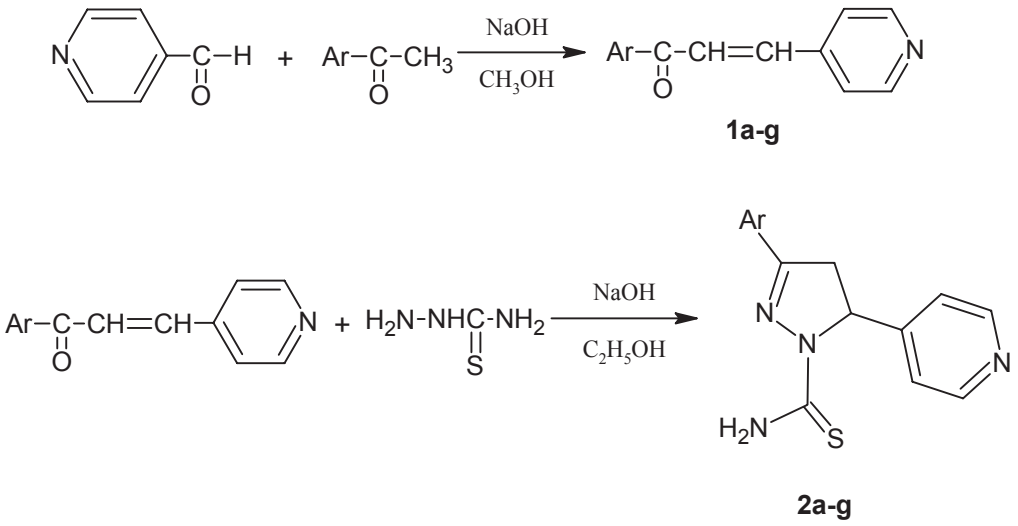
The animals of the control group received same volume of saline and standart drugs were carbamazepine (CARB) in PTZ test. Thirty minutes after the administration of the test compounds, mice were injected with PTZ 60 mg/kg intraperitoneally and observed for 15 minutes. Motor responses were graded 0-5 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 (Racine, 1972).

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 current was applied via ear clip electrodes for 450 mS. During 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 (Krall, 1978).

RESULTS AND DISCUSSION

The synthetic route of target compounds **2a-g** is outlined in Scheme 1. The intermediated chalcones (**1a-g**) were prepared by reacting equimolar aldehyde and ketone in presence of a base by conventional Claisen-Schmidt condensation. The chalcone derivatives **1d** and **1g** were original compounds and their chemical structures were confirmed by ^{1}H-NMR and elemental analysis. The reaction of the chalcones with thiosemicarbazide in alkaline medium afforded the corresponding 5-(4-pyridyl)-3-aryl-1-thiocarbamoyl-2-pyrazolines (**2a-g**). The compounds **2a-g** were isolated in satisfactory yields (40-72%) and purified by recrystallisation, using ethanol. The purity of the compounds was established by thin layer chromatography (TLC) and elemental analysis. Their chemical structures were confirmed by IR, ^{1}H-NMR and mass (MS-ES) spectral data.



Scheme 1. Synthetic route to the title compounds

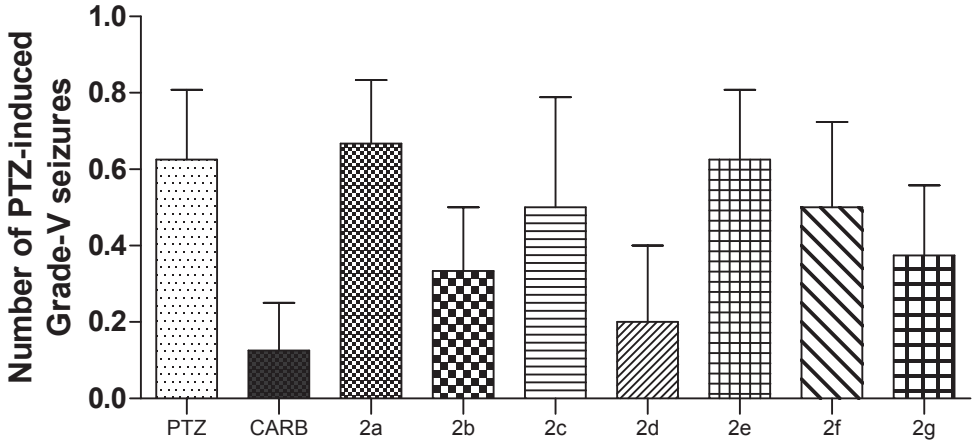
Ar: 2-thienyl **(1a, 2a)**, 4-pyridyl **(1b, 2b)**, 5-chloro-2-thienyl **(1c, 2c)**, 5-bromo-2-thienyl **(1d, 2d)**, 2-furyl **(1e, 2e)**, phenyl **(1f, 2f)**, 2-pyrrolyl **(1g, 2g)**.

