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Synthesis and anticonvulsant activity of certain chalcone based pyrazoline compounds

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Abstract

Convulsions are involuntary, violent, spasmodic and prolonged contractions of skeletal muscles. That means a patient may have epilepsy without convulsions and vice versa. Epilepsy is a common neurological abnormality affecting about 1% of the world population. The primary objectives of these synthesized compounds are to suppress seizures and provide neuroprotection by minimizing the effects from seizure attacks. Here some of the chalcones and chalcone based various pyrazolines were evaluated for anticonvulsant activity. Their structures have been elucidated on the basis of elemental analyses and spectroscopic studies (IR, ^{1}H-NMR & Mass spectroscopy). A preliminary evaluation of the prepared compounds has indicated that some of them exhibit moderate to significant anticonvulsant activity compared to a diazepam standard. All compounds were tested for their anticonvulsant activity using maximal electroshock induced convulsions (MES) in mice at a dose level of 4 mg/kg. b.w. The compounds Ph1, Ph2, Py2, Py3 and Py4 have shown to good anticonvulsant activity when doses are administered as 25mg/ kg. b.w, reduced the phases of seizures severity and found to be active and also increased survival rate. Remaining compounds are less efficacious.
Keywords: Anti convulsant, Diazepam, Maximal electric shock method, Pyrazolines

1. Introduction

The term "anticonvulsant" is applied to a drug used for the treatment of epileptic seizures, hence,it is also known as the "antiepileptic,". This term is applied to other agents such as ketogenic diet and procedures such as vagal nerve stimulation when used for control of seizures [1]. Anticonvulsants are also being used in the treatment of neuropathic painand as mood stabilizers in the treatment of psychiatric disorders [2-3]. The development of anticonvulsant drugs started with the introduction of bromides in 1857 and was followed by the discovery of the anticonvulsant effect of barbiturates in 1912. Phenytoin synthesized in 1908, was not introduced for the treatment of epilepsy until 1938 [6-7]. Although carbamazepine was shown to have antiepileptic properties in 1954, it was first approved in 1968 for the treatment of trigeminal neuralgia and was approved in 1974. During the past 2 decades, several new anticonvulsant drugs have been approved worldwide, and the use of anticonvulsant drugs in indications other than epilepsy has increased. Several new drugs are in development.

Maximal electric shock seizures are brief high intensity shock is applied to the head of a rodent produces tonic flexion-tonic extension-clonic convulsions. The tonic phase is selectively abolished by the drugs effective in generalized tonic-clonic seizures (GTCS). Activity in this model represents action on spread of seizure discharge. These are group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes of loss of consciousness, with or without characteristic body movements [5].

Pyrazolines are well known and important nitrogen containing five membered heterocyclic compounds and various methods have been worked out for their synthesis. Numerous pyrazoline derivatives have been found to possess considerable biological activities, which stimulated the research activity in this field. Many selective chloro substituted organic compounds show peculiar pharmacological and agrochemical properties. Based on the pharmacological activities exhibited by the pyrazoline compounds, here, the synthesis and pharmacological evaluation has done. The study of biological evaluation of pyrazoline derivatives has been an interesting field of medicinal chemistry. The synthesis of pyrazoline derivatives and investigation of their chemical and biological behaviour has gained more important in recent decades for biological and pharmaceutical reasons [10].

2. Materials and Methods

Synthesis of (chalcones) 3-(4-acetylphenyl)-2-(phenyl)-3H quinazoline-4-one derivatives (D) and Synthesis of pyrazolines (P_{1-4})/ N-acetylpyrazolines (Py_{1-4}) / N-phenylpyrazolines (Ph_{1-4}) derivatives has been an active field of research due to their established pharmacological effects. In this study, a series of chalcones were prepared with 0.01moles of Anthralinic acid is added to 0.02moles of benzoyl chloride in pyridine (100ml). Kept for a reflux for 1hr 45 min. The mixture was shaken for 10 min and then set aside at room temp for further 1hr with occational shaking. The reaction mixture was poured in to cold water with stirring then solid white color product was separated out, filtered and dried in a vacuum desiccator up to complete drying of compound. The compound was recrystallized from dioxane. Percentage yield 98%w/w was obtained and melting point was found to be 58-60^{0}C.To a mixture of compound (C) (0.01 moles) and p-amino acetophenone was heated at 150^{0}C on sand bath for 1hr. After cooling the crude mass was crystallised from ethanol twice to give reddish brown crystals. Structures of the synthesized compounds were confirmed by elemental analysis and spectra (IR, ^{1}H-NMR, ^{13}C-NMR, and mass) data.

