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ORIGINAL RESEARCH

Novel 2-pyrazoline derivatives as potential anticonvulsant agents

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Abstract A series of new 2-pyrazoline derivatives has been synthesized by reacting 3-(substituted-phenyl)-1-pyridin-2-yl-propenones using two routes one using thiosemicarbazide and the other by hydrazine hydrate. The chemical structures were established by IR, Mass, ^{1}H-NMR, ^{13}C-NMR spectroscopic data, and elemental analysis. The anticonvulsant activity of the synthesized compounds was evaluated by the "maximal electroshock seizure" (MES) test and pentylenetetrazole (PTZ) test using male albino mice. Compounds **2e,** 5-(naphthalene-1-yl)-3-(pyridine-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioic acid amide, and **3c,** *N*-ethyl-5-(naphthalene-1-yl)-3-(pyridine-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide showed appreciable activity in the MES as well as PTZ test at all the evaluated doses.

Keywords 2- Pyrazolines · Anticonvulsant activity · Claisen-Schmidt condensation · MES test · PTZ test

Introduction

Epilepsy is the most frequent neurologic affection, characterized by excessive temporary neuronal discharge, which may be due to a number of different causes leading to epileptic seizures (Jones, 2002). The overall prevalence of the disease is 0.5–1.0 % of the population and up to 50 million people worldwide (Lowenstein *et al.,* 2005). The anti-seizure drugs act mainly by three mechanisms: calcium channel blocking, sodium channel blocking, and GABA mediated potassium channel opening (Kwan *et al.,* 2001).

The interest in pyrazoles stemmed from their applications in drugs, dyes, and as anesthetics. Pyrazolines are less stable than the corresponding pyrazoles but can be converted into the latter using mild oxidizing agents, such as bromine or lead tetra-acetate (Vardanyan and Hruby, 2006). Increasing evidence suggests that pyrazoline derivatives possess a broad spectrum of biological activities such as antimicrobial, anticancer, tranquilizing, muscle relaxant, antidepressant, monoamine oxidase inhibitory (MAOI), anticonvulsant, anti-hypertensive, anti-inflammatory, and anti-amebic (Agrawal *et al.,* Online First, 16 November 2011; Rahman and Siddiqui, 2010; Bhatia *et al.,* 2010; Stirrett *et al.,* 2008; Revanasiddappa *et al.,* 2010; Dawane *et al.* 2010; Ghorab *et al.,* 2010; Palaska *et al.,* 2001; Rajendra Prasad *et al.,* 2005; Ozdemir *et al.,* 2007, 2008; Jayaprakash *et al.,* 2008; Ruhoglu *et al.,* 2005; Parmar *et al.,* 1974; Guniz Kucukguzel *et al.,* 2000; Turan-Zitouni *et al.,* 2000; Amir *et al.,* 2008; Rani *et al.,* 2004; Budakoti *et al.,* 2007; Budakoti *et al.,* 2008). Nowadays, the therapeutic interest of MAOIs falls into two major categories. MAO-A inhibitors have been used mostly in the treatment of mental disorders, in particular depression, anxiety, and convulsion; and MAO-B inhibitors which could be used in the treatment of Parkinson's disease and Alzheimer's disease (Bortolato *et al.,* 2008; Youdim *et al.,* 2006). The classical period of the MAO-inhibitors started with hydrazine derivatives and 2-pyrazolines can be considered as cyclic hydrazine moieties, reported to have MAO inhibitory, anti-depressant, and anticonvulsant activity (Ozdemir *et al.,* 2007, 2008; Manna *et al.,* 1998, 2002; Chimenti *et al.,* 2004,

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2010; Das *et al.,* 2012). Therefore, in the present study a series of pyrazoline derivatives were synthesized and screened for their anticonvulsant potential.

Materials and methods

The chemicals and reagents were procured from S.D. Fine and Sigma-Aldrich and were used as such. Melting points were determined using melting point apparatus and are uncorrected. Progress of the reactions was monitored by thin layer chromatography on silica gel G plates, using iodine vapors and UV chamber as visualizing agents. The synthesized compounds were subjected to physical and spectral analysis.

