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Synthesis and Antidepressant Activity of Certain Chalcones and Chalcone Based Simple Pyrazolines

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Abstract

Two classic animal behavioural model methods was followed in the form of despair tests the forced swimming test (FST) and the tail suspension test (TST) were used to evaluate antidepressant-like activity of a new chalcones and chalcone based simple pyrazolines in mice. It was observed that chalcones are at the dose of 1, 5, and 10 mg/kg significantly reduced the immobility time in the FST and TST in mice 30 min after treatment. It also produced a reduction in the ambulation in the open-field test in mice not previously habituated to the arena, but no effect in the locomotor activity in mice previously habituated to the open-field. It was found that chalcones and chalcone based simple pyrazolines significantly increased the concentrations of the main neurotransmitters 5-HT and NE in the hippocampus, hypothalamus and cortex.

Key words: Chalcones , Simple pyrazolines, Anti-depressant activity, Forced swimming test and Tail suspension test

INTRODUCTION:

Depression is the most common chronic condition in clinical practice and will become the second leading cause of premature death or disability worldwide. Approximately two-thirds of the anxious or depressed patients respond to the currently available treatments but the magnitude of improvement is still disappointing[3.] Although there are many effective antidepressants available today, the current therapies are inadequate and dis satisfactory results in about one third of all subjects treated. This necessitates the development of newer and more effective antidepressants drugs[1-2]. Chalcones are a group of compounds widely distributed in plant kingdom. They are both intermediates and end products in flavonoid biosynthesis, act as defensive compounds, participate in plant-insects interactions and contribute to the medicinal value of herbs. They comprise open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system. Chalcones are a group of flavonoids that exhibit a wide variety of pharmacological effects, including antibacterial, antifungal, antiviral, and analgesic properties[4-7]. In recent years, it has been reported that flavonoids possess antidepressant-like activities [8-11]. In this research to investigate the antidepressant activity by three classic animal behaviour tests like forced swimming test, the tail suspension test and locomotor activity by actophotometer was used to evaluate antidepressant-activity of chalcones and chalcone based simple pyrazolines, aectyl substituted pyrazolines and n-phenyl substituted pyrazolines in mice.

EXPERIMENTAL SECTION:

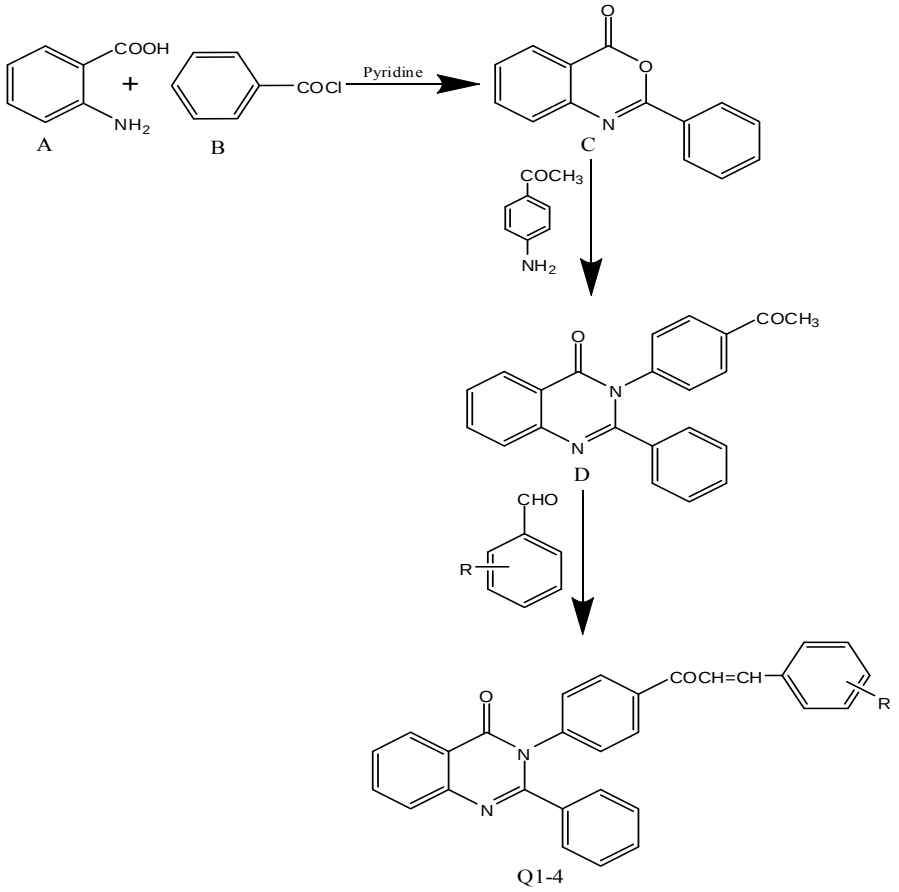
Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. IR spectra were recorded on BRUKER FT-IR spectrometer using ATR. ^{1}H-NMR spectra of the compounds in deutiriated dimethyl sulfoxide (DMSO) and $CDCl_3$ was recorded on BRUKER Av 400 spectrometer. 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.