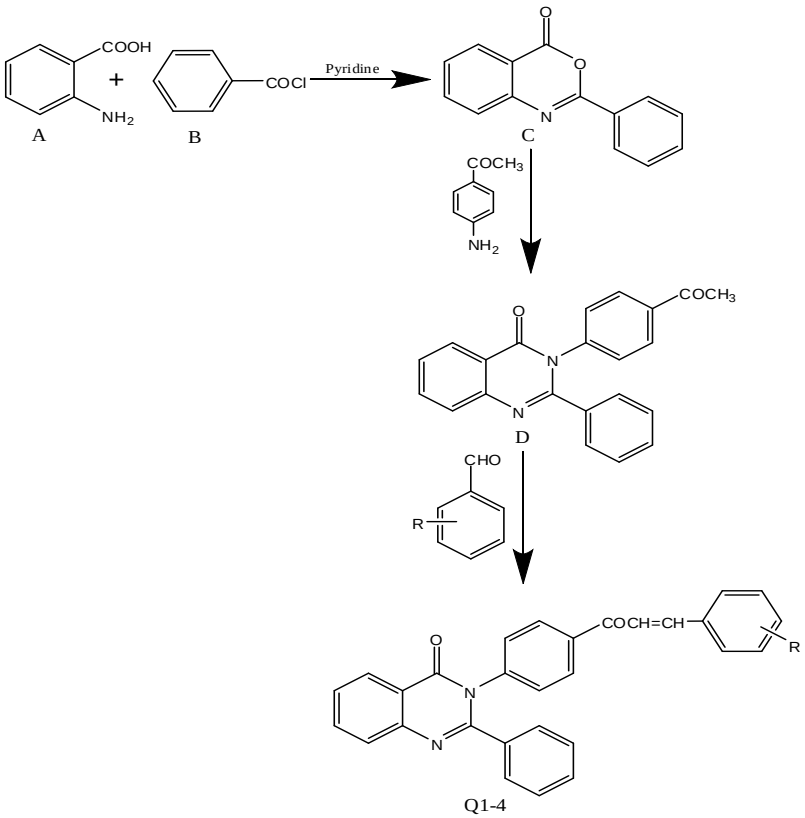
3. Experimental Section

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. IR spectra were recorded on BRUKER FT-IR spectrometer using ATR. ^{1}H-NMR spectra of the compounds in deutiriated dimethyl sulfoxide (DMSO) and $CDCl_3$ was recorded on BRUKER Av 400 spectrometer. Mass spectra were recorded on LCMS QP 5000 Shimadzu. Thin layer chromatography was performed using pre-coated aluminium plates, coated with silica gel GF_{254} [E.Merck]. Ethylacetate: Methanol in the ratio of 3: 2 was used as the eluent. The spots were visualized in the UV/Iodine chamber.