The IR spectra of the compounds afforded pyrazoline C=N stretching (1501-1576 cm^{-1}), thiocarbamoyl group N-H stretching (3430-3210) and C=S stretching (1180-1130) bands. The CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at 3.23-3.58 ppm (H_A), 3.80-3.96 ppm (H_B). The CH (H_X) proton appeared as a doublet of doublets at 5.57-5.74 ppm due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring (J_{AB} =17.1-17.6 Hz, J_{AX} = 7.0-7.5 Hz, J_{BX} =12.0-12.1 Hz). N-H protons of the thiocarbamoyl group were seen at 6.50-7.90 ppm generally as broad bands. The protons belonging to the aromatic ring and the other aliphatic groups are observed with the expected chemical shift and integral values. Mass spectra (MS-ES) of compounds showed a $[MH]^+$ peaks, in agreement with their molecular formula.

The anticonvulsant activities of the synthesized compounds were determined by using PTZ and MES tests. All tested compounds were administered at the dose of 50 mg/kg. The anticonvulsant activity results were shown in Figure 1 and 2. In PTZ induced convulsions although there is a tendency of anticonvulsant activity in terms of less Grade V seizures in **2b**, **2d** and **2g** data was not statistically significant (Figure 1A) most probably because of high standard deviation within the groups. None of the compounds found significant compaired to PTZ and CARB groups in terms of percentage of survival rate (Figure 1B) in the PTZ-induced seizure test. On the other hand, compounds 5-(4-pyridyl)-3-(4-pyridyl)-1-thiocarbamoyl-2-pyrazoline **(2b)** and 5-(4-pyridyl)- 3-(2-furyl)-1-thiocarbamoyl-2-pyrazoline **(2d)** prevented MES induced seizures (Figure 2A) but they were not able to reduce the mortality rate (Figure 2B).

In conclusion, the results of the present study demonstrate that 2-pyrazoline derivatives (**2a-g**) may have potential anticonvulsant effects. None of the compounds have anticonvulsant properties in PTZ-induced seizure test whereas some compounds showed anticonvulsant activity in MES test. Therefore, 2-pyrazoline compounds may have a promising therapeutic potential especially on tonic-clonic convulsions.