Synthetic procedures

*General procedure for the synthesis of 3-(4-substituted-phenyl)-1-pyridin-2-yl-propenones, i.e., chalcones (**1a–e**)*

These were synthesized by condensing 2-acetyl pyridine with benzaldehyde derivatives in the presence of sodium hydroxide at temperature between 10 and 20 °C by Claisen-Schmidt condensation (Furniss *et al.,* 2007; Horning, 1985).

*General procedure for the synthesis of 5-(substituted-phenyl)-3-(pyridine-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioic acid amides (**2a–e**)*

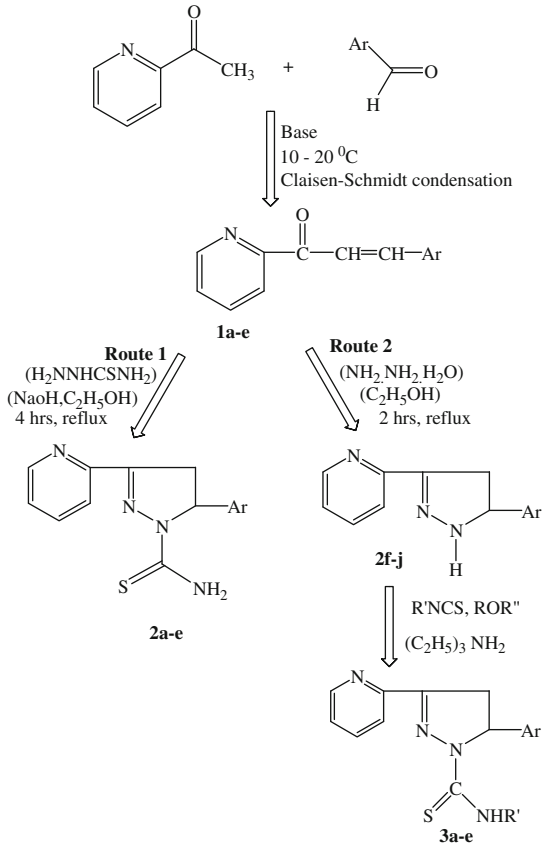
To the solutions of appropriate **(1a–e)** derivatives in ethanol, thiosemicarbazide was added and the reaction mixture was refluxed for 2–3 h. The crude product was poured on crushed ice, filtered through a Buchner funnel, and re-crystallized from methanol.

*General procedure for the synthesis of N-ethyl-5-(substituted-phenyl)-3-(pyridine-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3a–e**)*

To the solution of appropriate **(1a–e)** derivatives in ethanol, hydrazine hydrate was added and the reaction mixture was refluxed for 2–3 h. The crude product was stirred at room temperature for another 4 h, with a few drops each of triethylamine, diethyl ether, and potassium thiocynate (Scheme 1).

Spectral data of synthesized compounds

Compound ***2a*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,049.25), C=N (1,642.74), N–C=S (1,157.21); MS: *m/z*: 316.81 (M^++1 = 317.1); ^{1}H NMR ($CDCl_3$, δ): 7.89 (s, 1H), 7.51 (s, 1H), 6.89–7.35 (m, 8H), 4.89 (s, 1H), 3.38



Ar= 4-Cl C_6H_4, 3-Cl C_6H_4, 4-$OCH_3C_6H_4$, 4- $C_{13}H_{11}O$, $C_{10}H_7$; **R' =** C_2H_5.

Scheme 1 Synthesis of 2-pyrazoline derivatives

(s,2H); ^{13}C NMR ($CDCl_3$, ppm): 41.1 (CH_2 pyrazoline), 51.3 (CH pyrazoline), 156.5 (C pyrazoline), 126.7 (2CH pyridine), 137.1 (CH pyridine), 148.6 (CH pyridine), 154.1 (C pyridine), 127.9 (4CH benzene), 132.2 (C benzene), 138.8 (C benzene), 183.9 (C thioamide); Anal. Calcd for $C_{15}H_{13}ClN_4S$: C, 55.35; H, 3.98; N, 18.44; S, 10.55. Found: C, 55.32; H, 3.96; N, 18.42; S, 10.51.