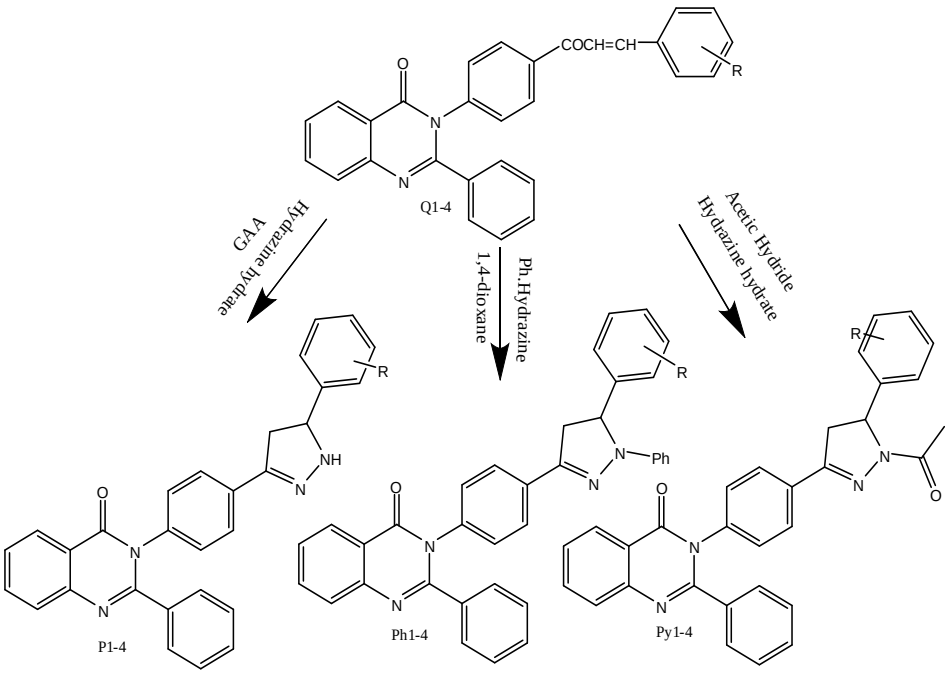
Synthesis of 3-(4-acetyl phenyl)-2-(phenyl)-3H quinazoline-4-one derivatives (D)

To 0.01moles of Anthralinic acid is added to 0.02moles of benzoyl chloride in pyridine (100ml). Kept for a reflux for 1hr 45 min. The mixture was shaken for 10 min and then set aside at room temp for further 1hr with occational shaking. The reaction mixture was poured in to cold water with stirring then solid white color product was separated out, filtered and dried in a vacuum desiccator up to complete drying of compound. The compound was recrystallized from dioxane. Percentage yield 98%w/w was obtained and melting point was found to be 58-60^{0}C.To a mixture of compound (C) (0.01 moles) and p-amino acetophenone was heated at 150^{0}C on sand bath for 1hr. After cooling the crude mass was crystallised from ethanol twice to give reddish brown crystals.

Scheme-I



Scheme-II



3.1. Method of Synthesis

Synthesis of 3(4(3(4-substituted phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-one (Q_{1-4})

Equimolar mixture of compound D (0.01mole) and the appropriate aromatic aldehydes (0.01mole) *p*-chlorobenzaldehyde, *p*-nitro benzaldehyde, *p*-methylbenzaldehyde and *p*-methoxybenzaldehyde were dissolved in ethanol and cold solution of 40% NaOH (15mL) was added in portion keeping the temperature below 10C with continuous stirring. The reaction mixture was kept overnight. Then it was acidified with dilute HCl and poured ice cold water with stirring. The product obtained was filtered, washed with cold water dried and recrystallised from ethanol.

Synthesis of pyrazolines (P_{1-4})/ N-acetylpyrazolines(Py_{14})/Nphenylpyrazolines (Ph_{1-4})

Mixture of compound Q_{1-4} (0.01mole) and phenyl hydrazine/hydrazine hydrate dissolved in 20 ml of 1, 4 dioxane/gla. aceticacid/ ethanol. To this reaction added 2-3 drops of sulphuric acid and the contents were refluxed for 4-8 hrs. After cooling the reaction mixture pour the contents in ice cold water. The obtained solid allow drying and recrystallized from ethanol (Scheme-I).

3.1.1Synthesis of chalcones

Synthesis of 3(4(3(4-substituted phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-one Equimolar mixture of compound D (0.01mole) and the appropriate aromatic aldehydes (0.01mole) p-chlorobenzaldehyde, p-nitro benzaldehyde, p-methylbenzaldehyde and p-methoxybenzaldehyde were dissolved in ethanol and cold solution of 40% NaOH (15mL) was added in portion keeping the temperature below 10C with continuous stirring. The reaction mixture was kept overnight. Then it was acidified with dilute Hcl and poured ice cold water with stirring. The product obtained was filtered, washed with cold water dried and recrystallised from ethanol.