METHOD OF SYNTHESIS

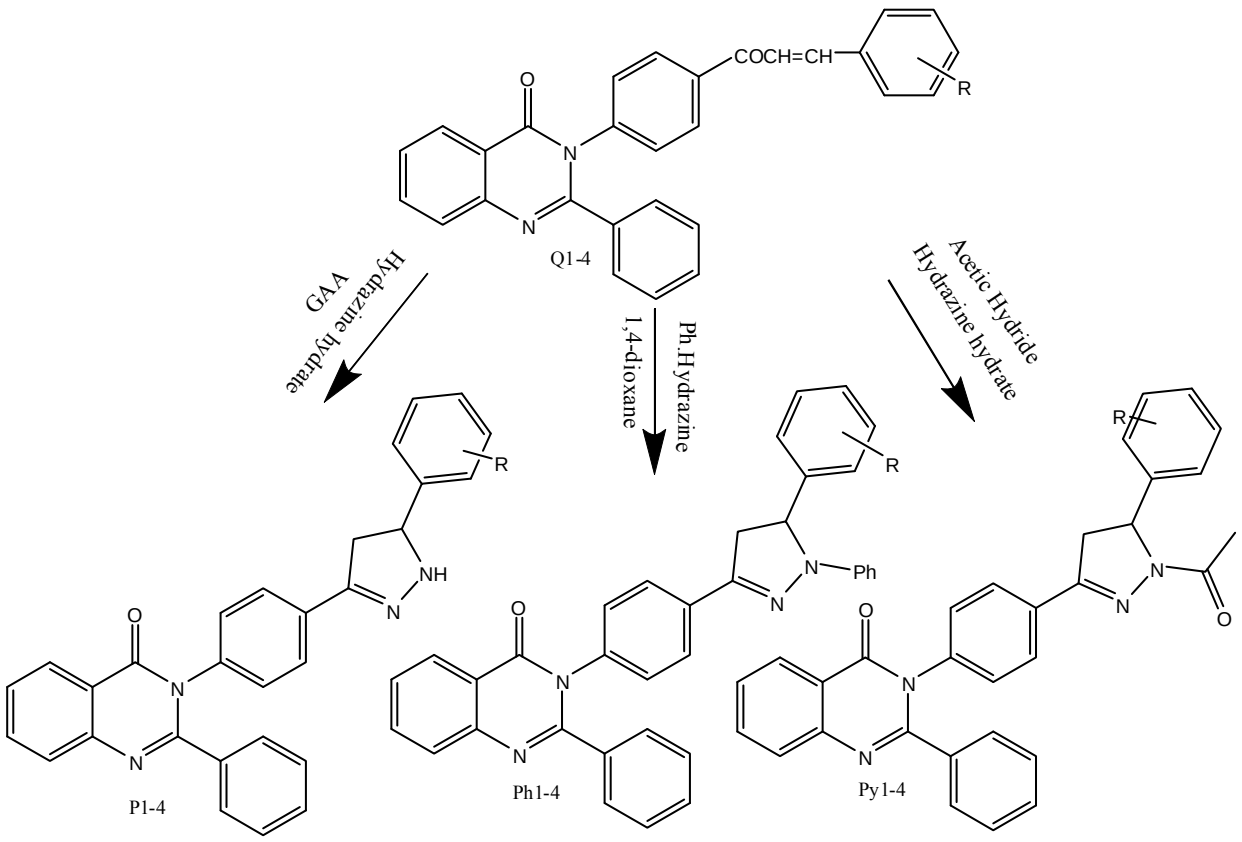
Synthesis of 3-(4-acetyl phenyl)-2-(phenyl)-3H quinazoline-4-one derivatives (D)