Compound ***2b*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,151.3, 3,019.2), C=N (1,678.1), N–C=S (1,216.8, 1,101.0); MS: *m/z*: 316.81 (M^++1 = 317.2); ^{1}H NMR ($CDCl_3$ δ): 7.1–7.6 (q, 6H), 6.0–6.05(dd, 1H), 7.4–7.6 (m, 2H), 8.0–8.6 (t, 1H), 3.8–3.9 (t, 1H), 3.3–3.8 (d, 1H); ^{13}C NMR ($CDCl_3$, ppm): 41.5 (CH_2 pyrazoline), 51.8 (CH pyrazoline), 155.6 (C pyrazoline), 125.7 (2CH pyridine), 136.3 (CH pyridine), 149.2 (CH pyridine), 155.8 (C pyridine), 128.9 (2CH benzene), 125.9 (CH benzene)133.9 (C benzene), 142.6 (C benzene), 184.4 (C thioamide); Anal. Calcd for $C_{15}H_{13}ClN_4S$: C, 56.87; H, 4.14; N, 17.68; S, 10.12. Found: C, 56.86; H, 4.16; N, 17.71; S, 10.08.

Compound ***2c*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,151.47), C=N (1,685.67),N–C=S (1,244, 1,170.71); MS: *m/z*: 388.14 (M^++Na^+ 411.2); ^{1}H NMR ($CDCl_3$, δ):

6.6–8.7 (m, 16H), 3.39–4.20 (m, 2H); ^{13}C NMR ($CDCl_3$, ppm): 40.5 (CH_2 pyrazoline), 51.9 (CH pyrazoline), 155.7 (C pyrazoline), 125.1 (2CH pyridine), 136.2 (CH pyridine), 150.4 (CH pyridine), 154.3 (C pyridine), 114.2 (2CH benzene), 128.7 (2CH benzene), 135.1 (C benzene), 161.3 (C benzene), 77.3 (CH_2 aliphatic), 127.6 (3CH benzene), 129.2 (2CH benzene), 141.7 (C benzene), 182.9 (C thioamide); Anal. Calcd for $C_{22}H_{20}N_4OS$: C, 67.18; H, 5.10; N, 14.92; S, 8.54. Found: C, 67.20; H, 5.07; N, 14.94; S, 8.54.

Compound ***2d*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,153.40), C=N (1,691.46), N–C=S (1,249.79, 1,176.50); MS: *m/z*: 312.39 (M^++1 = 313.3); ^{1}H NMR ($CDCl_3$, δ): 6.8–8.6 (m, 9H), 3.6–3.8 (m, 4H); ^{13}C NMR ($CDCl_3$, ppm): 39.8 (CH_2 pyrazoline), 52.1 (CH pyrazoline), 154.8 (C pyrazoline), 125.1 (2CH pyridine), 135.5 (CH pyridine), 150.2 (CH pyridine), 153.1 (C pyridine), 113.3 (2CH benzene), 127.7 (2CH benzene), 134.5 (C benzene), 160.2 (C benzene), 55.8 (CH_3 aliphatic), 182.5 (C thioamide); Anal. Calcd for $C_{16}H_{16}N_4OS$: C, 61.52; H, 5.16; N, 17.93; S, 10.26. Found: C, 61.50; H, 5.16; N, 17.90; S, 10.29.

Compound ***2e*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,145.68), C=N (1,696.95), N–C=S (1,114.78); MS: *m/z*: 332.11 (M^++1 = 333.0); ^{1}H NMR ($CDCl_3$, δ): 6.66–8.27 (m, 13H), 4.6–4.9 (m, 3H); ^{13}C NMR ($CDCl_3$, ppm): 39.3 (CH_2 pyrazoline), 50.9 (CH pyrazoline), 153.9 (C pyrazoline), 126.2 (2CH pyridine), 134.8 (CH pyridine), 149.1 (CH pyridine), 156.6 (C pyridine), 122.8 (CH naphthalene), 125.4 (2CH naphthalene), 127.1 (3CH naphthalene), 129.2 (CH naphthalene), 133.1 (2C naphthalene), 134.1 (C naphthalene), 185.1 (C thioamide); Anal. Calcd for $C_{19}H_{16}N_4OS$: C, 67.69; H, 4.73; N, 17.54; S, 10.04. Found: C, 67.73; H, 4.75; N, 17.53; S, 10.01.