3.1.2. Synthesis of pyrazolines

To a mixture of compound Q1-4 (0.01mole) and hydrazine hydrate (0.01m) in ethanol and added a fue drops of glacial acetic acid and refluxed for 8hrs. The reaction mixture was poured in to crushed ice. The separated solids were filtewred and recrystallised form ethanol.

3.1.3. Synthesis of N-phenylpyrazolines

Mixture of compound Q1-4 (0.01mole) and phenyl hydrazine dissolved in 20 ml of 1, 4 dioxane. To this reaction added 2-3 drops of sulphuric acid and the contents were refluxed for 4hrs. Then add 5ml of glacial acetic acid and continue the reflux another 2 hrs. After cooling the reaction mixture pour the contents in ice cold water. The obtained solid allow drying and recrystallized from ethanol.

3.1.4. Synthesis of N-acetylpyrazolines

The mixture of compound Q1-4 (0.01mole), hydrazine hydrate (0.01m) and glacial acetic acid (10ml) refluxed for 8hrs. The reaction mixture was poured in to crushed ice and the obtained mass was dried and recrystallised form ethanol.

4. Spectral study of synthesised compounds

Q1:3(4(3(4-chloro phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-one m. p. 140-142^{o}C; yield (%): 63; R_f: 0.43; IR (ATR,Cm-^{1}): 1644 (C=O of chalcone, str), 1701 (C=O of quinazolinone, str), 1610 (C=N, str), 1567 (C=C, str), 2970 (C-H Ali, str), 3107 (C-H Aro, str), 819 (C-Cl, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 7.10-9.12 (17H, m, Ar-H), 6.75 (2H, s, chalcone); Mass: m/z 142.

Q2:3(4(3(4-nitro phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-one m. p. 168-170^{o}C; yield (%): 73; R_f: 0.68; IR (ATR,Cm-^{1}): 1647 (C=O of chalcone, str), 1707 (C=O of quinazolinone, str), 1608 (C=N, str), 1565 (C=C, str), 2979 (C-H Ali, str), 3117 (C-H Aro, str), 1463 (N=0, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 7.3-9.9 (17H, m, Ar-H), 6.79 (2H, s, chalcone); Mass: m/z 170.

Q3:3(4(3(4-methyl phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-one m. p. 210-212^{o}C; yield (%): 79; R_f: 0.88; IR (ATR,Cm-^{1}): 1651 (C=O of chalcone, str), 1707 (C=O of quinazolinone, str), 1596 (C=N, str), 1560 (C=C, str), 2935 (C-H Ali, str), 3113 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 7.10-9.12 (17H, m, Ar-H), 6.75 (2H, s, chalcone); Mass: m/z 212.

Q4: 3(4(3(4-methoxy phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-one m. p. 178-180^{o}C; yield (%): 83; R_f: 0.94; IR (ATR,Cm-^{1}): 1668 (C=O of chalcone, str), 1701 (C=O of quinazolinone, str), 1608 (C=N, str), 1556 (C=C, str), 2955 (C-H Ali, str), 3104 (C-H Aro, str), 1117 (C-O-C, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 7.2-9.0 (17H, m, Ar-H), 6.45 (2H, s, chalcone); Mass: m/z 180.

P_1:3 (4-(5-(p-chlorophenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) one m. p. 190-192^{o}C; yield (%): 43; R_f: 0.79; IR (ATR,Cm-^{1}): 1710 (C=O of quinazolinone, str), 3610 (N-H, str), 1555 (C=C, str), 1598 (C=N, str), 2930 (C-H Ali, str), 3097 (C-H Ar, str), 788 (C-Cl, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 5. 60 (1H, s, N_1-H), 8.05 (1H, s, N_3-H), 7.11-9.08 (17H, m, Ar-H),3.20 (2H, dd, C_4-pyrazole), 2.20 (1H, s, C_5-H-pyrazole); Mass: m/z 192.