A



B

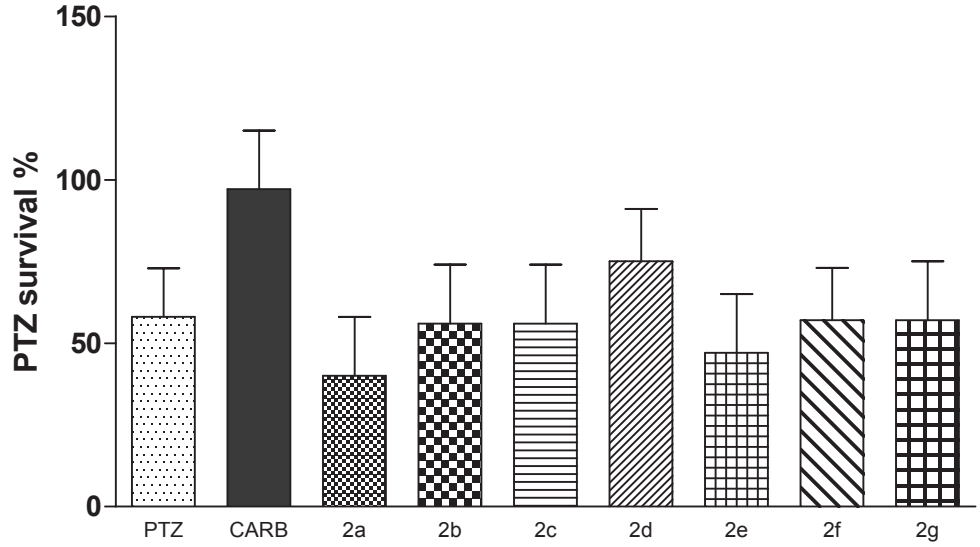
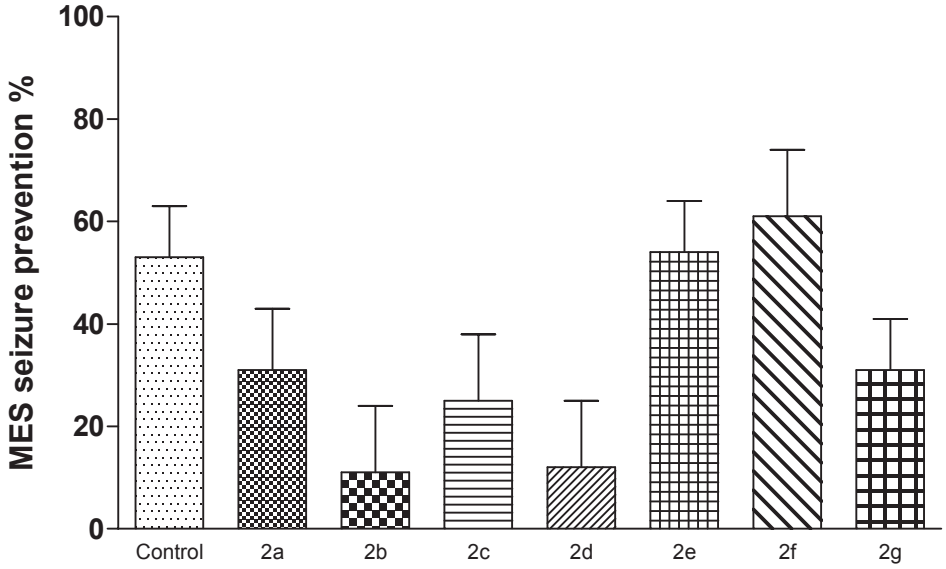


Figure 1. The number of Grade V seizures (A) and percentage of survival rate (B) in the PTZ-induced seizure test. Each group consists of 6-10 mice and compounds were compaired to PTZ and CARB groups.

A



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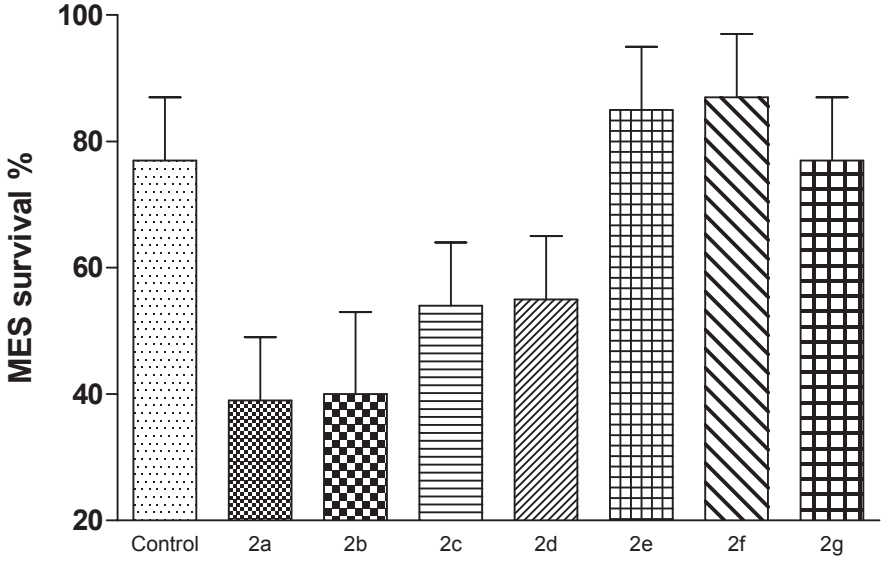

Figure 2. The percentage of seizure prevention (A) and survival rate (B) in MES test (60 Hz, 25 mA, 450mS). Each group consists of 6-10 mice. Compounds were compaired to conrol group and * $p<0.05$ considered significant.

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