Compound ***3a*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,138.26), C=N (1,600.81), N–C=S (1,174.57, 1,058.85); MS: *m/z*: 344.09 (M^++ 1 = 344.12); ^{1}H NMR ($CDCl_3$, δ): 7.7–7.8 (d, 1H), 7.72–7.77 (s, 1H), 7.72–7.76 (q, d, 2H, 1H), 7.2–7.3 (m, 3H), 3.04–3.06 (d, 3H); ^{13}C NMR ($CDCl_3$, ppm): 41.5 (CH_2 pyrazoline), 51.8 (CH pyrazoline), 155.6 (C pyrazoline), 125.7 (2CH pyridine), 136.3 (CH pyridine), 149.2 (CH pyridine), 155.8 (C pyridine), 128.9 (2CH benzene), 125.4 (CH benzene)133.9 (C benzene), 142.6 (C benzene), 184.4 (C thioamide), 43.5 (CH_2 aliphatic), 16.4 (CH_3 aliphatic); Anal. Calcd for $C_{17}H_{17}ClN_4S$: C, 59.21; H, 4.97; N, 16.25; S, 9.30. Found: C, 59.25; H, 4.98; N, 16.22; S, 9.27.

Compound ***3b*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,042.1), C=N (1,613.4),N–C=S (1,247.8, 1,178.3); MS: *m/z*: 340.14 (M^++1 = 340.17); ^{1}H NMR ($CDCl_3$, δ): 7.6–7.8 (s, 1H), 7.62–7.65 (d, 1H), 7.1–7.2 (m, 2H) 7.15–7.20 (m, 2H),6.7–6.9 (t, 2H) 4.8–4.9 (t, 1H), 3.48–3.52 (t, 2H) 3.04–3.16 (d, 7H); ^{13}C NMR ($CDCl_3$, ppm): 40.1 (CH_2 pyrazoline), 52.5 (CH pyrazoline), 154.7 (C pyrazoline), 125.8 (2CH pyridine), 135.1 (CH pyridine), 149.9 (CH pyridine), 153.5 (C pyridine), 113.6 (2CH benzene), 128.4 (2CH benzene), 134.9 (C benzene), 160.6 (C benzene), 55.3 (CH_3 aliphatic), 182.5 (C thioamide), 43.7 (CH_2 aliphatic), 15.2 (CH_3 aliphatic); Anal. Calcd for $C_{18}H_{20}N_4OS$: C, 66.76; H, 5.94; N, 16.51; S, 5.40. Found: C, 66.79; H, 5.90; N, 16.52; S, 5.44.

Compound ***3c*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,011.9), C=N (1,608.8), N–C=S (1,219.1, 1,175.7); MS: *m/z*: 360.14 (M^++1 = 360.18); ^{1}H NMR ($CDCl_3$, δ): 8.54–8.57 (s, 1H), 7.7–8.5 (d, 1H), 7.6–7.7 (m, 2H) 7.42–7.45 (m, 2H), 7.39–7.45 (m, 6H), 7.34–7.36 (m, 2H), 7.1–7.2 (t, 4H), 4.9 – 5.08 (m, 3H); ^{13}C NMR ($CDCl_3$, ppm): 39.8 (CH_2 pyrazoline), 50.3 (CH pyrazoline), 154.8 (C pyrazoline), 126.5 (2CH pyridine), 134.3 (CH pyridine), 148.9 (CH pyridine), 155.7 (C pyridine), 123.2 (CH naphthalene), 125.8 (2CH naphthalene), 127.7 (3CH naphthalene), 128.2 (CH naphthalene), 133.4 (2C naphthalene), 134.5 (C naphthalene), 184.7 (C thioamide), 42.7 (CH_2 aliphatic), 16.2 (CH_3 aliphatic); Anal. Calcd for $C_{21}H_{20}N_4S$: C, 69.97; H, 5.59; N, 18.44; S, 8.90. Found: C, 69.99; H, 5.60; N, 18.45; S, 8.93.