P_2: 3 (4-(5-(p-nitrophenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) one m. p. 110-112^{o}C; yield (%): 85; R_f: 0.76; IR (ATR,Cm-^{1}): 1708 (C=O of quinazolinone, str), 3590 (N-H, str), 1562 (C=C, str), 1596 (C=N, str), 2976 (C-H Ali, str), 3111 (C-H Ar, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 5. 82 (1H, s, N_1-H), 7.21-8.98 (17H, m, Ar-H),3.20 (2H, dd, C_4-pyrazole), 2.20 (1H, s, C_5-H-pyrazole); Mass: m/z 112.

P_3:3 (4-(5-(p-methylphenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) one m. p. 234-236^{o}C; yield (%): 56; R_f: 0.82; IR (ATR,Cm-^{1}): 1699 (C=O of quinazolinone, str), 3608 (N-H, str), 1560 (C=C, str), 1590 (C=N, str), 2970 (C-H Ali, str), 3127 (C-H Ar, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 5. 82 (1H, s, N_1-H), 7.32-9.01 (17H, m, Ar-H),3.10 (2H, dd, C_4-pyrazole), 2.36 (1H, s, C_5-H-pyrazole), 1.56 (3H, s, Ar-methyl); Mass: m/z 236.

P_4: 3 (4-(5-(p-methoxyphenyl)4,5 dihydro-1H-pyrazol-3-yl)phenyl quinazoline 4(3H) one m. p. 161-163^{o}C; yield (%): 78; R_f: 0.68; IR (ATR,Cm-^{1}1699 (C=O of quinazolinone, str), 3627 (N-H, str), 1550 (C=C, str), 1593 (C=N, str), 2989 (C-H Ali, str), 3115 (C-H Ar, str); ^{1}HNMR (δppm; $CDCl_3$/DMSO-d_6) : 5. 82 (1H, s, N_1-H), 7.32-9.01 (17H, m, Ar-H),3.10 (2H, dd, C_4-pyrazole), 2.36 (1H, s, C_5-H-pyrazole), 2.06 (3H, s, Ar-methoxy); Mass: m/z 163.

P_{h1}:3 (4-(1-phenyl- 5-(p-chlorophenyl) 4,5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 176-178^{o}C; yield (%): 59; R_f: 0.93; IR (ATR,Cm-^{1}): 1706 (C=O of quinazolinone, str), 1556 (C=C, str), 1598 (C=N, str), 2908 (C-H Ali, str), 3110 (C-H Aro, str), 820 (C-Cl, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 7.32-9.01 (23H, m, Ar-H), 3.10 (2H, d, CH_2 of pyrazole), 4.36 (1H, s, CH-pyrazole), 1.56 (3H, s, Ar-methyl); Mass: m/z 178.

P_{h2}:3 (4-(1-phenyl- 5-(p-nitrophenyl) 4,5 dihydro-1H-pyrazol-3-yl)phenyl quinazoline-4(3H) one m. p. 267-269^{o}C; yield (%): 81; R_f: 0.82; IR (ATR,Cm-^{1}): 1710 (C=O of quinazolinone, str), 1522 (C=C, str), 1610 (C=N, str), 2918 (C-H Ali, str), 3120 (C-H Ar, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 7.32-9.01 (23H, m, Ar-H), 2.96 (2H, d, CH_2 of pyrazole), 4.05 (1H, s, CH-pyrazole), 1.23 (3H, s, Ar-methyl); Mass: m/z 269.

P_{h3}:3 (4-(1-phenyl- 5-(p-methylphenyl) 4,5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 155-157^{o}C; yield (%): 63; R_f: 0.43; IR (ATR,Cm-^{1}): 1712 (C=O of quinazolinone, str), 1530 (C=C, str), 1588 (C=N, str), 2899 (C-H Ali, str), 3100 (C-H Ar, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 7.32-9.01 (23H, m, Ar-H), 3.12 (2H, d, CH_2 of pyrazole), 4.16 (1H, s, CH-pyrazole), 1.81 (3H, s, Ar-methyl); Mass: m/z 157.