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



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*-chloro benzaldehyde, *p*-nitro benzaldehyde, *p*-methylbenzaldehyde and *p*-methoxy benzaldehyde 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 simple pyrazolines (P_{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).

Synthesis 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-chloro benzaldehyde, p-nitro benzaldehyde, p-methylbenzaldehyde and p-methoxy benzaldehyde 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

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.

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.

Table 1. Physical data

S.No	Code	Mol.wt	Mol.formula	Melting point	% yield
1	Q_1	450.5	$C_{28}H_{19}N_2O_2Cl$	140-142ºC	63
2	Q_2	461	$C_{28}H_{19}N_3O_4$	168-170 ºC	73
3	Q_3	430	$C_{29}H_{22}N_2O_2$	210-212 ºC	79
4	Q_4	446	$C_{29}H_{22}N_2O_3$	178-180 ºC	83
5	P1	478.5	$C_{29}H_{21}N_4OCl$	190-192 ºC	43
6	P2	473	$C_{29}H_{21}N_4O_3$	110-112 ºC	85
7	P3	470	$C_{30}H_{24}N_5O$	234-236 ºC	56
8	P4	472	$C_{30}H_{24}N_4O_2$	161-163 ºC	78

ANTIDEPRESSANT ACTIVITY

Forced swimming test (FST)

The synthesized compounds were screened for their antidepressant activity using forced swimming test[12], male mice about (20-24 g) was used in the forced swimming test under standard conditions with free access to food and water. They housed in groups of six. On the test day, mice were dropped one at a time into a plexi glass cylinder (height 25 cm, diameter 10 cm) containing 10 cm of water at 23-25 ℃[13]. On this day, mice were assigned into different groups (n=10 for each group). The compounds are chalcones like 3(4(3(4-substituted phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-one **(Q_{1-4})** (10mg/kg b.w) , simple pyrazolines like 3 (4-(5-(p-chlorophenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) one (**P_{1-4})** and Imipramine is tricyclic antidepressant acts as a reference drug (6.5 mg/20 g b.w of mice) were dissolved DMSO injected intraperitoneally (i.p.) in a standard volume of 0.1 mL/20g body weight, 30 min prior to the test. Then, the mice were dropped individually into the pelxi glass cylinder and left in the water for 6 min. After the first 2 min of the initial vigorous struggling, the animals were immobile. A mouse was judged immobile if it floated in the water in an upright position and made only slight movements in order to prevent sinking. The duration of immobility was recorded during the last 4 min of the 6 min test. All test swim sessions were recorded by a video camera positioned directly above the cylinder. Two competent observers, who were unaware of the treatment each mouse had received, scored the videotapes. Immobility period was regarded as the time spent by the mouse floating in the water without struggling and making only those movements necessary to keep its head above the water. Following swimming sessions, they were then towel dried and returned to their housing condition. The animals were used only once in this test. All FSTs were performed between 16:00 p.m. and 19:00 p.m.