Compound ***3d*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,049.0), C=N (1,548.9), N–C=S (1,221.8, 1,087.5); MS: *m/z*: 478.17 (M^++1 = 479.3); ^{1}H NMR ($CDCl_3$, δ): 7.1–8.6 (m, 13H), 3.47 (s, 8H); ^{13}C NMR ($CDCl_3$, ppm): 41.1 (CH_2 pyrazoline), 52.2 (CH pyrazoline), 154.7 (C pyrazoline), 125.5 (2CH pyridine), 135.8 (CH pyridine), 150.1 (CH pyridine), 155.3 (C pyridine), 114.7 (2CH benzene), 128.2 (2CH benzene), 135.6 (C benzene), 160.3 (C benzene), 78.1 (CH_2 aliphatic), 127.4 (3CH benzene), 129.1 (2CH benzene), 140.7 (C benzene), 183.9 (C thioamide), 41.8 (CH_2 aliphatic), 16.8 (CH_3 aliphatic); Anal. Calcd for $C_{24}H_{24}N_4OS$: C, 69.20; H, 5.81; N, 13.45; S, 7.70. Found: C, 69.18; H, 5.85; N, 13.46; S, 7.74.

Compound ***3e*** IR (KBr, v cm^{-1}): C–H Str (Ar) (3,019.2), C=N (1,578.1),N–C=S (1,216.8); MS: *m/z*: 344.09 (M^++1 = 344.12); ^{1}H NMR ($CDCl_3$, δ): 7.9–8.5 (s, 1H), 7.6–7.9 (q, 1H), 7.0–7.6 (m, 9H), 6.91–6.98 (q, s, 4H, 2H), 3.02–4.96 (m, 3H); ^{13}C NMR ($CDCl_3$, ppm): 41.4 (CH_2 pyrazoline), 51.3 (CH pyrazoline), 156.5 (C pyrazoline), 126.7 (2CH pyridine), 137.1 (CH pyridine), 148.6 (CH pyridine), 154.1 (C pyridine), 127.9 (4CH benzene), 132.2 (C benzene), 138.8 (C benzene), 183.9 (C thioamide), 42.5 (CH_2 aliphatic), 15.9 (CH_3 aliphatic); Anal. Calcd for $C_{17}H_{17}ClN_4S$: C, 59.21; H, 4.97; N, 16.25; S, 9.30. Found: C, 59.19; H, 5.01; N, 16.26; S, 9.29.

Anticonvulsant activity

The anticonvulsant activity studies were performed using maximal electroshock seizure (MES) and pentylenetetrazole

(PTZ) method. The MES test is associated with the electrical induction of the seizure, whereas PTZ test involves a chemical induction to generate the convulsion. MES seizures were elicited using the apparatus with corneal electrodes [Medicraft Electro-Convulsiometer]. Pentylenetetrazole was supplied by Sigma Chemical Co. The rota-rod used in the neurotoxicity test was made by Medicraft. The synthesized compounds were administrated to animals (male albino mice, weighing 30–45 g) intraperitoneally (i.p.) at three doses (30, 100, and 300 mg/kg, suspended in 10 percent aqueous PEG-400). Phenobarbital (30 mg/kg, subcutaneous.) was taken as standard drug and all the assays were performed at 0.5 and 4 h. Five animals for each dose level were used for the study. Animals were procured from the Animal House, Faculty of Pharmacy, BBDNIIT, Lucknow, U.P., India and housed in polypropylene cages with steel net, in temperature controlled room under standard living conditions of 25 ± 5 °C and relative humidity of 55 ± 5 with regular 12 h light and 12 h dark cycles and allowed free access to standard laboratory food and water. All the animals were treated humanely in accordance with the guidelines laid down by the Institutional Animal Ethics Committee (IAEC). The anticonvulsant activity was approved by the IAEC with protocol no. BBDGEI/IAEC/09/2010.

Maximal electroshock seizure (MES) test

Maximal electroshock seizures are elicited with a 50 Hz alternating current of 50 mA intensity (5–7 times that is required to elicit minimal electroshock seizures) delivered for 0.2 s via corneal electrodes. A drop of 0.9 % saline is instilled in the eye prior to application of the electrodes in order to prevent the death of the animal. Abolition of the hind limb tonic extension component of the seizure is defined as protection (Ozdemir *et al.,* 2007).

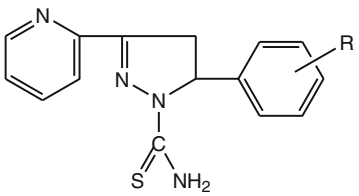
Pentylenetetrazole (metrazol) (PTZ) test

Pentylenetetrazole (85 mg/kg) (produces seizures in greater than 95 % of mice) is administered as a 0.5 % solution subcutaneous in the posterior midline. The animals were observed for 30 min, failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 s duration) was defined as protection (Ozdemir *et al.,* 2007).