P_{h4}:3 (4-(1-phenyl- 5-(p-methoxyphenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 122-124^{o}C; yield (%): 72; R_f: 0.91; IR (ATR,Cm-^{1}): 1706 (C=O of quinazolinone, str), 1556 (C=C, str), 1598 (C=N, str), 2908 (C-H Ali, str), 3110 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 7.32-9.01 (23H, m, Ar-H), 2.96 (2H, d, CH_2 of pyrazole), 4.21 (1H, s, CH-pyrazole), 1.28 (3H, s, Ar-methyl); Mass: m/z 124.

P_{y1}:3 (4-(N-acetyl-5-(chlorophenyl)-4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 190-192^{o}C; yield (%): 68; R_f: 0.49; IR (ATR,Cm-^{1}): 1698 (C=O, str), 1706 (C=O of quinazolinone, str), 1592 (C=N, str), 1459 (C=C, str), 2930 (C-H Ali, str), 3097 (C-H Aro, str), 828 (C-Cl, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 2. 91 (2H, d, CH_2 of pyrazoline), 4.66 (1H, s, CH of pyrazoline), 7.2-7.4 (17H, m, Ar-H), 2.06 (3H, s, CH_3 of acetyl); Mass: m/z 192.

P_{y2}:3 (4-(N-acetyl-5-(nitrophenyl)-4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 217-219°C; yield (%): 63; R_f: 0.43; IR (ATR,Cm-^{1}): 1698 (C=O, str), 1706 (C=Oof quinazolinone, str), 1592 (C=N, str), 1459 (C=C, str), 2930 (C-H Ali, str), 3097 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 3.08 (2H, d, CH_2 of pyrazoline), 4.45 (1H, s, CH of pyrazoline), 7.2-7.4 (17H, m, Ar-H), 1.90 (3H, s, CH_3 of acetyl); Mass: m/z 219.

P_{y3}:3-(4-(N-acetyl-5-(methylphenyl)-4,5 dihydro-1*H*-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 132-134°C; yield (%): 78; R_f: 0.84; IR (ATR,Cm-^{1}): 1698 (C=O, str), 1706 (C=O of quinazolinone, str), 1592 (C=N, str), 1459 (C=C, str), 2930 (C-H Ali, str), 3097 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 2.81 (2H, d, CH_2 of pyrazoline), 4.72 (1H, s, CH of pyrazoline), 7.2-7.4 (17H, m, Ar-H),1.89 (3H, s, CH_3 of acetyl); Mass: m/z 134.

P_{y4}:3 (4-(N-acetyl-5-(methoxyphenyl)-4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 97-99°C; yield (%): 80; R_f: 0.59; IR (ATR,Cm-^{1}): 1698 (C=O, str), 1706 (C=O of quinazolinone, str), 1592 (C=N, str), 1459 (C=C, str), 2930 (C-H Ali, str), 3097 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 2. 80 (2H, d, CH_2 of pyrazoline), 4.69 (1H, s, CH of pyrazoline), 7.2-7.4 (17H, m, Ar-H),1.96 (3H, s, CH_3 of acetyl); Mass: m/z 99.

5. Anticonvulsant activity

Animal were weighed, numbered and divided into two groups each consisting of six mice. One group were used as control and the other for sample compound treatment. The corneal electrodes were placed on the cornea of the animal and the prescribed current was applied. The readings of different stages of convulsions i.e. (a) tonic flexion, (b) tonic extensor phase, (c) clonic convulsions, (d) stupor and (e) recovery or death were noted [4]. The time (sec) spend by the animal in each phase of the convulsions were noted. The whole procedure was repeated with other animals of control group also. The sample compound was injected intraperitoneally to a group of 4-5 mice. After 30 min, the animals were subjected to electroconvulsions as described in above step. The reduction in time or abolition of tonic extensor phase of MES- convulsions were noted [6-9].