Tail suspension test (TST)

The tail suspension test was based on the method of Steru[14]. Briefly, each mice was individually suspended by its tail using a clamp (2 cm from the end) for 6 min in a box (25×25×30 cm) with the head 5 cm from the bottom. Testing was carried out in a darkened room with minimal background noise. On this day, mice were assigned into different groups (n=10 for each group). The synthesized compounds chalcones and chalcone based simple pyrazolines (10 mg/kg) and Imipramine as a reference antidepressant drug (6.6 mg/20g.b.w of mice) were dissolved DMSO injected intraperitoneally (i.p.) in a standard volume of 0.1 mL/20g body weight, 30 min prior to the test. After the first 2 min of the initial vigorous struggling, the animals were immobile. The duration of immobility was recorded during the last 4 min of the 6 min test. All test sessions were recorded by a video camera positioned directly above the box. Two competent observers blind to treatment scored the videotapes. Mice consider immobile only when they hung passively and completely motionless. The animals were used only once in this test. All TSTs were performed between 14:00 p.m. and 16:00 p.m.

Table 2. Anti-depressant activity of synthesized compounds (Q_{1-4} and P_{1-4}) through FST

Compound	Forced swimming test (FST)		Anti-depressant activities
	Dose mg/kg	Duration of immobility	change from control
Q1	10	120	-30
Q2	10	125	-25
Q3	10	125	-25
Q4	10	128	-22
P1	10	134	-16
P2	10	136	-14
P3	10	138	-12
P4	10	140	-10
Imipramine	10	110	-40
Control		150	-----

Table 3: Anti-depressant activity of synthesized compounds (Q_{1-4} and P_{1-4}) Through TST

Compound	Tail suspension test (TST)		Anti-depressant activities
	Dose mg/kg	Duration of immobility	change from control
Q1	10	105	-35
Q2	10	110	-30
Q3	10	112	-28
Q4	10	115	-25
P1	10	120	-20
P2	10	130	-10
P3	10	133	-07
P4	10	134	-06
Imipramine	10	95	-45
Control		140	-----

RESULTS AND DISCUSSION:

The forced swimming test is a behavioral test used to predict the efficacy of antidepressant treatments. It is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors and atypical antidepressants [15]. All procedures used in the present study were in accordance with the guidelines for the Care of animals are followed as per institutional animal ethical committee approved by CPCSEA ,Chennai. The obtained data on the antidepressant activity of the compounds and reference drug (Imipramine) are given in table 2. These compounds exhibited the antidepressant activity and promoted a significant decrease in the immobility time in which there is significant difference between Imipramine and the test compounds, and reduced the duration of immobility time by 30 % and 25 %, respectively, at a dose of 10 mg/kg compared with the control (p <0.05) in the FST. Compounds Q_{1-4} and P_{1-4} with good antidepressant activity was administered (10 mg/kg, i.p.) in mice. The Compounds Q_{1-4} and P_{1-4} are exhibited antidepressant-like activity and promoted a significant decrease in the immobility time in which there is significant difference between Imipramine and the test compounds.

The FST and TST are rodent behavioral tests that have good predictive validity for antidepressant effects in humans. Immobility has been shown to reflect a state of "behavioral despair and variants" .The immobility displayed in both rodent behavioral test of behavioral despair has been hypothesized to reflect depressive disorders in humans. There was a significant correlation between clinical potency and the potency of anti-depressant in both models.

CONCLUSION:

In our investigation the Compounds which are chalcone and chalcone based simple pyrazolines are Q_{1-4} and P_{1-4} exhibited antidepressant-like activity and promoted a significant decrease in the immobility time in which there is significant difference between Imipramine and the test compounds.The immobility displayed in both rodent behavioral test of behavioral despair has been hypothesized to reflect depressive disorders in humans.These drugs produced the good anti-depressant activity.

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