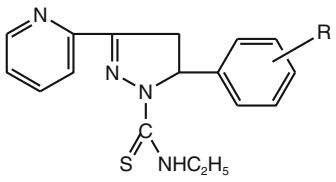
Neurotoxicity

The rota-rod test was used to evaluate neurotoxicity. The cardinal feature of the test is to ascertain the impairment of motor performance, ataxia, loss of skeletal muscular strength, and acute neurotoxicity produced by drugs in preclinical studies. The animals were placed on a 1 in. diameter knurled wooden rod rotating at 6 rpm. Normal mice remain on a rod rotating at this speed indefinitely. Neurologic toxicity was defined as the failure of the animal to remain on the rod for 1 min (Ozdemir *et al.,* 2007).

Table 1 Structure and chemical data of synthesized 2-pyrazoline derivatives (**2a–e** & **3a–e**)



(2a-2e)



(3a-e)

Compounds	R	Formula	State	Melting point (°C)	Purification	Partition coefficient (log *P*)
2a	4-Chloro	$C_{15}H_{13}ClN_4S$	Solid	58–60	Methanol	4.21
2b	3-Chloro	$C_{15}H_{13}ClN_4S$	Solid	70–72	Methanol	4.15
2c	4-Benzyloxy	$C_{22}H_{20}N_4OS$	Solid	78–80	Methanol	1.17
2d	4-Methoxy	$C_{16}H_{16}N_4OS$	Solid	76–78	Methanol	2.82
2e	1-Naphthyl	$C_{19}H_{16}N_4S$	Solid	86–88	Methanol	4.51
3a	3-Chloro	$C_{17}H_{17}ClN_4S$	Solid	98–100	Methanol	3.20
3b	4-Methoxy	$C_{18}H_{20}N_4OS$	Semi-solid	–	Methanol	2.92
3c	1-Naphthyl	$C_{21}H_{20}N_4S$	Semi-solid	–	Methanol	4.70
3d	4-Benzyloxy	$C_{24}H_{24}N_4OS$	Semi-solid	–	Methanol	1.46
3e	4-Chloro	$C_{17}H_{17}ClN_4S$	Semi-solid	–	Methanol	3.64

Results and discussion

A series of 2-pyrazoline derivatives was synthesized via Claisen-Schmidt condensation and all the synthesized pyrazoline derivatives **(2a–e and 3a–e)** were characterized by chemical, spectral, and elemental data (Melting Point, IR, Mass, NMR, and Elemental Analysis) (Table 1). Infrared spectra were recorded on Shimadzu 8400S and Perkin-Elmer AX-1 spectrometers and the values are expressed in cm^{-1}. Mass spectra were recorded on a JEOL-Accu TOF, JMS-T100LC spectrometer. Proton Nuclear Magnetic resonance spectra were recorded on Bruker DRX-300 (at 300 MHz) spectrometer and ^{13}C-NMR data were recorded on Advance-400 MHz, Bruker (Switzerland) spectrometer. Chemical shift values were reported in parts per million (delta value), taking TMS as an internal standard. Elemental analysis was performed on a Elemental Vario EL III analyzer. All the spectral studies were