Albino mice were kept under hygienic conditions and on standard laboratory diet (diet composition A. O. A. C.: vitamin mix. 1%, mineral mix. 4%, sucrose 20%, cellulose 0.2%, 5% pure casein 10.5%, starch 54.3%) and water. electrodes and generated by a stimulator (UgoBasile ECT Unit, delivering an alternating 50 Hz current), the stimulus duration was 0.2 second and the end point was tonic hind limb extension. The maximum electro-shock was determined. Then the data are calculated & expressed as mean extensor phase duration in sec. followed by % protection and % potency in comparison with the standard using the following formula:

$$\%\text{Protection} = \frac{MEPDnc - MEPD\ Sample}{MEPD} \times 100$$

Where, MEPDnc is the mean extensor phase duration of normal control (MEPDnc) in sec. and MEPD is the mean extensor phase duration of sample or standard in sec.

Table 1: Physical data of newly synthesized compounds

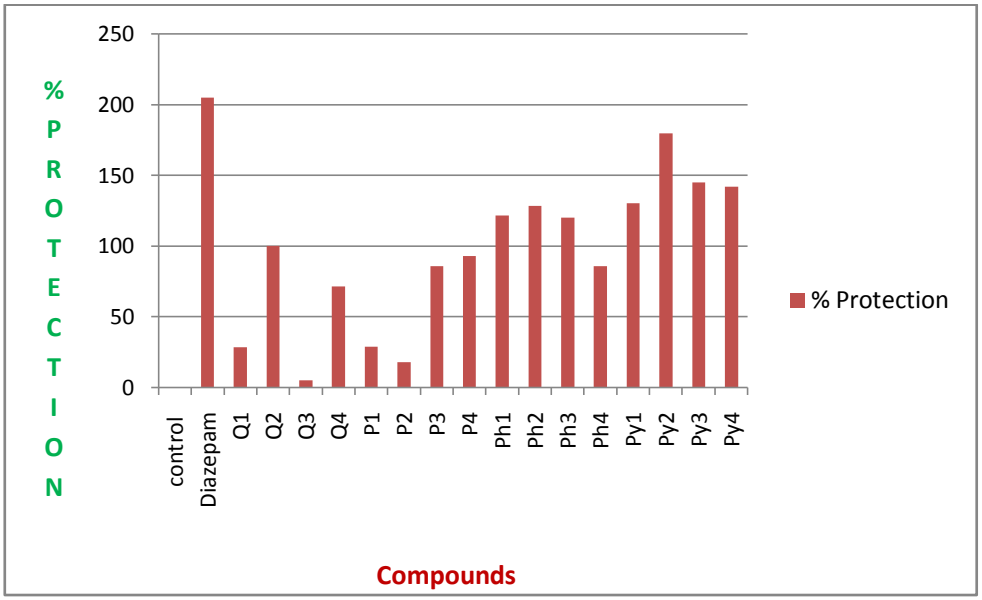
S. No	Code	Mol. wt	Mol. formula	Melting point (°C)	% yield
1	Q_1	450.5	$C_{28}H_{19}N_2O_2Cl$	140-142	63
2	Q_2	461	$C_{28}H_{19}N_3O_4$	168-170	73
3	Q_3	430	$C_{29}H_{22}N_2O_2$	210-212	79
4	Q_4	446	$C_{29}H_{22}N_2O_3$	178-180	83
5	P1	478.5	$C_{29}H_{21}N_4OCl$	190-192	43
6	P2	473	$C_{29}H_{21}N_4O_3$	110-112	85
7	P3	470	$C_{30}H_{24}N_5O$	234-236	56
8	P4	472	$C_{30}H_{24}N_4O_2$	161-163	78
9	Ph1	554.5	$C_{35}H_{25}N_4OCl$	176-178	59
10	Ph2	549	$C_{35}H_{25}N_4O_3$	267-269	81
11	Ph3	532	$C_{36}H_{28}N_4O$	155-157	63
12	Ph4	548	$C_{36}H_{28}N_4O_2$	122-124	72
13	Py1	520.5	$C_{31}H_{23}N_4O_2Cl$	190-192	68
14	Py2	529	$C_{31}H_{23}N_5O_4$	217-219	63
15	Py3	498	$C_{32}H_{26}N_4O_2$	132-134	78
16	Py4	514	$C_{32}H_{26}N_4O_3$	97-99	80

Table 2: Anticonvulsant activity of diazepam and newly synthesized compounds

Compounds	Mean convulsion thresh hold±S.E	% Protection	% Potency
Control	2.33±0.17	0	0
Diazepam	7.11±0.33	205	---
Q1	3.00±0.27	28.76	42.19
Q2	4.67±0.27	100.43	65.68
Q3	2.45±0.31	5.15	34.45
Q4	4.00±0.31	71.67	70.0
P1	3.00±0.41	29.0	56.25
P2	2.33±0.14	18.0	0
P3	4.33±0.45	85.84	60.90
P4	4.50±0.20	93.13	63.29
Ph1	5.17±0.50	121.8	72.7
Ph2	5.33±0.18	128.76	74.96
Ph3	5.0±0.20	120.4	71.8
Ph4	4.33±0.41	85.84	60.90
Py1	5.67±0.28	130.3	75.0
Py2	6.9±0.20	180.0	82.0
Py3	6.2±0.30	145.0	80.0
Py4	6.1±0.20	142.0	78.0

Values representing the means of six animal's ± standard error

5.1. Graphical representation of comparison between control, reference drug and synthesized compounds regarding (percentage protection vs compounds)



6. Results and Discussion

Synthesis of 16 novel compounds involve in three steps. The key intermediate compound D was prepared fromAnthralinic acid and benzoyl chloride in presence of pyridine to give 2 [phenyl]-benzo (1,3) oxazine-4-one and further treated with *p*-amino acetophenone to give 3-(4-acetyl phenyl)-2-(phenyl)-3H quinazoline-4-one derivatives. The later refluxed with different substituted aromatic aldehydes in ethanol and cold solution of 40% alkali yielded the chalcone compounds Q_{1-4} and further treated with hydrazine hydrateand acetic acid yielded the desired compound $P_{1-4,}$ Ph_{1-4}& Py_{1-4}in good yield. For Q_{1-4} the IR spectra showed intense peaks at 1698 cm-1 for (C=O of chalcone, str), 1725 cm-1 for (C=O of quinazolinone, str), 1550-1585 cm-1 for (C=C, str) and 1590-1620 cm-1 for (C=N, str). The H^1NMR showed singlet at 6.50-6.65 (2H, s, CH=CH) indicating the presence of chalcone group. The targeted compounds P_{1-4}, Ph_{1-4}& Py_{1-4} obtained from Q_{1-4} in presence of hydrazine hydrate and acetic acid in good yield. The IR showed intense peak at 3650-3590 cm-1 for (NH of pyrazoline, str) presence at P_{1-4}absence in Ph_{1-4} and Py_{1-4}.The H^1NMR showed singlet at 5.6-6.4 (1H.s. NH for pyrazoline).The mass spectra of the all 16 compounds showed molecular ion peaks at corresponding to their molecular

formula. The newly synthesized compounds were screened for anticonvulsant activity and it was found that the compounds were chalcones (Q_{1-4}) and chalcone based simple pyrazolines(P_{1-4}) showed no significant activity and the compounds were acetyl substituted and n-phenyl substituted pyrazolines (Ph_{1-4} and Py_{1-4}) showed good activity when compared to standard.

7. Conclusion

The present studies reveals on synthesis and evaluation of various pyrazolines based on chalcones shown significant protection against maximal electric shock induced convulsions as compared to control. The synthesized compounds provide protections against seizures induced by maximal electric shock method are generally effective against toxic clonic seizures. But the animals were observed for all phases as well as the duration. The maximum activity shown by the compounds was Ph1, Ph2, Py2 and Py3 in extensor phase. The abolition of extensor phase in treated group animals was taken as experimental criteria for anticonvulsant activity. There by totally four compounds produced the anticonvulsant activity among synthesized compounds.

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