Table 2 Anticonvulsant activity of the synthesized compounds

Comp.	Dose (mg/kg)	Activity MES time (h)		Activity PTZ time (h)		[a]Toxicity time (h)	
		0.5	4.0	0.5	4.0	0.5	4.0
2a	30	0/1	0/1	0/1	0/1	0/4	0/4
	100	1/1	0/1	0/1	0/1	0/4	0/4
	300	1/1	1/1	1/1	0/1	1/4	0/4
2b	30	1/1	0/1	0/1	0/1	0/4	0/4
	100	1/1	0/1	0/1	0/1	0/4	0/4
	300	1/1	1/1	1/1	1/1	1/4	0/4
2c	30	0/1	0/1	0/1	0/1	1/4	0/4
	100	0/1	0/1	0/1	0/1	4/4	2/4
	300	0/1	0/1	0/1	0/1	4/4	3/4
2d	30	0/1	0/1	0/1	0/1	0/4	0/4
	100	0/1	0/1	1/1	0/1	0/4	0/4
	300	0/1	0/1	1/1	0/1	0/4	0/4
2e	30	1/1	0/1	0/1	0/1	0/4	0/4
	100	1/1	1/1	1/1	0/1	0/4	0/4
	300	1/1	1/1	1/1	1/1	0/4	0/4
3a	30	0/1	0/1	0/1	0/1	0/4	0/4
	100	1/1	0/1	0/1	0/1	0/4	0/4
	300	1/1	0/1	1/1	0/1	1/4	0/4
3b	30	0/1	0/1	1/1	0/1	0/4	0/4
	100	0/1	0/1	1/1	0/1	0/4	0/4
	300	0/1	0/1	1/1	1/1	0/4	0/4
3c	30	0/1	0/1	0/1	0/1	0/4	0/4
	100	1/1	0/1	1/1	0/1	0/4	0/4
	300	1/1	1/1	1/1	1/1	0/4	0/4
3d	30	0/1	0/1	0/1	0/1	0/4	0/4
	100	1/1	0/1	0/1	0/1	0/4	0/4
	300	1/1	0/1	1/1	0/1	1/4	0/4
3e	30	0/1	0/1	0/1	0/1	0/4	0/4
	100	1/1	0/1	0/1	0/1	0/4	0/4
	300	1/1	0/1	1/1	0/1	0/4	0/4
Control	–	0/1	0/1	0/1	0/1	0/4	0/4
Standard		1/1	1/1	1/1	1/1	0/4	0/4

Control = PEG-400 (10 % suspension), Standard = Phenobarbital (30 mg/kg), 0/1 = No activity at dose level, 1/1 = Noticeable activity at dose level, $n = 5$ (Number of animals tested at each dose level)

MES Maximal electroshock seizure, *PTZ* Pentylentetrazol (Metrazol)

[a] Evaluated in rota-rod test (number of animal exhibiting toxicity/number of animal tested)

performed at Central Drugs Research Institute, Lucknow, India and the observed values were found in agreement with calculated values.

The results presented in Table 2 showed that compounds **2e**, **3c**, **3b, 2a**, **2b**, and **3a** exhibited appreciable anticonvulsant activity. Naphthyl group containing compounds **2e** and **3c** were found to be the most active compounds in the series showing good protection against both MES and PTZ induced seizures. Chloro-substituted derivatives **2a, 2b,** and **3a** were found to possess good anticonvulsant activity but more active against maximal electroshock induced seizures. It was also pointed out that some of the compounds (**2d** and **3b)** having 4-methoxy substitution in phenyl ring showed a positive response in the PTZ test but they did not show protection in MES-induced convulsions at the same doses and times evaluated. The 4-benzyloxy benzaldehyde derivative of 2-pyrazoline **2c** was not found to possess anticonvulsant activity as compared to other compounds synthesized in **Route 1**, but the same synthesized in **Route 2** having ethyl substitution **3d** showed average activity. Log *P* is indicative of lipophilicity of a compound. Thus, log *P* value of the compounds was calculated using method of Hansch (Harrold and Yee, 2005) and it was observed that the anticonvulsant activity of the synthesized compounds increased with increment in log *P* values. Noticeable neurotoxicity was observed for the compound **2c** at the evaluated doses. It is worth saying that the compounds having 2-pyridyl substitution at 3rd position of 2-pyrazoline are important for the activity, as almost all the derivatives bearing this substitution were found to be pharmacologically active. Therefore, such compounds would represent a fruitful matrix for the development of a new class anticonvulsant agent and would deserve further investigation and derivatization as a promising scaffold.

Conclusion

Results of the present study conclude that:

- 2-Pyridyl substitution at 3rd position of 2-pyrazoline is important for the activity, as almost all the derivatives bearing this substitution were found to be active.
- Highly hydrophobic (such as naphthyl or chlorophenyl) substitution at the 5th position of 2-pyrazoline nucleus increases the anticonvulsant activity.
- The presence of electron releasing (such as methoxy) substituent on the benzene ring at the 5th position of 2-pyrazoline results in decrease in the anticonvulsant activity and was found to be active against only PTZ induced seizures.
- Anticonvulsant activity increases with the increment in log *P* values.
- *N*-ethyl substitution at 1st position increases log *P* value but no marked effect was observed on the activity.
- Noticeable toxicity was observed for the compound **2c** at the evaluated doses.

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